Clinical trials for medical devices: FDA and the IDE process

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What is a Medical Device?

The Section 201(h) of the Food, Drugs and Cosmetics 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 robotic surgery devices**

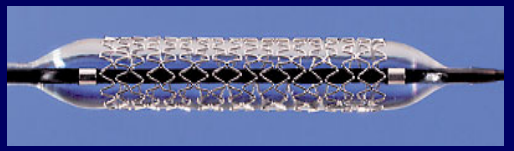
Device Classification

Medical Device Classes

- Class I
  - General Controls
  - Most exempt from premarket submission

- Class II
  - Special Controls
  - Premarket Notification [510(k)]

- Class III
  - Premarket Approval
  - Require Premarket Application [PMA]



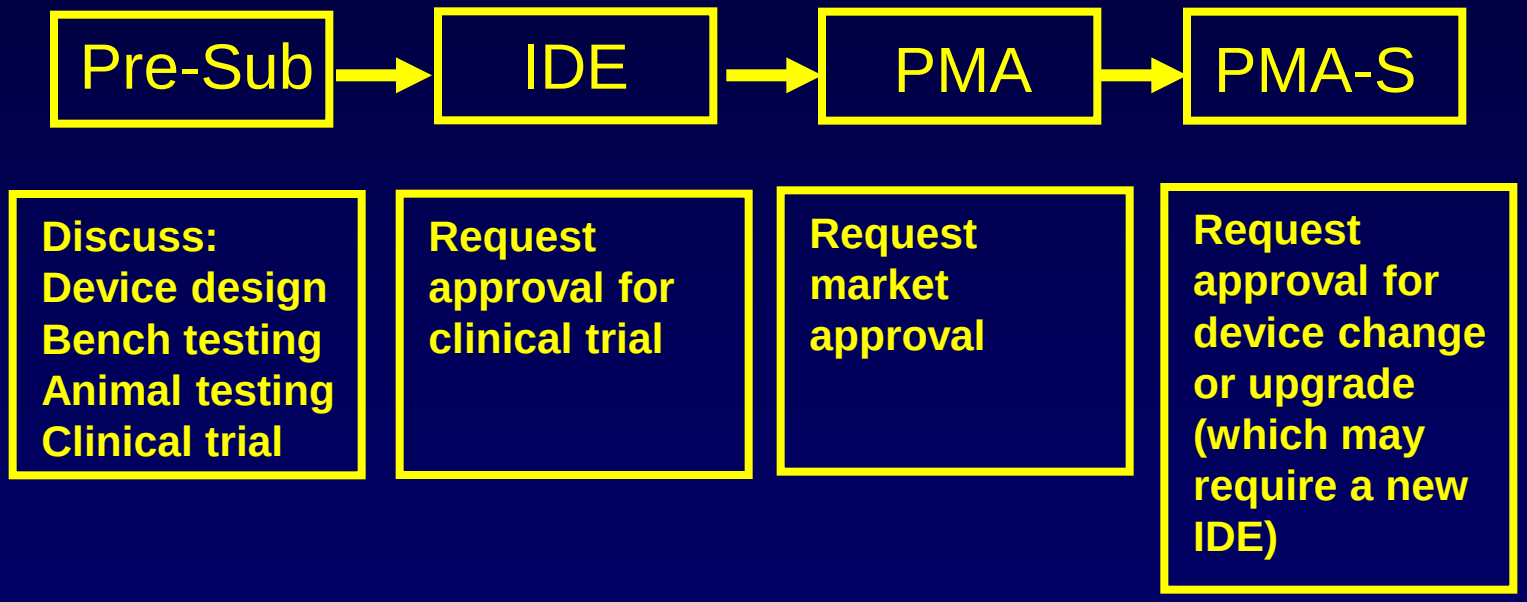
510(k) Premarket Notification

- Substantial equivalence
- 10-15% require clinical data
- Performance testing
- Usually confirmatory
- Type of study dictated by:
  - Ability of bench and animal testing to answer questions
  - Amount of difference between subject device and predicate

