THE FOOD & DRUG LETTER®

Issue No. 859
Jan. 14, 2011

Abstract: *Traditionally, neither the United States nor the European Union has regulated medical devices as heavily as they have pharmaceuticals. However, the current trend is toward increased medical device regulation. The March 21, 2010, kickoff of the updated EU Medical Device Directive confronted global devicemakers with quite a few changes in how their products are approved and sold in Europe. Some of these changes widened the already-substantial gulf between the U.S. and EU approaches to device regulation, in areas including clinical trials, reclassification of some devices, postmarket surveillance requirements and even the definition of the term "medical device." Moreover, devicemakers have noted areas of ambiguity in the new EU directive, such as how European regulators define the term "substantial changes" as it applies to postmarketing device modifications. Both regions continue to hold ongoing discussions about potential changes, including some intended to harmonize these requirements. This issue of* The Food & Drug Letter *outlines some of the key differences and similarities in how the U.S. and EU regulate medical devices.*

EU Medical Device Directives Bring Confusion to Industry

The issuance of the new Medical Device Directives in the EU has caused confusion for companies.

For example, some companies didn't realize that the March 21, 2010, deadline — announced in 2007 — was a sunset date and not the start of a transitional period.

The update has also raised questions about already-approved products. Companies are unsure whether they should have these devices re-approved, or if any existing approval for EU marketing is sufficient.

According to the European Commission guidance, manufacturers in this situation do not have to comply with the new requirements — though they may want to do so on a voluntary basis. In fact, experts say compliance in this case is not really voluntary at all.

For that reason, it is in the best interests of devicemakers to ensure they know the new rules and that their devices — whether new or already on the market — comply with them.

Another critical question companies face, and one that may have a different answer depending on which side of the Atlantic Ocean they ask, is this: Who is ultimately responsible for compliance with the directive?

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In the EU, the answer to this question is quite simple: the manufacturer remains the sole entity responsible for the approval and regulatory compliance of a device sold under its name, regardless of whether any or all of these operations are carried out by that particular entity or by a third party under contract.

This means that devicemakers must be able to demonstrate that adequate quality systems are in place at any contract researcher or manufacturer. In the U.S., on the other hand, federal regulations do not specify a blanket requirement for who must submit the 510(k) or premarket approval (PMA) application.

With some exceptions, the establishment "engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of a device" must submit the application.

This could include a manufacturer making a product according to its own specifications or a specs developer that creates the specifications and introduces the device to the U.S. market. A contract manufacturer producing a device under contract and according to another company's specifications is not required to submit a PMA or 510(k).

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Other possible scenarios include:

- Repackagers or relabelers must submit an application if they significantly change the labeling or otherwise affect any condition of the device;
- Foreign manufacturers/exporters or U.S. representatives of such companies that are introducing a device to the U.S. market must submit an application; and
- Certain establishments, including foreign companies, must register with the FDA and bear responsibility for marketing approval.

For manufacturers just establishing an EU presence, one rule remains particularly important: The companies must have an EU-based authorized representative to deal with regulatory authorities on their behalf.

This was already provided for with some devices. The updated directive recognizes this and specifies that such a person now must be designated for each and every device sold in the EU. This individual will be considered responsible for the product in Europe. It is worth noting that the same representative must be appointed for all devices of the same model.

While many larger, more established companies likely already have officials operating in the EU, companies new to the market will have to incorporate this position into their operational plans. They also must identify the authorized representative as part of the approval process.

Finally, responsibility for approval and regulatory compliance in both the EU and U.S. hinges largely on understanding exactly what is and what is not defined as a medical device under the respective laws.

This is not as simple as it may seem at first. The new EU directive introduced some critical changes to the way it defines that term. One example is the inclusion of software associated with a medical product — a change U.S. regulators are also contemplating.

EU Regulations Remain Fragmented When Compared With US

When comparing the EU and U.S. approaches to regulating medical devices, one of the most important things manufacturers need to remember is that, despite ongoing efforts at harmonization, regulations in the EU remain much more fragmented than they do in the U.S.

