

Regulatory Impact On Commercialization Strategy: Premarket Considerations

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Overview

- FDA regulation of medical devices
- Deciding whether this authority extends to your product or activity
- Successfully addressing key premarket regulatory issues
- Questions and answers

What is Premarket?

- Activities that occur prior to the clearance or approval of a medical device:
 - Product development
 - Bench testing
 - Animal testing
 - Clinical testing
 - Advertising and promotion
- FDA position on animal testing
 - The agency does not actively regulate the use of devices in animals

Today's Medical Device Regulatory Paradigm

- Designed to ensure that medical devices are safe and effective for their labeled intended use/indications for use
- Based on marketing
 - Considered to be placing a device into commerce
 - No explicit purchase required
- Level of regulatory scrutiny tied to product risk
 - Depends on both intended use/indications for use and technological characteristics
 - True throughout the product lifecycle
- Considerable discretion on the part of FDA
 - How to classify devices
 - When to assert regulatory authority

Implications for Premarket Activities

- FDA may view a wide range of premarket activities as marketing-related and subject to regulatory oversight
 - Clinical research
 - Advertising and promotion
- Investigators and sponsors have some control over how the device will be viewed by the Agency
 - Intended use/indications for use
 - Technological characteristics
- Inherent premarket challenge for medical device developers
 - Tension between making sure a medical device is sufficiently safe and effective for investigation or commercial marketing and the cost of collecting those data
 - Successfully engaging a regulatory agency that may have limited sensitivity to cost constraints

Considerations for FDA Regulatory Oversight

- Whether the product is regulated under the FDCA
 - For medical device-like products, whether the product meets the statutory definition of a medical device
- If the device-related activity constitutes marketing in the United States
 - Some type of marketing-related activity is necessary for FDA to assert its regulatory authority
 - No agency jurisdiction outside of the United States
- The risk inherent to the medical device
 - Examine both indications for use and technological characteristics of the device

Definition of a “Medical Device” Under the Food, Drug, and Cosmetic Act

- Section 201(h) of the Act
- “An instrument, apparatus, implement, machine, contrivance, implant or in vitro reagent, or other similar or related article, including a component, part, or accessory, which is:
 - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
 - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
 - intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”

Implications of the Definition

- Extremely broad
 - FDA has tremendous discretion in interpretation
 - Can easily interpret this definition to either establish or avoid regulation
- Caveat
 - Even if a product does not meet the definition of a medical device, it may be regulated under other provisions of the FDCA, such as when a product is considered a drug

Applying the Medical Device Definition

- Certain products are almost certainly medical devices
 - Products that provide diagnostic information on which treatment decisions are based
 - Products that provide a therapeutic action for a specific medical condition
 - Products whose indications for use make medical claims
- Certain products are unlikely to be considered medical devices
 - Product with a general use that are only incidentally used in a medical setting and are not labeled for medical purpose
 - Office furniture in a hospital or outpatient setting
 - Generic word-processing software used in a medical setting

Products Where Status May be Unclear

- Products providing physiological data for a non-medical purpose
 - Sports monitors and related equipment
 - Home infant monitors
- General purpose products adapted for medical purpose
 - Software to track patient usage of drugs

Approaching Products for Which the Medical Device Status is Unclear

- Sponsor analysis with or without an outside regulatory opinion
 - Avoids need for FDA involvement
 - The Agency may always disagree with the sponsors determination
- Gaining FDA input
 - Pre-IDE submission
 - May involve a meeting or teleconference with FDA
 - Used in these circumstances only where the questions or complexity of the situation demands a meeting
 - 513(g) petition
 - Generally the submission of choice to clarify whether a product is a medical device

The 513(g) Petition

- A formal request for FDA classification of a product made under Section 513(g) of the Food, Drug, and Cosmetic Act
- Written petition to FDA
- 60-day response deadline
- Potential outcomes
 - Considered a medical device and placed in a specific class (I, II, or III)
 - Deemed not a medical device
- Advantages
 - Certainty of results
 - Avoids risk of subsequent Agency action if FDA disagrees with a sponsor's internal analysis
- Disadvantages
 - Very difficult to appeal
 - No formal interaction prior to Agency decision

Does the Use of the Medical Device Implicate a Marketing Activity?