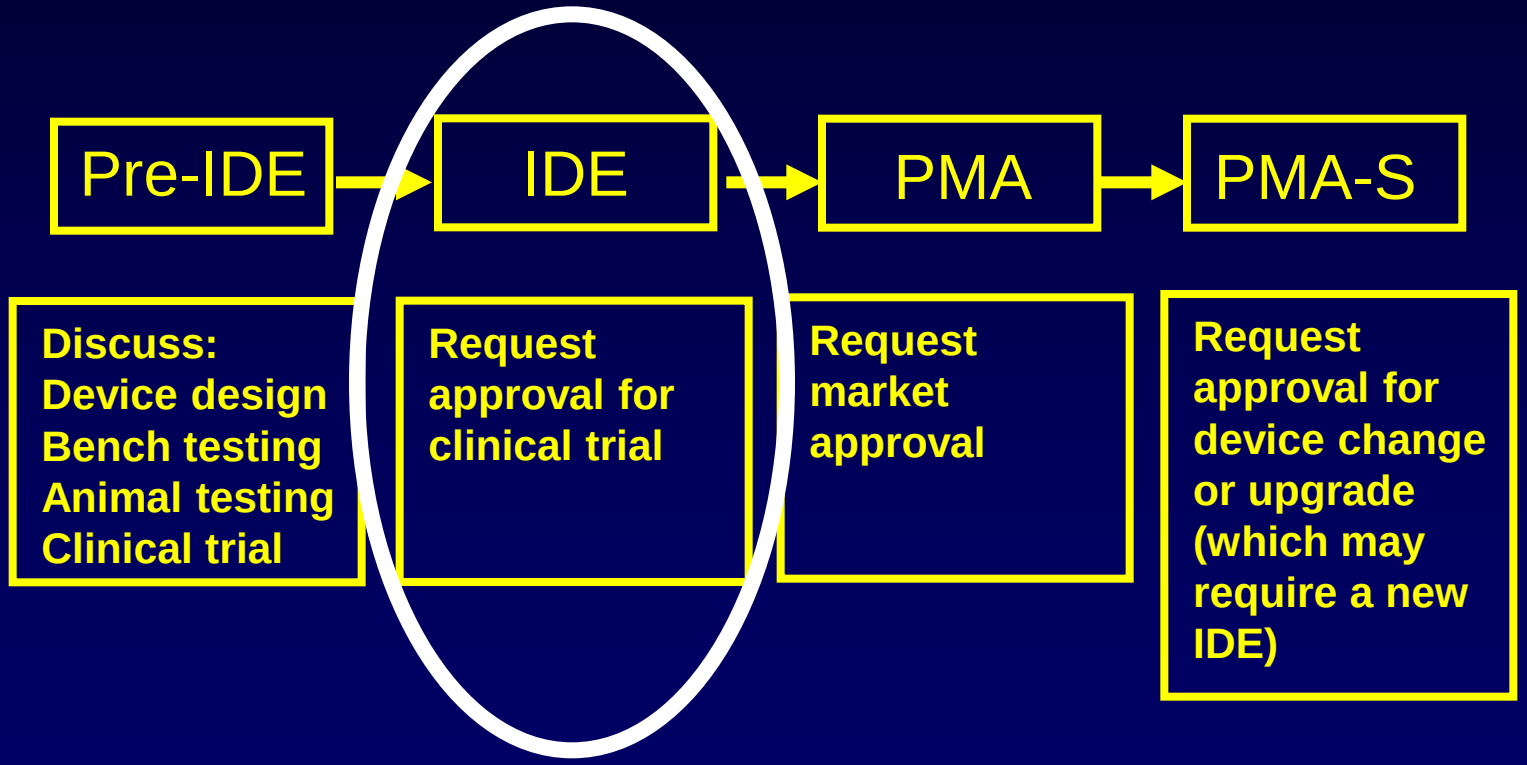
PMA
Premarket Approval Application

- Establish reasonable assurance of safety and effectiveness
- Bench-Animal-Human
- Clinical Studies
  - Feasibility and pivotal

Stages of review for PMA device



Today's focus:



What is an Investigational Device Exemption (IDE)?

