FDA Regulatory Processes for Getting Acute Ischemic Stroke Medical Devices to Market

Stroke Treatment Academic Industry Roundtable (STAIR)

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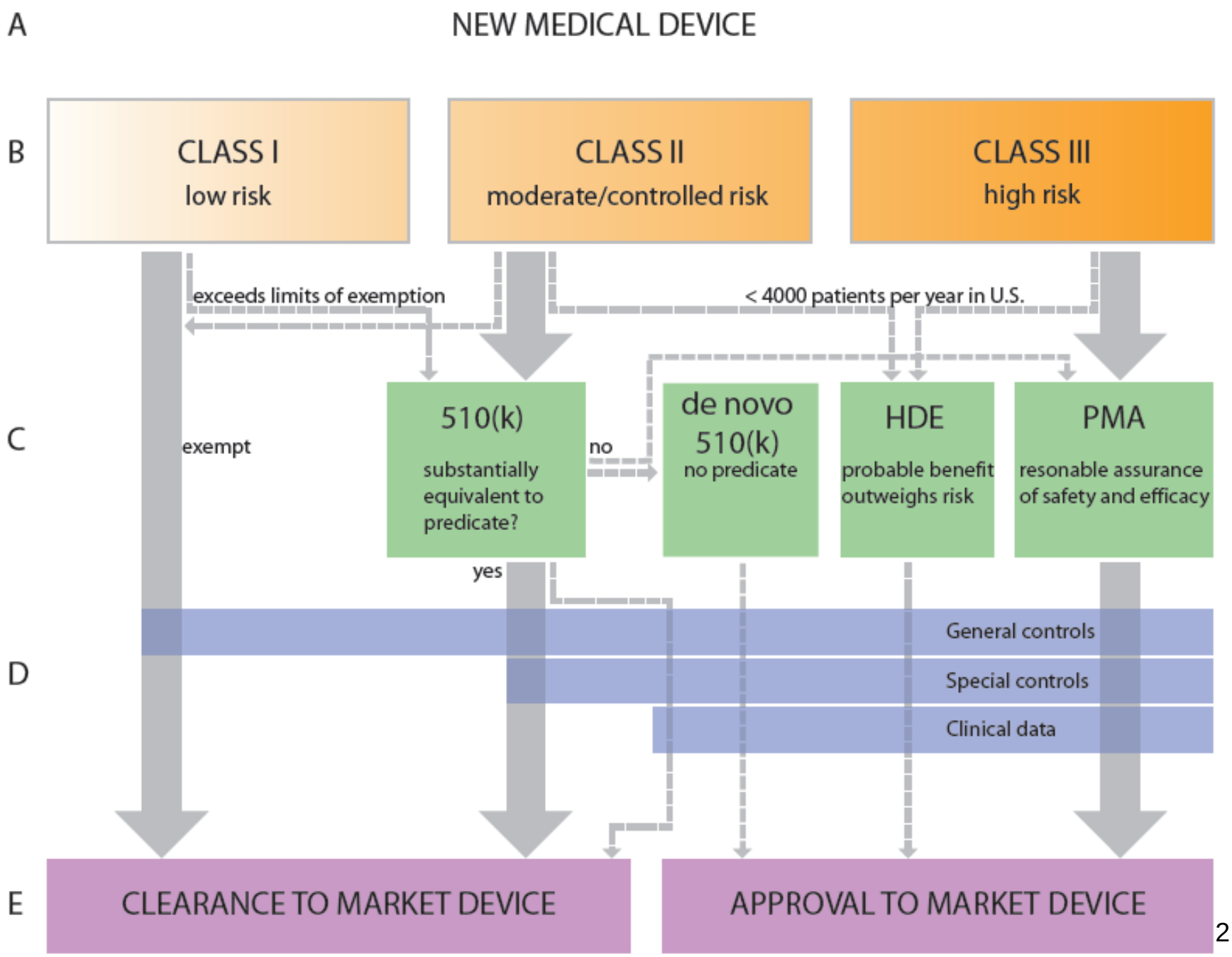
Center for Devices and Radiological Health

Food and Drug Administration


A
NEW MEDICAL DEVICE
B
CLASS I
low risk
CLASS II
moderate/controlled risk
CLASS III
high risk
exceeds limits of exemption
< 4000 patients per year in U.S.
C
exempt
510(k)
substantially equivalent to predicate?
no
de novo 510(k)
no predicate
HDE
probable benefit outweighs risk
PMA
resonable assurance of safety and efficacy
yes
D
General controls
Special controls
Clinical data
E
CLEARANCE TO MARKET DEVICE
APPROVAL TO MARKET DEVICE

Premarket Notification [510(k)] Program

- New guidance document issued July 28, 2014 ("The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]"

- Establishes substantial equivalence (SE) to a legally marketed primary predicate device.
  - The same intended use and the same technological characteristics as the primary predicate device.