Device manufacturers, distributors and importers deal with four main players on a daily basis in the EU: the European Commission; various national regulators, known as competent authorities; notified bodies, or private third parties that play a role in approving devices; and other entities.

That last group may include ethics committees or, to a very limited degree (i.e., for combination products and other types of devices related to pharmaceuticals), the European Medicines Agency or the EU's central competent authority.

Medical Device Directives

"The level of integration and harmonization achieved in the U.S. is, by far, bigger than the one we are attempting to achieve in the EU," Cristiana Spontoni, partner with Squire, Sanders & Dempsey, says.

The Medical Devices Directives, were meant to create an open, internal market for medical devices within the EU, meaning that devices made in one member nation could be freely circulated in all others without barriers, she explains.

Other directives that affect some device-makers are the Active Implantable Medical Devices Directive (90/385/EEC) and the In Vitro Diagnostic Medical Devices Directive (98/79/EC).

However, the general Medical Devices Directive is of the greatest concern for two reasons: It covers the bulk of products cleared for sale in the EU and was updated most recently.

Basically, the EU offers a two-level system. The Medical Devices Directive exemplifies EU-wide legislation. These laws apply throughout all EU member states. However, key national requirements also remain applicable and can have a huge impact on medical device manufacturers.

Each member country incorporates the basic rules of the harmonized directives into its respective national laws. Generally speaking, that translation of a directive into national law happens in such a way that the national legislation reflects almost perfectly the rules contained in the directive. However, flexibility is allowed and some EU members have tweaked the requirements of directives.

For example, one critical exception to the free circulation of devices concerns labeling requirements. The directive states that member countries can require specific labeling parameters under their national laws. This can grow quite cumbersome for manufacturers, with 27 member nations and a large number of official languages to consider.

Thus, manufacturers wishing to sell their products in the EU must pay close attention not only to the broader EU directive, but also to the national laws of the specific nations in which they seek to sell their devices.

Knowledge of the legislation — EU or national — does not, in itself, suffice. When looking at the laws of the EU, guidance documents adopted by the European Commission in consultation with member nations and notified bodies remain as important as the regulations themselves.

In Vitro Devices

One of the more striking differences between the U.S. and EU regulations affects in vitro diagnostic devices. While the U.S. has a separate FDA office to handle the devices, it does not maintain separate regulations for them, as the EU does.

Devices in the U.S. are approved under one of two programs: the premarket approval (PMA) or the 510(k) premarket notification. Whether a device falls into one program or another depends on its risk classification.

The 510(k) program is undergoing transformation. Maureen Bennett, partner with Squire,

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Sanders & Dempsey, notes that U.S. regulations could undergo a substantial change in the relatively near future. Such a change would follow, in terms of scope, the lines of the update to the EU directives. The Center for Devices and Radiological Health is in the process of an in-depth self-examination of the device regulatory process, with numerous task forces reviewing various aspects of the program.

Two of the task forces — the 510(k) working group and a task force on use of science in regulatory decisionmaking — issued their preliminary reports and recommendations in August 2010.

A great deal of interesting commentary came out of the task forces, Bennett notes. Industry expects to receive new guidance documents at the very least and could see new regulations and/or legislation. However, the FDA has yet to narrow down the issues.

Defining Devices Can Challenge Manufacturers in US, EU

Whether in the U.S. or the EU, regulations are meaningless without a clear definition of the products they regulate. The definition of a "medical device" challenges manufacturers on two fronts.

First, there are some notable differences in the specifics of the EU versus the U.S. definitions. Second, the update to the EU definition under the new Medical Device Directives expanded the number of products covered.

As already noted, a key update to the EU definition in the Medical Device Directives was the inclusion of software, when specifically intended for medical uses, in the formal definition. That is not included in the U.S. definition, though this could change.

Another obvious difference: While the U.S. definition specifically includes devices meant for use in animals, the EU definition focuses solely on products intended for human use.

And while the U.S. includes in vitro diagnostics and implantable products under a single definition covering all medical devices, the EU does not. Implantable devices and in vitro diagnostics sold in the EU are covered under their own respective directives.