FDA approval of an IDE is required for US human study of a significant risk device which is not approved for the indication being studied.

Device trials are unique

- Trials tend to be smaller than drug trials
- Some novel, many “me-too”
- Many difficult to blind, randomize, control
- Many depend on physician technique
- Device modifications occur during trial
- Endpoints highly diverse
- Typically, single pivotal trial follows feasibility stage(s)
- Designed to support a “reasonable assurance of safety and effectiveness” for the marketing application

Types of IDEs

- Feasibility study
  - May provide support for a future pivotal study or may be used to answer basic research questions
  - Not intended to be the primary support for a marketing application
  - Endpoints and sample size generally not statistically driven
  - Often required by FDA prior to pivotal study to assess basic safety and potential for effectiveness
  - Generally ~10-40 patients but may be larger
  - FDA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk

Types of IDEs

- Pivotal study
  - Generally intended as the primary clinical support for a marketing application
  - Designed to demonstrate a “reasonable assurance of safety and effectiveness”
  - Endpoints and sample size statistically driven
  - Designed to assess both safety and effectiveness
  - FDA review is much more complex

FDA's Feasibility IDE Review

- Focused on safety
- Critical issues
  - Reasonable study conceptually?
  - Adequate preclinical validation of device?
    - Why is clinical really the next necessary step?
  - Appropriate mitigation of potential risks?
  - Appropriate enrollment criteria?
  - Patients adequately informed?
  - Sample size appropriate?

FDA's Pivotal IDE Review

- Focused on safety and plan for collecting and evaluating study data
- Additional critical issues
  - Trial endpoints
  - Randomization, blinding, follow-up, etc
  - Study conduct and monitoring
  - Statistical analysis plan

Basic Submission Elements

- Background of medical issue, the study goals, and why this study will further the science
- Detailed description of the device under study
- Previous studies (preclinical and clinical)
  - Summary of available data
  - Why is a clinical study needed at this stage?
  - What evidence supports the safety of this study/device and the potential for the study data to be meaningful?
  - Are there outstanding safety questions that should be addressed with preclinical data?

Basic Submission Elements

- Risk analysis
  - What are the potential risks to the patient?
  - Does the study mitigate the risks where possible?
  - Are the risks outweighed by the potential for benefit and/or value of the study
- Patient monitoring and follow-up plan
- Inclusion and exclusion criteria
- Informed consent document
- Sample size and number of investigational centers, with justification

Submission Elements, Pivotal IDEs

- Primary and secondary endpoints
  - Discussion of appropriateness of endpoint parameters, hypotheses, and success criteria
- Basic trial design
  - Controlled? If not, why not?
  - Randomized? If not, why not?
  - Blinded? If not, why not?

Submission Elements, Pivotal IDEs

- Trial conduct and study monitoring
  - Data handling and adjudication process
  - Sponsor blinding
  - Independent committees
  - Case report forms
    - Is the right information being gathered to support the study endpoints and are investigators adequately prompted to report adverse events?

Submission Elements, Pivotal IDEs

- Statistical analysis plan
  - Clearly defined S & E hypotheses
  - Type-1 error and multiplicity
  - Missing data handling
  - Sample size calculations and assumptions
  - Assessment of critical covariates
  - Adaptive design plans
  - Interim analyses and early stopping rules
  - Data handling

Primary Endpoint Design

- Should evaluate the safety and effectiveness of the device in the population expected to be indicated.
- Generally divided into
  - 1 or more “safety” endpoints
  - 1 or more “effectiveness” endpoints
- A study would be considered successful if both the safety and effectiveness endpoints are met.