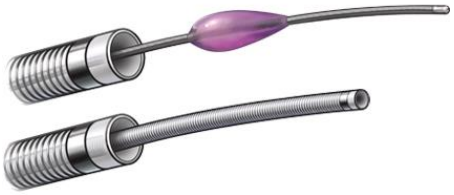
OR

  - The same intended use and different technological characteristics, but the different technological characteristics:
    - Does not raise different questions of safety and effectiveness, and
    - Performance data is available to demonstrate that the new device has a similar safety and effectiveness profile as the primary predicate.

[from 21 CFR §807.100(b)]

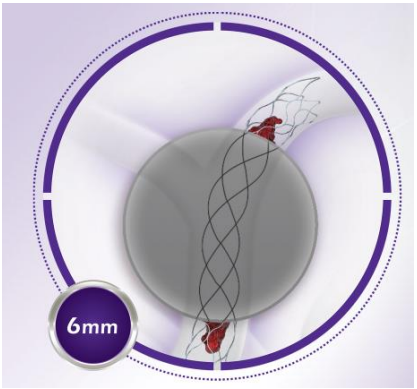
Cleared Mechanical Neurothrombectomy (Clot Retrieval) Devices

MERCI Retriever



Penumbra Reperfusion System

Medtronic/Covidien Solitaire Revascularization Device



Stryker Neurovascular Trevo ProVue Retriever

Intended Use: Restoring blood flow or revascularization in intracranial vessels within 8 hours of acute ischemic stroke symptom onset. For patients who are ineligible to receive or who failed intravenous tissue plasminogen activator (IV t-PA).

de novo

- Appropriate for low to moderate risk devices that do not fall within any classification regulation, based on:
  - A Not Substantially Equivalent (NSE) decision to a legally-marketed predicate device through the 510(k) process, or
  - Direct submission because the device is believed to be appropriate for classification into Class I or II, and there is no legally marketed predicate device.
- General controls or general and special controls that can be written to provide reasonable assurance of the safety and effectiveness of the device, and address all of the known risks.
- Generates a new device regulation.

Premarket Approval (PMA)

- No acute ischemic stroke devices have been approved in a PMA to date
- Used for approval of Class III devices (highest risk)
- Majority of PMA applications are supported by clinical data generated under an Investigational Device Exemption (IDE)
- Subject to annual reporting after approval
- May be subject to post-approval studies (PAS) as a condition of approval
- Requires concurrent Manufacturing/GMP and Bioresearch Monitoring Review Prior to Approval

New Expediting Access Program to Address Unmet Medical Needs

Guidance Issued April 13, 2015

- Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

- Only for devices that are subject to premarket approval applications (PMA) or are eligible for *de novo* requests

Humanitarian Device Exemption (HDE)

- Humanitarian use designation determined by the Office of Orphan Products Development

- Section 520(m) of the Food, Drug and Cosmetic Act states:

"… to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States" [yearly]

- Only needs to demonstrate safety and probable benefit for approval.

Investigational Device Exemptions (IDEs)

IDE Study Types

- **Early Feasibility Study (EFS):**
  - a limited clinical investigation (n <15)
  - early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application)
  - intended to provide proof of principle and initial clinical safety data
- **First in Human (FIH) Study:** a device for a specific indication is evaluated for the first time in human subjects.

A FIH can be an EFS, but not all FIH studies would be considered an EFS.

IDE Study Types (cont.)

- **Traditional Feasibility Study:**
  - to capture preliminary safety and effectiveness information on a near-final or final device design
  - to adequately plan an appropriate pivotal study.
  - does not necessarily need to be preceded by an early feasibility study
- **Pivotal Study:**
  - to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects.
  - may or may not be preceded by an early and/or a traditional feasibility study.

FDA Decisions on IDEs

Three Outcomes

- **Approval**
- **Conditional Approval**
- **Disapproval**

FDA Additional Comments on IDEs

- **Study Design Considerations**
  - Additional modifications that FDA believes are needed in order for the study design to support a marketing approval or clearance (Pivotal Trial) or a future study (Feasibility Study)
  - Recommended (not required) modifications to the investigational plan

- **Future Considerations**

  Additional considerations which FDA considers important for the support of a future submission, e.g., non-clinical testing not required for IDE but at the time of marketing application

Safety

- All adverse events regardless of perceived relationship to the procedure or device
- From time of consent vs. time of treatment
- Adequate follow-up of AEs occurring in subjects who discontinue/withdraw
- Standardized nomenclature
- Clinical Events Committee

Endpoints

- Primary
  - Functional outcome
  - Surrogates – “tool claim”
    - Reperfusion
    - Cerebral blood flow
- Secondary
  - Importance when there is only one trial
  - If clinical relevance not inherent in the primary

Clinical Trial Design Considerations

- Well-Defined Study Population
- Well-Controlled Randomized Study
- Blinded, If possible
- Use of Ancillary Treatments Including Off-Label Use
- Informed Consent
- Statistical Analysis Plan (Dr. Laura Thompson)