Other differences lie in the respective regulatory procedures of each region. Under the EU device certification system, the device manufacturer's claim marks the starting point for deciding whether a product is a device or a drug.

Scientific Evidence

But a claim on its own is not decisive; companies must provide scientific evidence to justify a claim that a product should be regulated as a medical device in the EU, according to Cristiana Spontoni, partner with Squire, Sanders & Dempsey.

This separation can lead to some confusion in the cases of combination products or some drug-delivery systems. Further, the EU's stance raises questions in borderline cases, such as bone cements and dental-filling materials.

Spontoni notes that fluoride dental preparations are considered drugs, unless the fluoride has merely an ancillary role, adding, "That is another headache for those who deal with European legislation, because there isn't a clear definition of 'ancillary role,' so these definition questions have to be dealt with on a case-by-case basis."

Some examples of devices that contain drugs playing an ancillary role include drug-eluting coronary stents, bone cement containing antibiotics and soft tissue fillers incorporating anesthetics.

Drug-delivery products can be regulated in the EU as either medicinal products or medical devices, depending on the exact type of product. For instance, a product shall be regulated as a drug if it comprises a device that includes a pharmaceutical product, exclusively in

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combination, and is intended for single use (i.e., it is non-reusable).

However, even though these products must go through the medicinal product review and approval process, the safety and performance of the device portion (i.e., the delivery mechanism) must satisfy all the requirements of the device directives.

In contrast, when a product is intended to deliver a pharmaceutical but does not include the drug when presented to the public, it is regulated as a medical device. An obvious example here is an empty syringe.

Likewise, products incorporating ancillary medicinal substances are regulated as medical devices. Spontoni characterizes this as an exception to the general rule that combination products are typically regulated as medicinal products.

For these cases, a notified body would have to consult with either a pharmaceutical competent authority at the national level or the European Medicines Agency in London on both the quality and safety of the medicinal substance before the device may be certified.

Notified Body Plays Key Role

In any case of doubt as to the correct classification of a product as either a device or pharmaceutical, the notified body will play the key role in making the final determination. Under EU regulations, the stricter pharmaceutical rules apply if there is any ongoing question of whether a product is a drug or a device.

The EU offers extensive guidance on the correct definition of various products as devices or pharmaceuticals. Among these is a May 2010 manual on borderline device classification.

The overall structure is quite different in the U.S., with the government highly engaged in device approval. U.S. regulation mirrors that of the EU in that there is a substantial difference in the regulatory framework for devices, compared with drugs. However, unlike in the EU, the FDA is responsible for approving new devices, either through the premarket approval or the 510(k) program.

Also as in the EU, combination or borderline products can pose a challenge, though the more uniform U.S. system is somewhat easier to navigate. One factor that makes the U.S. system simpler is the FDA Office of Combination Products (OCP), established by the Medical Device User Fee & Modernization Act of 2002.

This office is responsible for promptly identifying how a particular product should be regulated — that is, whether the agency's drug, device or biologic centers should oversee it. As in the EU, the FDA looks primarily at the product's mode of action in determining how it will regulate a given product.

"It's important to note that, even if the product is selected to be reviewed by one of the particular centers — biologics, devices or drugs — that does not limit the FDA's ability to draw upon and have participation from the other centers," Bennett says.

If the assignment is unclear, or if the device-maker doesn't agree with OCP's determination, the company can submit a request for designation of the product. Doing so constitutes a type of appeals process.

Classification Determines Approval Approach

The first area of regulation that manufacturers must consider is how medical devices are classified under the different systems.

In both the EU and U.S., device classification is risk-based. Regulators on both sides of the Atlantic consider patient risks, invasiveness and duration of use among other factors in assigning devices to different classes. But there are as many differences between the EU and U.S. approaches as there are similarities.