- FDA regulation is focused on approving or clearing medical devices for market for specific indications for use
 - Authority extends only to the United States
 - Outside of the United States (OUS) use is beyond the Agency's jurisdiction
- Collection of data to support a subsequent US marketing application is considered a marketing activity
 - Applies to new devices
 - Applies when studying a new indication for use for a previously cleared or approved device
- The Agency lacks regulatory authority over activities that are medical practice and not marketing-related
 - Includes off-label use of an approved or cleared medical device by a medical professional in the care of his or her patients

Practice of Medicine Doctrine

- Use of medical device by a medical professional in the care of his or her patients outside the product's cleared or approved indications for use
 - Clearly applies to off-label use of medical devices that cleared or approved for other indications for use
 - Applicability to non-cleared or approved devices less certain
- Long-acknowledged exception to FDA's regulatory authority
 - Reflects that medical practice is regulated by the states, not the federal government
 - FDA respects this limitation; however, Agency policy requests that the healthcare professional keep records of the off-label use

Limitations on the Practice of Medicine Doctrine

- Cannot engage in activities that may be seen as marketing-related
 - Regular clinical use could potentially be seen as implicating marketing of the device for the indications for use that are neither cleared nor approved
- Data from devices used off-label under the Doctrine (i.e., not under protocol as part of a formal investigation complying to FDA's regulations) cannot be used to subsequently support a marketing application
 - May use this data as “first in human” to support a pilot clinical study
 - Agency will almost certainly not accept such data as either pilot or pivotal study data
- Provider is subject to malpractice claims as is the case with all medical practice
 - Heightened awareness of plaintiff's bar to off-label use
- FDA may assert regulatory authority in instances where there is a potential public health issue, i.e., patient injury

Risk of the Device in a Clinical Investigation

- Assessment applies to any instance where a medical device is under clinical investigation
 - New or modified device
 - New indications for a previously cleared or approved device
- Analysis unique to medical devices
 - No corresponding provisions for drugs
- Provisions found at 21 CFR § 812.3(m)
 - Tied to the definition of a “significant risk” device
- Medical devices meeting the definition are “significant risk” devices
 - Medical devices not meeting the definition are “nonsignificant risk” devices

Definition of a Significant Risk Device

- A significant risk device is an investigational device that:
 - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - Is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;
 - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
 - Otherwise presents a potential for serious risk to a subject.

21 CFR § 812.3(m)

- Guidance: January 2006 Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors on Significant Risk and Nonsignificant Risk Device Studies
 - Provides additional details as to how the definition is to be applied

Determinations of Significant Risk Device Status

- Determination may be made at several levels
 - The responsible institutional review board (IRB) as part of its review of the clinical protocol
 - FDA as part of a pre-IDE or IDE submission
- Rules governing significant risk device determination
 - Should any IRB determine that the study is significant risk, the device is considered significant risk for all involved centers
 - Prevents “forum shopping”
 - If a sponsor believes that a study is nonsignificant risk, never present the protocol to an IRB without a justification for nonsignificant risk status
 - FDA determinations are controlling on all IRBs
 - In practice, FDA will only disagree with IRB determinations that a device is nonsignificant risk
- Significant risk device and the relationship to a significant risk study
 - A determination that a device is significant risk generally means that a study involving that device is a significant risk study
 - FDA has made rare distinctions with significant risk devices being used in nonsignificant risk studies

Factors to Consider in Making Significant Risk Device Determinations

- Outlined in FDA's January 2006 Guidance Document
- Key factors include:
 - The proposed use of the device in the investigation and not the device alone
 - The nature of the harm that may result from the use of the device
 - Whether the subject will need to undergo an additional procedure as part of the study
- Agency list of significant risk and nonsignificant risk devices in January 2006 Guidance Document
 - Significant risk devices outlined for a number of medical specialty-specific device categories

