

Nonclinical Development Activities for Medical Devices

By Rosina Robinson, RAC



Although the statutory requirements, regulations and non-clinical activities for bringing new human therapeutics and medical devices to market differ, the fundamental processes used to determine the appropriate nonclinical development activities are similar. By understanding and applying these fundamentals, a regulatory affairs professional who specializes in drugs or biologics can navigate the product development maze, from concept to market authorization, for medical devices without encountering too many blind alleys.

This article describes a three-step process to determine the applicable nonclinical development activities for medical devices and how it compares with the development processes for human therapeutics. The information presented reflects US requirements and assumes that the product is a medical device as defined in the Food, Drug and Cosmetic (FD&C) Act.

This article does not address the process for combination products or the Food and Drug Administration's quality system regulation preproduction design control requirements. Because medical devices range in complexity from the novel, first-of-a-kind device to the very common "me-too" products and have many different uses, not all nonclinical activities are appropriate for all medical devices.

Development: Human Therapeutics Vs. Medical Devices

Pharmaceutical companies, academic institutions, government facilities and other laboratory facilities develop hundreds, if not thousands, of compounds for each new drug that reaches the market. A development time of approximately 8.5 years¹ from discovery to marketing is considered typical. The product life cycle from discovery to obsolescence can be many years and, in some circumstances, exclusivity can be extended by the patent protections afforded by the law.

Unlike the fairly standardized drug development process, the development processes for new medical devices can vary considerably. The idea for a new device can originate from many sources, including companies that already commercialize similar products, medical device manufacturers expanding their product offerings, healthcare professionals, caregivers involved with patients, patients' loved ones who see the need to adjust a device to the special needs of a patient and patients themselves.

Medical devices generally become obsolete or their designs become outdated more rapidly than drugs and, other than patent protection, devices are generally not protected from competition by the types of exclusivity provisions afforded by the drug laws. When comparing the development process for drugs with that for medical devices, the vast majority of new devices proceed from the preclinical research phase directly to the premarket review phase without undergoing the phase 1, 2 and 3 clinical trials that are common to the drug development process.

Whereas large or established medical device manufacturers have the technical expertise (i.e., engineers and scientists) and regulatory staff, as well as sufficient product development experience to manage the nonclinical development processes for their products, some small or newly established medical device companies have limited resources or no resources in these areas and are, therefore, unprepared to identify or meet the nonclinical development requirements for their products. The limited resources of small medical device companies may also make the nonclinical development process a significant burden.

For small companies, the burden of managing nonclinical development activities can be reduced if the process of identifying the required elements is understood. Ideally, the device manufacturer will incorporate a regulatory affairs professional early in the process, because many of the nonclinical development activities are included in the required premarket submissions to the Food and Drug Administration (FDA) and early regulatory involvement can reduce project time and, therefore, costs. **Figure 1** illustrates the three-step process for determining the nonclinical development activities. Because of the large variability among devices, this article focuses on the process and not the details of the activities.

