



Global Development of an Innovative Medical Device for the US Market

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Creating a new medical device based on new technology is a daunting task. This is particularly true for medical devices that target life-threatening conditions and that could potentially pose a high risk to the patients if not used appropriately, namely Class III devices.

Not only does the creation involve a unique combination of engineering and medical sciences, the regulatory pathway for demonstrating its safety and efficacy to the US Food and Drug Administration (FDA) is quite complex and very different from that in any other country. Marketing approval in the US requires a unique development plan including nonclinical and clinical studies and detailed manufacturing information to satisfy FDA reviewers.

The process can be made less painful by developing a detailed strategy describing the regulatory hurdles and gaps in knowledge that must be overcome, in effect laying out what is known and what is unknown. It should include the scientific rationale for the device, performance standards, nonclinical tests, clinical trials, a description of design and manufacturing information (also called quality system information), regulatory pathway and documents to be generated. If there are other similar medical devices on the US market, the strategy should also include a comparison to those.

What happens if there is no similar device on the market? How can a regulatory strategy be developed when FDA has not approved a similar device and may have never even reviewed such device?

This article describes the basic requirements for getting marketing approval of medical devices in the US, with practical tips from personal experience on how to create a good regulatory development strategy for high-risk medical devices.

Building the Scientific Rationale

When developing a regulatory strategy for a new, innovative medical device, the first step is to understand the basic science behind it. The rationale for a given device should provide the background on the current state of scientific understanding behind the device's fundamental design concept, and the adaptation of the scientific principle to the medical application.

Medical devices routinely employ principles of physics and engineering to address a medical need. The application of this combination should be adequately explained in light of available information from peer-reviewed literature and any other credible source. The basic scientific principles for the medical device form the basis of the regulatory strategy.

Developing a scientific rationale starts with a thorough search of the peer-reviewed literature. Since a medical device will routinely straddle different fields of science, it may be necessary to conduct a wider literature search. Chances are the sponsor, designer, manufacturer or anyone else involved with the development of a given device will have a library of articles they have found or published themselves.

Although these articles will be good in understanding the product, they may not give a full explanation of the science behind it. A search for any articles that contradict or raise concerns regarding the scientific concept being established also should be conducted. It is possible that the device in question is marketed in other countries and human exposure information is available.

The pros and cons of using non-US clinical experiences are described later in this article. However, even if there are no obvious concerns, the strategy team should brainstorm about possible gaps in the rationale and ways to fill it.

Unlike drugs and biologics, there is scant available guidance from FDA on the specific nonclinical and clinical studies needed to demonstrate medical device safety and efficacy. Studies supporting marketing approval applications for medical devices always need to be customized to the device in question. The peer-reviewed literature and self-collected unpublished data together help establish which studies are needed and why.

The scientific rationale should justify key elements of the device design concept such as the physical description, the intended function, intended patient population, intended clinical use designated by the medical condition or lesion type to be treated or assessed (anatomical location and limitations), the conditions of use/intended *in vivo* environment, directions for use, key design features for the mechanism of action and minimum design-life of the device. This justification is needed to guide the regulatory strategy for further evaluation.

Once a reasonable scientific rationale is constructed and studies conceptualized to fill gaps in the information, it may be prudent to create a written clinical development plan for discussion with FDA before embarking on the planned studies. Clinical studies can only be conducted after FDA has approved the Investigational Device Exemption (IDE) application.

All significant risk medical devices require clinical trials under an IDE. Two kinds of clinical studies are usually required for development of a new medical device: the proof-of-concept (POC) or first-in-human studies, and the pivotal or marketing approval studies. The major difference between a POC and pivotal study is that the latter is used for devices that are not yet fully developed.

Devices in POC trials are frequently modified to address the concerns identified in clinical trials. For devices that are not expected to change much based on the clinical evidence, one can ask for permission to conduct pivotal studies as the first clinical studies under an IDE. The fate of the IDE application depends on the strength of the scientific rationale built to support it.

Preclinical and Laboratory Testing

Most devices go through extensive nonclinical testing during design. These tests usually include laboratory tests, but could involve *in vitro* and animal tests using the device prototypes.

Nonclinical laboratory and animal testing are considered essential to provide critical safety information that it is not possible to collect from human subjects. For example, it may not be possible to investigate the clinical consequences of catastrophic device failure for an implanted device in a clinical trial. The nonclinical tests can be divided into two broad categories: bench and laboratory testing/computational modeling, and *in vivo* animal studies.

FDA recognizes that any device could go through several changes as new information about its usage becomes available, so it allows some flexibility about the nonclinical tests needed to support the clinical trials at different stages in development. The amount of nonclinical testing required to support a POC study is thus lower than that to support a pivotal study.

For bench testing, sponsors are encouraged to consider the relationship between an attribute or device failure mode and its anticipated clinical consequences to determine the testing needed to support the IDE application. Innovative medical devices will require extensive bench testing to provide sufficient evidence of performance and of meeting specification requirements.