Examples of Significant Risk and Nonsignificant Risk Devices

- Significant Risk Devices

- New therapeutic devices that impart energy or are invasive
- Invasive or implantable diagnostic devices
- Cleared or approved therapeutic devices that impart energy or are invasive being evaluated for a new indication for use
- Cleared or approved therapeutic devices that impart energy or are invasive being evaluated for modified instructions for use

- Nonsignificant Risk Devices

- Cleared or approved devices being used in a manner consistent with their labeling
 - Evaluations intended to gather additional data for a cleared or approved indications for use
- Noninvasive diagnostic devices where the data is not being used to make a clinical decision

Implications of a Significant Risk Determination

- Significant risk device studies require FDA approval of an investigational device exemption (IDE) under 21 CFR Part 812 before a clinical study may be conducted in the United States
- Nonsignificant risk devices are only subject to “abbreviated” IDE requirements
 - No formal FDA approval required
 - IRB oversight and protocol approval consistent with 21 CFR Part 56 is required
 - Must obtain patient informed consent consistent with 21 CFR Part 50 from all experimental subjects
- IRB oversight and informed consent requirements apply to significant risk device studies

Elements of an IDE

- Outlined in 21 CFR Part 812
 - No application per se, but a list of elements required for complete evaluation
 - Size and scope heavily dependent on the medical device at issue
- Key elements include
 - A description of the device
 - A report of prior investigations outlining the studies that have been performed on the device
 - An investigational plan (protocol) for the clinical study
 - Manufacturing information for the device
- May range from less than 100 pages to thousands of pages in multiple volumes

FDA Review of an IDE

- Limited to 30 days by statute
 - Should a sponsor not receive a response within this timeframe, the study is deemed to have been approved
 - FDA typically responds on day 30 and is reluctant to communicate with the sponsor during the review
- Basis of review
 - Focused on the risk the device poses to patients
 - FDA often considers evidence of the device's benefit in making this determination
 - Devices with little evidence of effectiveness often are subject to a more stringent review
 - Completeness of submission
 - Absence of key information will often preclude a complete review

FDA Actions on an IDE

- Full approval
 - The sponsor may begin the study in accordance with the IDE reporting requirements of 21 CFR Part 812
 - Specifies the number of patients and centers for which approval is granted
- Conditional approval
 - The sponsor may begin the study, often with several conditions (i.e., modification of the informed consent form)
 - However, full approval is generally subject to the sponsor providing additional information
 - Typically 45 days to respond, although extensions are possible and routinely granted
 - Often not advisable to begin enrollment under a conditional approval if the items identified by the Agency may alter the study population, endpoints, or how endpoints are measured
- Disapproval
 - FDA supplies a detailed list of the items that must be addressed to gain approval

IDE Review: Typical Sponsor Experience

- Full IDE approval with initial submissions are uncommon, even with a pre-IDE meeting
 - Typical IDE undergoes two to three rounds of review
- Conditional approval or disapproval requires submission of an IDE Supplement
 - 30-day review time for each response, in addition to the time necessary to gather the requested information and draft the response
- Plan on a minimum of three to six months to obtain full approval for most significant risk devices

Investigator Sponsored IDEs

- No specific regulatory provisions for investigator sponsored IDE submissions
 - Unlike investigational drug (IND) regulations, which have separate regulatory provisions for investigators
- FDA typically less stringent with IDE review of investigator-sponsored studies
 - Still careful to protect patient safety
 - More flexibility with regard to patient populations, endpoints, and analysis
 - May be more forgiving with certain aspects of software and manufacturing information, particularly development information

Potential Issues with Investigator Sponsored IDEs

- Approved IDE still subject to all regulatory reporting and record-keeping requirements
 - May be a heavy administrative burden
 - Individual investigators and institutions often not organized to meet these requirements
- Indirect involvement of a commercial sponsor
 - Sponsors occasionally wish to have an investigator hold the IDE to leverage FDA's more lenient evaluation of investigator sponsored IDE's
 - Issues to address:
 - Lack of control on the part of the commercial sponsor
 - Ownership of data: from FDA's perspective, IDE data is owned by the sponsor
 - May be able to address these issues contractually

