Medical Device Regulation

A primer for everyone

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It’s not as intimidating as it looks.

A medical device is…

- *The Section 201(h) of the Food, Drug and Cosmetic Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.*
- As simple as a tongue depressor or a thermometer
- As complex as robotic surgery devices

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

Device Classification

- Classification determines extent of regulatory control (Risk Based)
- 1700 generic groups of devices
- Classified within 16 medical specialties

- **862** = Chemistry/Toxicology
- **864** = Hematology/Pathology
- **866** = Immunology/Microbiology
- **868** = Anesthesiology
- **870** = Cardiovascular
- **872** = Dental
- **874** = Ear, Nose and Throat
- **876** = Gastro/Urology
- **878** = General Plastic Surgery
- **880** = General Hospital
- **882** = Neurological
- **884** = Ob/Gyn
- **886** = Ophthalmic
- **888** = Orthopedic
- **890** = Physical Medicine
- **892** = Radiology

Classification System Risk Categorization

Class I	General Controls	≈780 Low Risk
Class II	General Controls and Special Controls	≈800 Medium Risk
Class III	General Controls and Premarket Approval	≈120 High Risk

General Controls

- Adulteration / Misbranding
- Electronic Establishment Registration
- Electronic Device Listing
- Premarket Notification [510(k)]
- Quality Systems
- Labeling
- Medical Device Reporting (MDR)

Special Controls

- Guidelines (e.g., Glove Manual)
- Mandatory Performance Standard
- Recommendations or Other Actions
- Special Labeling (e.g., 882.5970, Cranial Orthosis)
- Guidance Documents

Background Information

- Regulatory Applications for Devices
  - United States
    - 510(k) – Substantial Equivalence w/ Predicate(s)
      - Intended Use / Indications for Use
      - Similar Technology
      - Assumed Safety and Effectiveness
    - PMA – Proves Safety and Effectiveness
      - No Predicate
      - Requires Animal and Human Trials

Background Information

- Regulatory Applications for Devices
  - United States
    - DeNovo – Risk Based Classification
      - 510(k) – NSE + DeNovo Application
      - Requires Special Controls Guidance Document
    - Others
      - 513(g) – Request for Classification
      - RFD – Request for Designation (combination products)
      - IDE – Investigational Device Exemption

Premarket Notification 510(k)

- Marketing Clearance Process
- No form - Application submitted at least 90 days before marketing.
- Demonstration of Substantial Equivalence (SE) to legally marketed device in U.S.
- SE means "**Substantial Equivalence" or "*Just as Safe and Just as Effective*".**

Demonstration of Substantial Equivalence

- A device is substantially equivalent if, in comparison to a predicate it:
- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;
  or
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device.

Changes in 510(k) Program

- Requirements have become more stringent
- Clinical data is now being required more often
- Limitations in how/what predicate devices are used

When is a 510(k) Required?

- Marketing for First Time, or
- Significant Change to Existing Device that can affect safety and effectiveness (S&E).

Devices Exempt from 510(k)

- ≈800 devices or 47% of Total Classified Devices are exempt from 510(k).

- Class I 93% or ≈730 devices
- Class II 9% or ≈70 devices

Premarket Approval (PMA)

- Only applies to Class III devices
- Classification requires PMA
- Device found **Not** "SE" or "NSE"
- "New" - no basis for "SE"
- Proof of reasonable assurance of safety and effectiveness

PMA Data Requirements

- Must contain valid scientific evidence consisting of data from either controlled clinical investigations or adequate case histories
- Good science and scientific writing is key to approval
- Lack of valid clinical information and scientific analysis on sound scientific reasoning will delay FDA review and approval
- PMAs have historically suffered from inadequacies in clinical study design, conduct, data analyses, presentation, and conclusions

Investigational Device Exemption(IDE) "Clinical Trials"

- Unapproved Devices
  - Significant risk (SR)
  - Non-significant risk (NSR)
- Used on human subjects to collect safety and effectiveness data
- Protection of human subjects

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.

Examples of Significant 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

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

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

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

The Pre-submission Process

- Formal process through which a sponsor may gain FDA feedback in response to questions on product development, including nonclinical evaluation plans and clinical protocols
- 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
- Extremely useful in facilitating IDE approval or eventual product clearance or approval

FDA Action on a Pre-submission

- Internal Agency 75-90-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-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-submission process is simply being used to confirm uncontroversial points

Pre-submission Follow-up

- Quite variable and depends heavily on FDA feedback
- Sponsor submits meeting minutes
- Often the next step will be a premarket or IDE submission
  - –Specific details may only be addressed with detailed submission
  - –Still best to resolve major outstanding issues prior to filing IDE
- Pre-submission 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

When to File an IDE

- Prior-IDE submission usually helpful
  - –Lack of prior Agency contact may lead to additional rounds of review
  - –Exception: Well-establish study design for a 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 conducing 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

Thank You!