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EU Versus U.S. Device Classification	
EU	U.S.
Four categories: Class I, IIa, IIb, III	Three categories: Class I, II, III
National authorities may have their own regulations and guidances.	States rarely override federal regulations and procedures.
Notified body recommendations weigh heavily in classification decisions; companies can appeal.	The FDA makes classification decisions; companies can appeal de novo classification into Class III.

Whether seeking approval for a new device in Europe or the U.S., devicemakers should understand each region's classification procedure, as this determines the specific procedures necessary to gain marketing approval.

EU Approach

Under the EU system, devices fall into any one of four classes. It begins with the lowest risk category, Class I, followed by Class IIa, Class IIb and ending with the highest-risk category, Class III (*see box below*).

The European Commission revised the guidance on medical device classification in June 2010. Some of the changes in the guidance document included the addition of several implanted devices to Class III, namely breast implants, as well as hip, knee and shoulder joint replacements. The new guidance now discusses how some of the trickiest cases are most likely to be handled.

Placement in a particular class determines which assessment procedures devicemakers must follow to gain approval to sell their products in the EU. Companies should be familiar with guidance from various national authorities on how to classify products.

In the EU, notified bodies play a decisive role in defining a new device's designated class. These independent bodies are authorized by the national competent authorities to certify device compliance with the requirements of the EU directive for CE (Conformité Européenne, French for European conformity) marking. Generally, the manufacturer will have a contract with one of these private entities, meaning their decisions are not fully independent.

This point has drawn criticism, with detractors suggesting that the EU system should be more like the U.S. model, where all such decisions are in the hands of the regulatory authority.

While the opinions of these private entities are not binding, they are usually followed when it comes to the classification of a new medical device.

If a manufacturer does not agree with a notified body's opinion on classification, the company can seek a decision from the competent authority of the nation in which it seeks approval for its product.

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EU Device Classification System

- **Class I:** Low-risk and noninvasive. Includes such products as wheelchairs, conductive gels and corrective lenses and frames.
- **Class IIa:** Includes products that are noninvasive and connected to an active MD, along with most surgically invasive devices meant for short-term use, such as temporary filling materials.
- **Class IIb:** Higher-risk implantable devices and long-term surgically invasive devices, such as intraocular lenses, stents and valves.
- **Class III:** Invasive devices used in complicated procedures (e.g., neurological catheters) and some implants, such as breast implants, as well as hip, knee and shoulder replacements.

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This is one of the areas where the system isn't working that well, according to Cristiana Spontoni, partner with Squire, Sanders & Dempsey.

There are huge differences in approaches and opinions, depending on the nationality of the notified body and competent authority, she explained. This means there is a great deal of fragmentation in how devices may be classified among different EU countries.

"That's why the commission and the authorities in Brussels are trying to, basically, cover more and more types of products, in order to avoid this market fragmentation," Spontoni explains. Nonetheless, changes to the system will not come anytime soon. Indeed, notified bodies will continue to play a key role in medical device certification for the foreseeable future.

US Approach

Even as the EU eyes some aspects of the U.S. approach to regulation, U.S. authorities are considering modifications that would mirror the current EU system.

For instance, as opposed to the four-category classification system used in the EU, U.S. regulators classify medical devices into just three groups. These classifications are also risk-based, with Class I devices posing the lowest risks to patients and Class III products the highest.

Meanwhile, a federal working group is considering a change that would split Class II, subjecting some products in this category to tighter approval standards.

Under the current system, for Class I devices the concept is that general controls, such as good manufacturing practice compliance and requirements to prevent adulteration or misbranding, suffice in ensuring patient safety. On the other hand, Class II products pose a higher potential for risk, requiring both general and some special controls. The products also are subject to 510(k) review.

In the case of special controls, there is perceived to be enough information available that the Class II devices can largely be approved by proving substantial equivalence to an existing device.

Class III devices fall under the highest risk level and as such always require some sort of special controls. Companies must demonstrate to the FDA the effectiveness of these controls in providing a reasonable assurance of both safety and efficacy.

The FDA also subjects these devices to the rigorous premarket approval (PMA) process, which requires clinical data proving the products are safe and effective for their intended use.