Bench or laboratory tests should be customized to the device in question and should use scientifically valid and relevant systems. For devices using electronic components or electromagnetic fields, for instance, sponsors should consider the tests suggested in guidance from the International Electrotechnical Commission.¹

Wherever possible, computational modeling and simulations are encouraged for supporting information that cannot be obtained using other methods, such as predicting long-term durability of chronically implanted devices or to test catastrophic device failure conditions that cannot be replicated in an animal model and cannot be tested ethically in humans.

The most common *in vivo* animal tests are those to evaluate biocompatibility of implanted devices. Most medical devices do not require extensive animal testing before human testing and, in many cases, adequate justification for human testing may be built based solely on laboratory tests and computational modeling.

An animal study, when deemed necessary, should involve the use of a validated animal model for which the results are likely to predict risks in humans. When a validated animal model is unavailable, a focused animal study to address a limited range of safety issues may be conducted to complement the other nonclinical tests.

Animal studies should not be viewed as an alternative to adequate bench testing and, whenever possible, protocols should apply the principles of reduce, replace and refine. The size of the animal study depends on the device and assay (i.e., how well the animal model provides anatomic, physiologic and procedural similarities to humans). Recognizing the inherent variability of results, animal studies should be large enough to show consistency. Short-term animal studies

may be adequate for the initiation of an early feasibility study. Additional animal study data may be needed to support a larger clinical study with a near-final or final device design.

In vivo studies to evaluate medical devices should follow Good Laboratory Practice (GLP) for animal care and be conducted as specified in 21 CFR Part 58. Non-GLP study data may be used to support an IDE application for an early feasibility study if the deviations from GLP are identified and justified and do not compromise the validity of the study results.

For example, if an independent quality assurance unit is not used, a sponsor should describe how bias was mitigated and how the study was verified to be authentic and complete. Both GLP and non-GLP studies should include independent monitoring and assessments with full disclosure of study findings, including the raw data. Discussions with FDA on study protocols, including the evaluation of operator technique, safety outcomes and the effects of the biological system on the device, are encouraged prior to the initiation of *in vivo* animal studies.

Conducting the Proof of Concept or Pilot Studies

The first clinical study under an IDE application is usually the POC, or pilot study, which allows device testing under more limited conditions. The POC studies help strengthen the scientific rationale or, if unsuccessful, help re-design the medical device before large clinical trials.

The POC study for medical devices could be considered similar to a Phase I study for drugs and biologics. The only difference is, unlike the Phase I studies, the POC studies for medical devices collect both safety and efficacy data.

There are no established formats for POC studies. Each is unique to the device being tested. The POC clinical studies are done with a small number of subjects (5–10 patients) using one or few investigators, after getting approval from a relevant independent review board (IRB).

All clinical studies, including POC studies, must follow Good Clinical Practice (GCP). The clinical studies must use adequate informed consent. Study sites should have a sufficient level of clinical expertise and support to manage adverse events that may arise and provide appropriate alternative therapies, if needed. They should use adequately designed protocols and appropriate clinical and safety monitoring practices, report adverse events to FDA and IRBs in a timely fashion, and study reports should list all findings on device performance parameters (e.g., measurements of deliverability, stability, handling, visualization, patency and integrity).

For several clinical studies, a Data Monitoring Committee (DMC) composed of clinicians, scientific experts, statisticians and ethics experts is very helpful in evaluating data relatively early in the course of the study via interim analysis. Use

of a DMC could be helpful and may be proposed by a sponsor as an element of its risk mitigation strategy, particularly for studies where additional independent oversight would be valuable.

The pivotal studies for medical devices follow the same regulatory requirements as those described above for the POC studies. Clinical trial logistics for medical devices are no different from those for drugs and biologics.

The pivotal trials can be done only with the final iteration of a given medical device. In some cases, it is possible to expand the initial POC study to the pivotal study. If the device design is near-final or final, and the results of the early feasibility study support the device's initial safety and proof of principle, it may be more appropriate for the sponsor to pursue a pivotal study.

At this point, depending on the amount of nonclinical and clinical data available, a sponsor may justify adding additional subjects to the initial study approved in the IDE. Progression to a pivotal study must be requested as an IDE supplement and should include the information needed to justify initiation of the larger study.

Presenting Manufacturing Information

The device concept, design and manufacturing information undergoes several changes during the nonclinical and clinical testing phases. Seldom is a device in its final form at the time of initial testing. In parallel with these tests,

the device's design and development must be described and documented in the detailed design history file (DHF).

It is expected that by the time the device is ready for a pivotal trial, it has reached its final iteration and complete information for its manufacturing under medical device Good Manufacturing Practices or the Quality System Regulation (QSR) is available. The final QSR information should include detailed information on the design history, describing all the changes the device has gone through in its development, the final configurations, manufacturing process, quality control and quality assurance steps to assure a good quality product.

Along with the DHF, the sponsor must include the final specifications, final processes and final procedures in the device master record (DMR). Usually, the DHF starts around the time of laboratory testing and the DMR starts around the time of the pivotal clinical studies. The DHF and DMR are described in the QSR in 21 CFR 820.