Implications of Premarket Regulation for Device Sponsors

- Complex environment with many decision points
 - Is the product a device?
 - Is the premarket activity regulated?
 - Will an IDE be necessary?
- Failure to thoughtfully address the issues may lead to FDA action, particularly if patient injury results
 - Untitled or warning letters
 - Commercial sponsors have traditionally been held responsible
 - The Agency has recently demonstrated a willingness to take action against investigators and institutions
 - April 3, 2007, warning letter to Thomas Davis, M.D., for clinical study of off-label use of approved device without obtaining an IDE
 - Request for retrospective IDE
 - Loss of use of data for marketing purposes
 - More significant consequences

Sponsor Approaches to Premarket Issues

- Common issues for resolution
 - Is the product a medical device?
 - Is the medical device a significant risk device that requires an IDE?
 - The content of an IDE, if required
 - The regulatory pathway for the medical device: 510(k) versus PMA
- Frequently used regulatory strategies
 - Internal analysis with or without third party consultation
 - Informal contact with FDA
 - Pre-IDE meeting

Sponsor Regulatory Analysis

- Often used when a sponsor believes that a product is
 - Not a medical device; or
 - Not a significant risk medical device
- Typically consists of an analysis in which the sponsor defends a specific characterization of a product
 - May involve the opinion of outside consultants or regulatory counsel
 - Often results in a contemporaneous regulatory document defending the sponsor's characterization that is kept in that organization's files
- Advantages
 - No direct consultation with FDA
 - Less involved than other options
- Disadvantages
 - FDA may disagree with the analysis
- Generally only advisable where there is a straightforward analysis
 - Agency guidance on point

Informal Contact with FDA

- Communication with an individual FDA reviewer or manager for an informal opinion on a premarket regulatory issue
 - May be a sponsor, or often a third party on the sponsor's behalf
- Advantages
 - Relatively quick without the need for a formal submission
 - May provide useful information
- Disadvantages
 - Even the best information is completely non-binding
 - FDA has formal procedures for providing such opinions and opinions rendered outside of these channels represent personal opinions of the FDA staffer consulted
 - FDA may misunderstand the question or the product itself
 - Misimpression may lead to inaccurate advice
 - May raise Agency concerns where none should exist

When To Utilize Unofficial Contact with FDA

- Best used when the device and its issues are well-known to the Agency and the individual at FDA who is being consulted
 - Cleared or approved device with specific premarket question
- Not ideal for a new technology or novel indication for use
- Must be able to accept the risk that the advice is either incorrect or may not be honored
- Never wise to contact multiple FDA staff with the same informal question
 - Agency staff often internally discuss these informal requests for information
 - Multiple queries on the same issue may lead to the impression that a sponsor is attempting to “forum shop,” i.e., look for the most favorable response to the question

The Pre-IDE Process

- Formal process through which a sponsor may gain “informal” agency feedback on key aspects of the regulatory process
 - How the product is to be regulated
 - The data that will be necessary to support clearance or approval
- Provides an interactive process for discussing key premarket issues
 - Typically results in a face-to-face meeting or teleconference
 - Allows for detailed discussion and resolution of potential issues
- While technically informal, FDA will typically honor the agreements made in the pre-IDE process
 - Actual data may always influence the Agency’s thinking
- Extremely useful in facilitating IDE approval or eventual product clearance or approval

The Pre-IDE Submission

- Pre-IDE process requires a formal pre-IDE submission
 - FDA will not consider scheduling a pre-IDE meeting until a submission is filed
 - Submission clearly conveys background information and the sponsor's questions to FDA, limiting the risk of Agency misunderstanding
- Elements of a pre-IDE
 - Device description
 - Report of prior investigations
 - Proposed clinical protocol
 - Regulatory pathway analysis
 - Specific questions for FDA
 - Generally three to five questions
- Similar to an IDE in general content
 - Generally considerably less detail
 - Tension between providing enough information and avoiding detail that could either confuse FDA or delay the review