The U.S. could consider splitting Class II into two subclasses: IIa and IIb, similar to the case in the EU. This idea, under consideration by the 510(k) working group, would require Class IIb devices to face more rigorous premarket clearance requirements.

This could include the submission of clinical data, including some clinical trial data, as well as manufacturing and additional postmarket information.

This would be more similar to the current PMA process than to the premarket notification procedure. If implemented, it would mark a substantial and significant change for companies that make implantable life-sustaining or life-supporting devices that now fall into Class II.

In the U.S., there is also provision for de novo classification whereby new devices for which there is no predicate are automatically placed in Class III, the highest-risk category.

Companies, however, can challenge such a classification and request reclassification into Class I or II. Such an application must demonstrate, to the FDA's satisfaction, that the device in question offers a low risk profile and a well-understood control methodology. The agency has 60 days to respond to such petitions.

Differences in Approval Systems Can Be Tricky for Companies

In both the EU and the U.S., the chosen classification for a given device determines how the manufacturer proceeds in gaining marketing approval for the product. The lower the risk category, the less rigorous the approval process.

For devices in Class III, in both the U.S. and EU, the requirements for approval are the most rigorous, requiring clinical trial data and, often, special postmarketing requirements as well.

However, the similarities end there. The myriad differences between the EU and U.S. approval systems pose many challenges, which devicemakers must negotiate before they are permitted to sell their products in both markets.

EU Approach

The device approval procedure in the EU revolves around the acquisition of a CE mark. The legislation that created the CE mark intended to create a single market for devices carrying the emblem. Once a product is CE-marked, it receives an EU passport, which allows it to circulate among member nations with relatively few barriers.

Some restrictions apply; for instance, language barriers still exist. That means labeling and documentation must be adapted when moving from one country to another. However, the characteristics of a CE-marked device must be basically the same for it to be offered for sale in all EU member nations.

The CE mark is earned only after a company successfully demonstrates that its product meets a set of pre-defined "essential requirements."

The essential requirements are obligatory for every medical device. Some are very general in nature, while others are specific to a particular type of device. EU device directives define these requirements but do not establish predetermined technical solutions for demonstrating compliance with them.

Notified bodies play a role in assessing whether some devices conform to the essential requirements. Where a notified body is involved, the manufacturer will enter into a contract with that entity. The notified bodies will often inspect production sites and review the company's quality materials.

Notified bodies are not involved with Class I devices, where manufacturers are expected to self-certify compliance with the essential requirements.

Once the CE mark is earned, it is valid for five years and can be extended. It is important to note that manufacturers are responsible for gaining notified body approval for any changes to the design, production process or quality control procedures relative to a device.

In some cases, the changes require issue of a new certificate; in others, the old certificate may simply be amended. For self-certified devices, it suffices to include information on the changes in the company's self-certification documentation.

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On the other side of the Atlantic Ocean, the FDA offers two pathways to device approval: the PMA process and the 510(k) premarket notification procedure. A key difference from the EU approach is that, unless a device is specifically exempt, its manufacturer must actively engage with the FDA to obtain approval for marketing.

The PMA Process

Class III devices are subject to the rigorous PMA process, which scrutinizes the new device to the highest level. While the 510(k) procedure that applies to Class II devices merely requires comparison to an already-approved product, the PMA process requires the manufacturer to independently prove both a device's safety and efficacy, including through the conduct of clinical trials. The FDA generally has 180 days to act on a PMA application.

PMA submissions also must include a substantial amount of information on the manufacturing process, ensuring that it is compliant with good manufacturing practices.

Devicemakers also must pay particular attention to detailed reporting requirements, such as the device master record, device history record and complaint files, as well as to the requirements for the detection, prevention and address of any nonconformities.

The FDA is closely scrutinizing company standard operating procedures, particularly those that are device-specific, to assure appropriate manufacture, notes Maureen Bennett, partner with Squire, Sanders & Dempsey.

Most Class II devices are subject to approval via the 510(k) premarket notification process. These products must be proven "substantially equivalent," as defined in the regulations, to a device already on the market, called a "predicate" device. It is possible for more than one predicate or split predicates to be used, though these are rare.