The QSR describes the general regulatory requirements without prescribing specific ways to establish compliance. Hence, it is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures.

Manufacturers should use good judgment when developing their quality systems and apply those sections of the QSR that are applicable to their specific products and operations.

When operating within this flexibility, it is the responsibility of each manufacturer to provide sufficient information for evaluation by reviewers prior to conducting the pivotal studies.

Taking Advantage of Global Development Processes

US requirements for medical device approval are quite different from those in most other countries. It is not uncommon for devices to be approved for marketing in other countries long before they are approved in the US.

The requirements for initiating clinical trials with medical devices in other countries are also very different and, in many ways, easier than those in the US. This creates a unique opportunity for device manufacturers. The global regulatory environment can be employed to conduct many development steps in worldwide locations, where permitted, to effectively shorten the marketing approval timeline in the US.

For example, medical device clinical studies in the EU do not require similar applications to regulators for initiating clinical trials with medical devices. It is not uncommon for device manufacturers to conduct pilot and even pivotal studies outside the US before coming to FDA for regulatory discussions.

The US regulations are quite specific about the scientific requirements for marketing approval. However, the required studies do not necessarily have to be conducted in the US. FDA accepts data from non-US and non-IDE clinical trials provided the studies are conducted

according to the laws of the country where the trial is conducted, follow GCP, use qualified investigators and are auditable by FDA, if necessary.

The best way to assure FDA acceptance of non-US data is presentation of a clinical study report (CSR) containing full details of the clinical trial, procedures followed, tables and listings of the data and statistical analysis of data.

Additionally, non-US clinical experience could be invaluable to establish a given device's safety profile. It is critical that the clinical experience information be collected using a scientifically valid process that avoids bias. The clinical experience information could also be used to support effectiveness claims in addition to justifying the safe use of the device. Much of the information generated to secure marketing approval in non-US regions can be recycled for FDA discussions.

Similar to the clinical data, marketing data should also be all-inclusive, providing as much detail as possible about device usage, management of any safety events or complaints associated with the use of the device, the indications treated and the relationship of the treatment population with those targeted in the US.

Clinical experience information should include how physicians evaluated their patients to use the device, what specific criteria were required from the patient, demographics and other background medical information about the treated patients, common practices for device handling and administration to patients, and other similar elements that could help reviewers understand the clinical experience. It may help to

create a previous human experience report, very similar to the CSR, providing complete details about device experience.

It may be noted that while clinical and marketing experience outside the US may play an important role in FDA approving the IDE, and may also be part of the eventual Premarket Approval (PMA) application, it does mean additional clinical and/or nonclinical studies may not be required under an IDE. The best case scenario is usually if FDA allows the sponsor to proceed directly with pivotal studies under an IDE based on the previous non-US studies. For devices with very extensive non-US testing and clinical experience, it is possible to support a PMA with reports of all previous studies and a bridging study connecting the non-US data to relevant US populations.

To Meet or Not Meet With FDA

FDA meetings are one of the best resources available to a sponsor. The pre-submission meetings with FDA provide a venue to discuss the available information with the reviewers, seek clarifications about specific regulatory concerns, and learn potential FDA concerns regarding the device. This helps preempt the reviewer's concerns by providing appropriate additional information in the IDE/PMA application, thereby increasing the chances of FDA approval.

Despite all the obvious advantages of meeting FDA reviewers before submitting formal applications for review, these meetings could create a regulatory nightmare if not planned and conducted carefully.² The sponsor of a device with extensive nonclinical and clinical data may believe the available information adequately addresses the scientific rationale and may decide to forego some FDA meetings, such as the pre-IDE meeting. By deciding to address specific concerns upon FDA review of the IDE, the sponsor may potentially risk the IDE not being approved.

If the first clinical trial is planned to be a pivotal study, the pre-IDE meeting could provide valuable insights into FDA's concerns about completeness of the overall information for the PMA and whether the study planned under the proposed IDE meets its goals. This could avoid last minute surprises at the pre-PMA stage. The sponsor should be well prepared for the FDA meetings and have a detailed development strategy containing all the elements discussed in the previous sections.

Conclusions

From understanding the basic science to figuring out the necessary preclinical and clinical studies and being aware of QSR requirements, a regulatory strategist should have a good idea of what regulatory pathway would be most appropriate. Recently, FDA released two guidance documents describing the requirements for POC studies and IDE requirements.^{3,4}

There has also been extensive public discussion about the amount of scientific evidence

required to support marketing approval of a new medical device, particularly one based on previously approved or predicate devices. For new, low to moderate risk devices, FDA updated its approach to the reclassification process (*de novo* pathway) in its recent draft guidance.⁵

For new, high risk devices, the regulatory pathways are not expected to change much. In the current regulatory environment, the time and cost of new device approval in the US can be reduced significantly by using global development steps.

In the last few years, there has been increased shift of development steps, with more and more initial testing conducted in Europe and Asia and pivotal studies conducted in the US under IDEs. Global development is expected to play an increasing role in the development and approval of new medical devices in the US in the near future.

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