FDA Action on a Pre-IDE Submission

- Internal Agency 60-day deadline for review and resolution
 - Not as closely followed as deadlines for marketing submissions
 - Deadline may slip considerably in some branches depending on workload
- Generally can schedule a face-to-face meeting within four to six weeks of pre-IDE submission
- Other Agency options
 - Teleconference
 - Written comments
- Strategy regarding form of agency feedback
 - Highly dependent on nature of device and outstanding questions
 - Face-to-face meeting generally the best strategy when there is any possibility for substantial disagreement
 - Teleconference or even written comments may be adequate when questions are fairly straightforward and the pre-IDE process is simply being used to confirm uncontroversial points

Pre-IDE Follow-up

- Quite variable and depends heavily on FDA feedback
- Always advisable to provide the Agency with meeting minutes
 - Objective account of the session
 - Emphasize key issues for sponsor
- Often the next step will be an IDE submission
 - Specific details may only be addressed with detailed submission
 - Still best to resolve major outstanding issues prior to filing IDE
- Pre-IDE meeting may only be the first step in a dialogue to come to agreement on both the protocol and regulatory pathway

Epilogue: Regulation Following IDE Approval

- IDE approval is only the start of a heavily regulated process
- Sponsors have a number of administrative and reporting requirements
- Any changes to the device or experimental design may require further FDA approval

Sponsor Reports Required Under 21 CFR § 812.150

- Current list of investigators
 - Every six months the sponsor must submit a current list of the names and addresses of all participating investigators
- Annual Report
 - Every year the sponsor must update FDA on the status of the investigation including the number of patients treated, the participating investigators, any changes to the device or clinical study plan, and adverse events
- Unanticipated Adverse Device Effects
 - The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within ten working days after the sponsor first receives notice of the adverse effect
 - Always best to broadly draft the risks section of an IDE to avoid implicating this reporting requirement

Sponsor Reports Required Under 21 CFR § 812.150

- Withdrawal of IRB or FDA approval
 - All reviewing IRBs and investigators must be informed within five working days of receipt of any such notice.
- Recalls and device disposition
 - The sponsor must notify FDA and all reviewing IRB's of any request that an investigator return, repair, or dispose of any unit of an investigational device.
 - The notice must be made within 30 working days after the request is made and must state why the request was made.
- Final Report
 - Significant risk device: must notify FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor must also submit a final report to FDA, all reviewing IRBs, and participating investigators within six months after the completion or termination of the investigation.
 - Nonsignificant risk device: must submit a final report to all reviewing IRBs within six months after completion or termination.

Modifications to the Device or Protocol During an IDE Investigation

- Governed by FDA May 29, 2001, Guidance Document, “Changes or Modifications During the Conduct of a Clinical Investigation”
 - Reflects changes to the Food, Drug, and Cosmetic Act under the Food and Drug Administration Modernization Act of 1997
- May need prior FDA approval for certain modifications
 - Based on the impact that these changes have on patients and the investigational plan
 - Must inform the Agency of changes to the investigational plan regardless of the need for approval
- Three levels of notification
 - Annual Report
 - 5-Day Notice
 - IDE Supplement
 - Sponsor may not undertake changes described in an IDE supplement without prior Agency approval

Changes Submitted in the Annual Report

- Minor changes that would not affect the following:
 - The validity of the data or the information resulting from the protocol or the risk to benefit ratio faced by patients
 - The scientific soundness of the investigational plan
 - the rights, safety, or welfare of the subject involved in the investigation
- Examples of changes eligible for inclusion in the Annual Report
 - Changes to study monitoring
 - Change to the name of the device, if it does not imply a new intended use
 - Minor changes to the device itself
- FDA may always disagree with the sponsor's analysis and require a 5-Day Notice or IDE Supplement

The 5-Day Notice

- Allows for certain changes to be made provided that the Agency is informed within five working days of the change
- Includes
 - Developmental changes that do not constitute a significant change in design or in the basic principles of operation and that are made in response to information gathered during the course of an investigation
 - Changes or modifications to the clinical protocol that do not affect the following:
 - The validity of the data or the risk-benefit ratio of the device
 - The scientific soundness of the investigation
 - The rights, safety, or welfare of the study subjects
- FDA may disagree that a 5-Day Notice is adequate and require an IDE Supplement