Three basic elements apply to the analysis of a device's substantial equivalence to a predicate:

- Whether the device has the same intended use as the predicate;
- Whether the device has the same technological characteristics as the predicate; and
- If there are different technological characteristics, whether that would raise different safety or efficacy questions.

While each of these elements is largely fact-based, there is quite a bit of room for FDA officials to offer differing interpretations. For instance, the regulations do not clearly define "intended use" versus "indications of use," Bennett notes. Nor is there a single, accepted definition of either of those terms. This creates a concern that, in some cases, there could be interchangeable or inappropriate references to a device's intended use, as opposed to actual indications.

That is one current criticism of the 510(k) process, as was noted in a report from the 510(k) working group.

Bennett points to another criticism of the 510(k) process — also raised by the 510(k) working group — and one that may eventually lead to regulatory changes. A devicemaker can choose a predicate that has been sold for quite some time, though is not in active use.

The FDA typically has 90 days to act on a 510(k) submission; this period encompasses both administrative and scientific reviews.

The agency can, however, stop the clock on the review by requesting additional information about the device from the manufacturer. An administratively incomplete submission will earn a "Refuse to Accept" letter, which specifies what information the agency requires to continue pursuing the 510(k) clearance. If the company does not respond to those requests or fails to provide a complete application within 30 days, the FDA may delete the application.

If the agency deems the new device to be substantially equivalent to the chosen predicate

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product, it will issue an order permitting the device to be marketed in the U.S.

Class I devices in the U.S. generally are exempt from premarket notification procedures, though they still must comply with applicable FDA regulations. These products are deemed to pose a low risk to patients. Some Class II devices may also be exempt.

Clinical Trial Regulations Have Seen Changes in EU

The highest-risk devices in both the EU and U.S. must undergo clinical trials to demonstrate their safety and efficacy before they can gain approval. Though this is consistent between the two regulatory systems, the specifics often vary quite a bit.

Regulators can require postmarketing studies as well for some devices; the circumstances under which these are called for can also vary between the U.S. and EU.

The clinical evaluation and investigation for devices is one area that has seen significant changes recently in the EU. According to the recently updated Medical Device Directives, even low-risk Class I devices must demonstrate conformity with essential requirements via clinical evaluation.

At a minimum, a literature review will be required for all devices. A document containing data supporting the declaration of conformity must be included in the technical file submitted for any new device.

Companies should use the phrase "clinical evaluation" with care, says Cristiana Spontoni, partner with Squire, Sanders & Dempsey.

"That does not necessarily mean the triggering of clinical trials, i.e., clinical investigation," she explains. "Clinical evaluation, as it's defined here, is an assessment of clinical data pertaining to a medical device in order to verify safety and performance."

Manufacturers must perform this sort of evaluation continuously for a product, both before and after certification. In fact, Spontoni added, European authorities are paying more and more attention to the postmarket surveillance and vigilance aspect.

The clinical evaluation must be based on one of the following:

- A critical review of available scientific literature relating to the safety, performance, design characteristics and intended purpose of a device, with clearly demonstrated equivalence of the new device to the device(s) discussed in the available literature and compliance with the relevant essential requirements;
- A critical evaluation of the results of all clinical investigations performed; and
- A critical evaluation of the combined clinical data above.

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An actual clinical investigation or clinical trial is required for nearly all Class III and implantable devices. The only exception is if the manufacturer can provide documented justification that it is not necessary. Postmarket surveillance activities likely apply as well.

The conduct of a clinical trial is more complicated than a clinical evaluation. The manufacturer must submit a clinical investigation plan for authorization, and the design and implementation of the trial must comply with EN ISO 14155, Parts 1 and 2 ("Clinical Investigations of Medical Devices for Human Subjects") or a comparable standard. Trials also must comply with the Declaration of Helsinki and applicable local laws. Investigations that do not comply with the pertinent ethical and regulatory standards must be rejected.