Primary Endpoint Design

- The clinical protocol should clearly and prospectively detail:
  - Methods for obtaining endpoint data
  - Definitions for what will be counted as a primary event in the analysis
  - Situations in which patient data will be excluded
  - How missing data will be handled
  - How the impact of covariates will be assessed

Sample Size & Follow-Up

- Driven by either:
  - Primary safety endpoint
  - Primary effectiveness endpoint
- Minimum number of patients and/or minimum duration of follow-up may be required depending on:
  - Understanding of the safety and effectiveness of the device
  - Concerns regarding durability of device safety or effectiveness

Secondary Endpoints

- Generally used to evaluate additional meaningful claims
- Generally only considered if primary endpoints are successful
- Should be used to provide further insight into the device effects and mechanisms of action
- Definitions and analysis methods should be clearly detailed prospectively
- Not considered “statistically significant” unless a pre-specified alpha allocation plan is in the protocol, even if the p-value is < 0.05

Submission Elements, Pivotal IDEs

Provide enough detail to avoid ambiguity once the trial has started.

FDA's IDE Review Decisions

- Approval
  - Approves the trial for a specified number of patients and investigational centers
- Approval with Conditions
  - Allows sponsor to begin the trial if the sponsor agrees to address the conditions (deficiencies) from the conditional approval letter within 45 days
- Disapproval
  - Trial may not start until sponsor addresses the deficiencies from the letter, submits this information to FDA, and receives approval

Revision to FD&C Act, July 2012

FDA shall not disapprove an IDE because:

- *the investigation may not support a substantial equivalence or de novo classification determination or approval of a device;*
- *the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or an additional or different investigation may be necessary to support clearance or approval of the device.*

Recent Revision to FD&C Act

This means that an IDE cannot be disapproved on the basis of FDA's belief that the study design is inadequate to support a future PMA, 510(k), HDE, or de novo classification.

Does study failure imply PMA disapproval?

- Often but not always.
- PMA approval is based on a Benefit-Risk assessment
- FDA is always willing to review all available data to determine whether there is a reasonable assurance that the device safe and effective.

Does study failure imply device disapproval?

- Alternatives
  - Unexpected safety concerns are outweighed by stronger than expected benefit
  - Inconclusive study result is supplemented by other clinical or non-clinical data
  - Device is safe and effective for some limited indication or patient population
  - All of these alternatives may raise serious type-1 error concerns. FDA is therefore very conservative in its consideration of these alternatives.

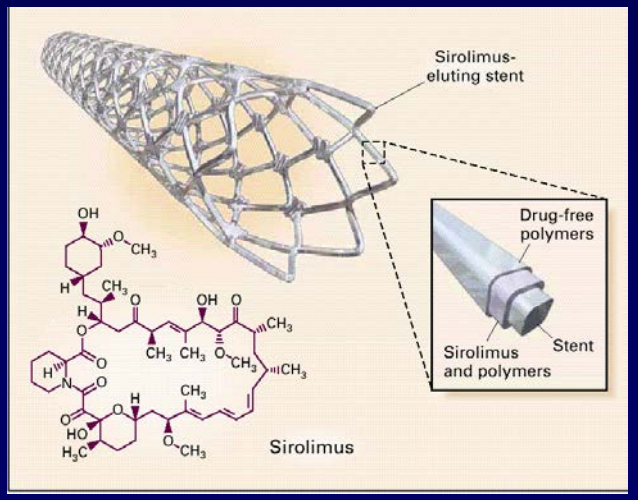
Does study success imply device approval?