Define the Product

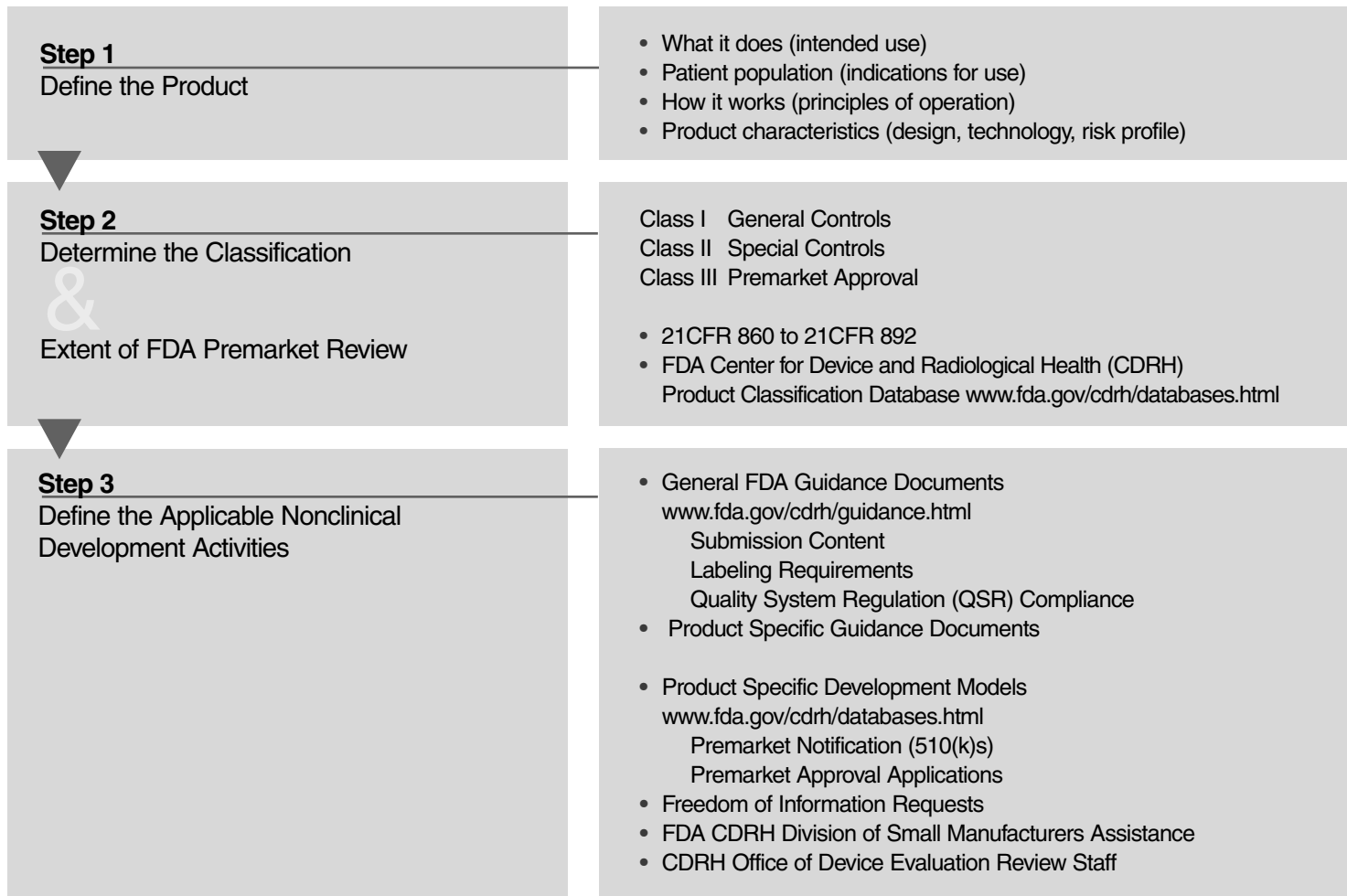
New medical devices, like new drugs, are developed to address unmet market or patient needs. As the first step in the process of identifying appropriate nonclinical development activities, it is important to define the product in general operational and descriptive terms:

- Intended use. What will the device do?
- Indications for use. For what clinical conditions or patient population will the device be used?
- Principles of operation. How does the device work?
- Characteristics and risk. What are the features of the product—i.e., is it electronic versus mechanical; controlled by software or other mechanism; invasive or noninvasive; implanted versus non-implanted; sterile versus nonsterile; disposable versus reusable—and what are the risks inherent in the use of the device?

The general product definition can be created early in the development period. The various elements of the device design should be based on the device requirements and the identified risks and updated as the device design is finalized. Using the product definition, the regulatory classification of the device can be determined, along with the extent and type of FDA premarket review. In addition, work can begin at this stage to identify the possible risks associated with the device, its design and its use (during normal use and considering user error). With this information, the appropriate nonclinical development activities to demonstrate that the device fulfills design and performance specifications can be identified.

This first step is unlike the early drug development stage, which often involves a compound without a precisely defined use. It may not be until later in the drug development process that the potential

Figure 1. Three-Step Process for Determining Non-Clinical Development Activities



clinical uses for a compound are finalized.

Classification and FDA Premarket Review

Early determination of the regulatory classification of the device (I, II or III) provides important information that may affect the manufacturer's desire or financial ability to pursue further product development. The regulatory burden, and therefore project cost, increases with the device's classification, not only before but also after marketing.

The classification process for medical devices is similar but not identical to that of drugs. Class I devices are low-risk products and are generally exempt from premarket review by

FDA but may be subject to general controls such as establishment registration, device listing and medical device reporting. Many class I devices are also exempt from quality systems requirements. The premarket resource commitments for a class I device are therefore very modest.