IDE Supplement

- Required for all substantive changes to the investigational plan
- Examples
 - Changes to the investigational device that could affect safety or effectiveness
 - Increases in the number of sites or subjects
 - Changes to study endpoints
- FDA review
 - 30-day review cycle, just as with original submission
 - Based on risk-benefit ratio

The Implications of an IDE

- A complex process that is regulated from inception until the conclusion of the clinical investigation
- Must be closely monitored by the sponsor
 - Although investigators may face FDA action for noncompliance, the Agency generally holds sponsors responsible for study monitoring
 - Includes use of the investigational device both in the context of and beyond the clinical study
- Once an IDE is approved, the sponsor is responsible until the Final Report is issued

Timing Issues: When to Move Forward

- Sponsors are often anxious to either meet with FDA or obtain an IDE
- Desire to move forward must be balanced with the risks of going to FDA too early
 - Pre-IDE or IDE is often a new sponsor's initial contact with FDA
 - The cliché regarding first impressions most definitely applies
 - Lack of data may lead to additional FDA questions
- An early meeting or submission may result in a process that is far more protracted than a meeting or submission that is well-timed

Early Steps

- Perform or obtain a formal regulatory analysis
 - Often possible to gain a good understanding of the regulatory issues facing a new medical device
 - Use that analysis to formulate a regulatory strategy
 - Integrate that analysis with the medical device's development plan
- May need to modify the device, the sponsor's expectations, or both
 - Indications for use are commonly modified based on regulatory considerations
- Crucial to have competent, experienced staff, consultants or regulatory counsel
 - Be cautious of informal advice from FDA on regulatory strategies
 - The Agency generally does not view providing a regulatory analysis as its role in the process

Initial Contact with FDA

- Informal contacts occasionally may be helpful
 - Need to be well managed
 - Expectations must be in line with informal nature of feedback
- Pre-IDE submissions
 - Generally recommend that the device design be frozen
 - If seeking feedback on a proposed pilot study, sponsor needs to have adequate preclinical data
 - For a proposed pivotal study, sponsor should have pilot data and adequate preclinical data

When to File an IDE

- Prior-IDE submission usually helpful
 - Lack of prior Agency contact may lead to additional rounds of review
 - Exception: Well-established study design for an existing device class
- Issues raised by the Agency during the pre-IDE process should have been addressed
- IDE for a pilot study to establish device safety
 - Requires preclinical bench and animal data supporting safety and offering preliminary evidence of efficacy
 - Biocompatibility, electrical safety, and electromagnetic compatibility as appropriate
 - Data generally less than what is required to support a pivotal study, although submitting without adequate data can lead to issues
- IDE for a pivotal study to support safety and effectiveness
 - All of the data required for a pilot study
 - Pilot data demonstrating the device's safety and preliminary evidence of effectiveness

Outside of the United States Data

- FDA has no authority to regulate clinical studies conducted outside of the United States
 - True even if there is a US sponsor or a US investigator involved
- The Agency may accept outside of the United States (OUS) data as pilot data to support a pivotal study IDE
 - Generally only true if FDA is given the opportunity to review the protocol in a pre-IDE submission prior to conducting the OUS study
 - The Agency is generally reluctant to accept OUS data in the absence of such prospective review

Summing Up

- FDA regulation of the premarket process, including oversight of clinical investigations, is complex
- Approaching the process casually may lead to unwanted surprises
 - Particularly true if the investigational device is significant risk or if the data from a clinical investigation is to be used to support a marketing application
- Always best to consider sponsor goals in light of FDA's requirements
- Consultants and regulatory counsel often very useful developing regulatory strategy

Questions on FDA Premarket Regulation

Resources

- FDA/CDRH Device Advice website:
<http://www.fda.gov/cdrh/devadvice/index.html>
- Call or e-mail any questions
 - John J. Smith, M.D., J.D.
 - e-mail: jjsmith@hhlaw.com
 - (202) 637-3638

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