- Often but not always
- Sometimes the primary endpoints do not capture a serious unexpected safety concern that is observed in the trial.
- Other clinical or non-clinical data may conflict with the study result.
- Can result in:
  - Device disapproval
  - Requirement for more data
  - Limited indication

Some Generic Case Examples

Cardiovascular Devices

- LVADs
- Pacemakers, ICDs, leads
- Cardiac resynchronization therapy
- Ablation catheters and generators
- Cardiac monitoring devices
- Heart valves
- Stents
- Cardiac occluders



Example 1: Novel heart failure device study

- Novel implantable stimulation device to treat heart failure
- Key characteristics
  - Implant has serious risks
  - Device is programmable
  - Benefit may be symptomatic/functional
  - Patients can feel the stimulation
- Previous data
  - Feasibility data promising but single-arm

Study Considerations

- Safety
  - Require long-term follow-up
  - Safety success criteria should be rigorous to balance symptomatic benefit
- Effectiveness
  - Must be randomized to assess benefit
  - Symptomatic/functional benefit requires blinding
  - But how does one blind this study?

Company Proposal

- Implant device in all subjects
- Randomize to on vs. sham stimulation
- 6-month follow-up, after which device may be turned on or off in any subject
- Safety: all subjects pooled, compared to objective performance criterion (OPC)
- Effectiveness: Responder’s analysis of quality of life (QOL) and six minute walk distance

Problems with this plan

- 6-month follow-up
  - What if effect is short-lived?
  - What if long-term safety concerns arise?
- Sham stimulation
  - Is there enough data to know how to design true sham?
  - Will blinding truly be maintained?

Problems with this plan

- Safety
  - Endpoint evaluates only procedure and presence of the device, not effect of the therapy
- Effectiveness
  - 6MW and QOL highly placebo sensitive
  - Even if demonstrated, will benefit in these endpoints result in appropriate risk-benefit?

FDA's advice

- 12 month follow-up
- Multiple, rigorous safety endpoints
- If sham, more data needed to support blinding
- More objective effectiveness endpoints
  - Mortality/hospitalization composite
  - VO2 max or ventilatory threshold
- Show reasonable risk-benefit profile

Example 2: MRI Conditional Pacemaker

- Concerns
  - Proper device function
  - Thermal or arrhythmogenic injury from MRI
- Design: Device implanted in all subjects, randomization to MRI or No-MRI.
- Safety/Effectiveness
  - MRI Adverse events
  - Pacing parameter changes (indicative of injury)
- Additional restrictions
  - At least 200 subjects to receive MRI

Example 2: MRI Conditional Pacemaker

- Limitations
  - Study not designed to assess basic device performance
  - Study not powered to detect low rate (but meaningful) safety issues
  - Clinical study considered confirmatory to comprehensive preclinical data
- Review focus
  - Trial design important, but…
  - Preclinical issues present the larger obstacle before FDA would allow proceeding to clinical

Example 3: Heart Valve

- Design: single-arm
- Effectiveness
  - Stenosis, leakage, and orifice area
  - Compared to normal published values
- Safety
  - 30-day and intermediate (1-year) complication rate
  - Compared to OPC
- Additional restrictions
  - 800 patient-years
  - At least 300 patients for at least 1 year

Conclusions

- One size does not fit all for device trials
- Pivotal studies should be designed to evaluate whether there is a “reasonable assurance of safety and effectiveness.”
- PMA approvability is based upon a Benefit-Risk assessment which strongly considers outcome of primary safety and effectiveness endpoints.

Conclusions

- Secondary endpoints are generally used to support claims if the primary endpoints are successful.
- All endpoint analyses and definitions should be clearly pre-specified in the approved clinical protocol.
- Trial design is challenging. We recommend talking to FDA early through the pre-submission process.

Online Resources

- CDRH Learn – Online Regulatory Training Tool
  - Over 50 Medical device and Radiological Health modules
  - Video and PowerPoint presentations available 24/7
  - Certificate of completion upon passing post-tests
  - Many modules are translated into Chinese and Spanish
  - http://www.fda.gov/Training/CDRHLearn/

- Device Advice – Online Regulatory Information
  - Searchable by topic
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/

- Division of Small Manufacturers, International, and Consumer Assistance (DSMICA) – Live Regulatory Assistance
  - Technical Assistance for the Medical Device Industry
  - Available 8:00 am – 5:00 pm EST
  - 800-638-2041 or 301-796-7100
  - DSMICA@fda.hhs.gov