Class II devices are those for which general controls are insufficient to provide reasonable assurance of safety and effectiveness but for which there is enough information to develop special controls such as performance standards, guidance documents and special labeling requirements. The vast majority of class II devices are subject to 510(k) premarket notification but typically do not require clinical studies to be performed.

The 510(k) premarket notification includes administrative information, a description of the device, testing to demonstrate that it meets design and performance specifications and information about how the new device is similar to one or more devices that are already legally marketed in the US. The premarket resource commitments for class II devices depend on the device complexity and its specific characteristics.

Class III devices are higher risk devices or those that use novel technologies for which general controls and special controls are insufficient to provide reasonable assurance of safety and effectiveness and for which there is insufficient information for development of special controls. The majority

of class III devices require FDA premarket approval (PMA) with clinical data to claims of support safety and effectiveness. Therefore, the premarket regulatory and development activities for class III devices consume considerable time and investment.

Device classification regulations are listed in 21 CFR, sections 860–892. FDA’s Center for Devices and Radiological Health (CDRH) Product Classification Database provides online access to this and other important information.

Queries made in the classification database yield hyperlinks to the classification regulation as well as other information about the device, such as its classification name, the applicable medical specialty, the three-letter product code and information such as whether the device is exempt from Good Manufacturing Practices (GMP) and quality system regulations (QSR) or premarket notification, or its eligibility for participation in FDA’s third-party review or Mutual Recognition Agreement (MRA) programs.

If the precise classification of the device cannot be found in the classification regulations but a similar device is legally marketed for the same intended use and indications for use, the applicable classification can be identified indirectly by searching CDRH’s 510(k) or PMA databases.

The output from the 510(k) Premarket Notification Database indicates the device classification name, the 510(k) number, device name, applicant, contact person, three-letter product code, FDA received date and decision date, classification panel, and the availability of a 510(k) summary, the type of 510(k), if the device was reviewed by a third party, and if it was the subject of an expedited review. If more than one premarket notification has been issued for a given product classification, a list of the 510(k)s is provided with links to each individual marketing clearance.

Nonclinical Development Activities

Defining the applicable nonclinical development activities is the most challenging part of the process. Using the elements of the product definition and device classification information, one can begin to identify the applicable nonclinical development and testing activities.

Devices can range in complexity from the truly novel and complex—such as an implantable cardiac assist device that is software controlled, life supporting, life sustaining with multiple components—to the very simple. However, most medical devices entering the marketplace each year are similar to others that are already on the market and thus have already undergone CDRH premarket scrutiny in PMAs and 510(k)s.²

Between 1998 and 2002, FDA received 48 to 71 PMAs a year and approved between 37 to 53. The number of 510(k) premarket notifications received during the same period ranged from 4,202 to 4,623. The number found substantially equivalent to other legally marketed devices of the same type ranged from 3,428 to 3,824.³

These data indicate that for most general device types, there are one or more potential development models. Based on this fact, the transparency of the US regulatory process for medical devices, along with the abundance of information available from FDA, can be a great benefit to medical device developers whose product is not a first-of-a-kind.

The similarity of one or more characteristics of a new device to those of an already legally marketed device and the availability of information about the premarket activities for the marketed device will help the developer identify many, if not most, of the preclinical development activities. The challenge is to find the most useful information from the many available sources.

With available information technology, the ease of identifying FDA’s

requirements has improved considerably within the past 10 years. Sources of information include guidance documents and policy statements, existing product-specific development models, information obtained through the Freedom of Information Act and information from FDA centers and staff.

FDA Guidance Documents

Each FDA center involved with human healthcare products (CDRH, Center for Drugs Evaluation and Research and Center for Biologics Evaluation and Research) has developed hundreds of guidance documents that cover issues ranging from regulatory submission requirements, FDA’s management of the submission, general and product-specific recommendations and requirements and compliance activities (i.e., inspection of manufacturing facilities, enforcement actions).

Although these guidance documents do not have the force of law, they are vital to the identification of nonclinical development activities. Since 19 September 2000, FDA has used Good Guidance Practices (GGPs) to ensure public input to the development of these documents. Additionally, the FDA Modernization Act of 1997⁴ requires FDA to consider the “least burdensome approach” to meeting regulatory requirements.