Under the new directive, devicemakers must request authorization from the competent authority in the nation or nations in which the trial will be conducted. A positive opinion from an ethics committee is also required. The competent authority has 60 days to approve a particular trial.

The manufacturer's statement remains another important item required by the directive. A device manufacturer (or authorized representative) must submit this document to the national competent authority. It must contain such information as:

- The clinical investigation plan;
- The investigator's brochure;
- Confirmation of insurance of subjects;
- Documents used to obtain informed consent;
- The ethics committee opinion;
- The investigation's place, start date and scheduled duration; and
- A statement that the device conforms to essential requirements.

Also new is the EU's expectation that device manufacturers will implement surveillance after a product's certification. Companies must update the information provided to users about their devices if they observe changes to the safety and efficacy patterns first seen during clinical trials.

Spontoni notes that more devices are requiring a postmarket clinical follow-up as a condition of approval.

In the U.S., the FDA requires clinical trials to generate original safety and efficacy data for all PMA submissions (i.e., all Class III device approvals).

Some 510(k) submissions may also include clinical trials. For instance, a devicemaker may choose to provide new clinical data as part of its premarket notification package. The FDA may also require clinical data in some circumstances.

The FDA is considering recommendations that it require all 510(k) submissions to include a list and description of all scientific information regarding safety and efficacy of the device, says Maureen Bennett, partner with Squire, Sanders & Dempsey.

The agency also is considering expanded clinical trial requirements. The first step for a manufacturer planning a clinical trial of a new device is the IDE, which allows the company to manufacture and ship the product in question for use in patients as part of that study.

Role of the IRB

An institutional review board (IRB) must approve each IDE; if the device is deemed to pose a significant potential risk to patients, the FDA must also approve the IDE. The device sponsor initially determines the risk status of the product; the IRB then reviews it, and either agrees or disagrees with the manufacturer's assessment.

In fact, the question driving the IDE process is basically whether the device under study is a significant-risk or a nonsignificant-risk product. For significant-risk devices, not only is the FDA's approval required, but that OK must be sought via a long-form IDE application. The agency can approve, disapprove or require modifications to any submitted proposal.

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In contrast, for a nonsignificant-risk device, the FDA allows an abbreviated procedure, involving shorter application forms, and approval by only the IRB. Once a company gains that approval, it may commence the study, though the FDA can overrule the IRB's decision.

The FDA requires several steps besides IDE approval before a device clinical trial can begin enrolling subjects. One key difference between the U.S. and EU is that the former's regulations specifically require disclosure of any financial interest a clinical investigator may have in the product or product sponsor.

U.S. clinical trial steps before enrolling patients include:

- Acquire IDE;
- Develop informed consent form for patients;
- Develop device labeling for investigational use only;
- Establish method for monitoring the study;
- Provide all FDA-required records and reports; and
- Disclose any investigator financial interest in the product or manufacturer.

There are some additional requirements and controls that apply to IDE studies. For instance, in addition to IRB approval, a study may require approval and oversight from other panels, such as a data monitoring committee. The sponsor is also obligated to update the FDA with any protocol amendments and adverse event reports, as well as study monitoring.

Bennett noted that the FDA exempts some types of studies from the IDE process. One example includes substantially equivalent devices cleared for marketing through the 510(k) process.

In addition to preapproval clinical trials, the FDA has in place several mechanisms for requiring postapproval studies. In the context of a PMA, for instance, it can require such ongoing studies as a condition of approval. Generally, the agency most often imposes such a requirement when there is an expectation that the device will be used in a substantial way in the pediatric population, Bennett notes.

Under current regulations, the agency can also require postmarketing studies if device failure would be reasonably likely to yield serious adverse health consequences. Likewise, if the product is meant to be implanted for more than one year or is a life-sustaining or life-supporting device for use outside a hospital setting, the agency also may require additional study.

Devices approved via the 510(k) process do not face a similarly broad requirement for postmarketing studies. However, FDA task forces are discussing whether additional clinical data — which could include some postmarketing studies — should be required either to create a new Class IIb category of devices or more broadly across the class of 510(k) products.

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