Applicable guidance documents can be identified by conducting an online search of CDRH guidance documents (www.fda.gov/cdrh/guidance.html). Each guidance document includes a description of the document scope so that the applicability of the document to the new device can be readily determined. In addition, typical guidance documents include statements of the purpose, definitions of terms used, general considerations and a list of referenced documents

Because guidance documents represent FDA’s opinion at a fixed point in time, some of the details may be out of

date. It is best to review the CDRH Standards Database to see if the limitations on recognition of a standard have changed or if new standards have been adopted for this general product type.

Additional information is also available using the “A-Z Topic Index” hyperlink on the CDRH Web site. In general, FDA guidance documents provide the best source of nonclinical development information. This is especially true of the documents developed since the implementation of GGP.

Product-Specific Development Models

As previously noted, most medical devices are generic types that have undergone previous FDA scrutiny, and many are “me-too” devices that are simple variations of currently marketed devices. The more closely the new device resembles the legally marketed device, the more the nonclinical development activities should be like those of the legally marketed device.

If the new product is class II, it is necessary to demonstrate that it is “substantially equivalent” to one or more legally marketed medical devices. Information about legally marketed medical devices is available in the CDRH Premarket Notification Database in the form of a 510(k) summary or statement. This database is searchable by device name, applicant name, 510(k) number, product code and other parameters.

In a 510(k) summary, the applicant is required to summarize the basis for its substantial equivalence justification. In a 510(k) statement, the applicant promises to provide a copy of the 510(k) (excluding confidential information or patient identifiers) to any person that requests it within 30 days of the request. Because the quality of the specific content requirements of the 510(k) summary is highly variable, the usefulness of

this information source is limited.

Alternatively, although compliance with the 30-day requirement for a 510(k) statement can be poor and several requests may be necessary, the information provided is typically more useful than that routinely provided in the 510(k) summary.

If the new device is class III and subject to premarket approval, information for already approved devices is available in the CDRH PMA database in documents that include the approval order, the summary of safety and effectiveness information (similar to the summary basis of approval for new drug approval applications) and the approved labeling.

The summary of safety and effectiveness information is a detailed summary of the nonclinical and clinical studies included in the PMA. This can be a major source of information for the nonclinical and clinical development plan. The PMA database is searchable by trade name, applicant name, PMA number and product code, as well as other search parameters.

Seeking Advice

CDRH’s Division of Small Manufacturers International and Consumer Assistance (DSMICA) manages the device advice information on the CDRH Web site. DSMICA staff members have expertise in specific areas and are available to answer questions about premarket and postmarket device requirements. A staff member directory is available at www.fda.gov/cdrh/dsma/dsmastaf.html.

FDA’s Office of Device Evaluation conducts premarket reviews of medical devices and can be an invaluable resource to the developers of a new medical device, providing insight into FDA’s expectations for nonclinical development activities.

The greater the difference between the new device and the marketed device (or if the new device or anything about it is truly novel in terms of intended use, indications for use, fundamental technology, design and materials), the greater the benefit gained from contacting FDA before finalizing the development plan.

Because medical device technology changes rapidly, FDA policies also evolve, resulting in new guidelines and new agency expectations. Therefore, for a complex device with a long development process, a single consultation with the agency may not be enough to ensure that all of the appropriate activities have been taken care of.

By using a systematic approach, like the three-step process described in this article, and the available resources, it is possible to identify many of the applicable nonclinical development activities required for a new medical device.

NOTES

1. The CDER Handbook. Center for Drug Evaluation and Research Web site. Available at: www.fda.gov/cder/handbook. Accessed 1 June 2004.
2. A 510(k) premarket notification, authorized by the Food, Drug and Cosmetic Act, as amended in 1976, is required for class II devices, reserved class I devices and pre-amendment class III devices for which FDA has not yet mandated the submission of premarket approval applications or product development protocols.
3. CDRH ODE Annual Report 2002. Center for Devices and Radiological Health Web site. Available at: www.fda.gov/cdrh/annual/fy2002/ode/2002.pdf. Accessed 1 June 2004.
4. The FDA Modernization Act of 1997 requires FDA to ensure the timely availability of safe and effective new products that will benefit the public to consider a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA.

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