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Why Do IDEs Fail To Get FDA Approval: Updates To The FDA 510(k) Program And Why They Are Important

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Disclosures

- Terumo Aortic employee
- Adjunct Professor at The University of Maryland
  - US Device & Pharmaceutical Regulation
- Former FDA Lead Reviewer

Note: Views communicated are my own & not reflective of an official Terumo Aortic position

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Agenda

- **Investigational Device Exemptions (IDEs)**
  - Overview of an IDE
  - Why do they fail to get approval?
- **510(k)s**
  - Program Overview
  - New FDA Guidances Available

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Investigational Device Exemptions (IDEs)

- An IDE **allows the clinical investigation** of medical devices in the United States.
- Per 21 CFR 812.1: "An approved investigational device exemption (IDE) **permits a device** that otherwise would be required to comply with a performance standard or to have premarket approval **to be shipped lawfully for the purpose of conducting investigations of that device**."
- **In summary**: It's the means by which a manufacturer or physician is able to clinically investigate a new medical device (unapproved) or new use of an approved device in the United States
  - e.g., Early Feasibility Study, Feasibility Study, Pivotal Study
  - e.g., physician modification of a commercial device, new ascending endovascular graft or an expanded indication for a TEVAR device (for example, transection)

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Reasons for Disapproval

- Reasons per 21 CFR 812.30(b) & Section 520 of FD&C Act
  - **Failure to comply with the requirements** of 21 CFR 812 , Section 520 of FD&C Act, or any other applicable regulation
  - Application has an **untrue statement of material fact or omits information** required by 21 CFR 812
  - Sponsor **fails to respond to request** for additional information in the time that FDA prescribes (21 CFR 812.30(b)(3))
  - Reason to believe that **risks to subjects are not outweighed by anticipated benefits** to the subjects & the importance of the knowledge to be gained (21 CFR 812.30(b)(4)
    - Inadequate safety in the investigational plan
  - **Inadequate informed consent** (21 CFR 812.30(b)(4)
  - **Scientifically unsound** clinical investigation (21 CFR 812.30(b)(4)
  - Reason to believe that the **device will be ineffective** (21 CFR 812.30(b)(4)
    - Inadequate potential benefit

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Most Common Reasons for IDE Disapproval

- **Inadequate Report of Prior Investigations**
  - **Missing or inadequate information** (e.g., animal study, engineering testing, biocompatibility evaluation)
  - **Inadequate sample size and/or sample dimensions** evaluated to provide confidence/reliability on performance aspects of the device in the intended patient population
  - **Inadequate clinical mitigations** for any risks that can't be addressed via testing (e.g., animal, engineering, other)
  - **Insufficient discussion** as to how the **benefits outweigh the risks** for the intended patient population
  - **Inadequate discussion as to how the totality of the data/information provided supports that the benefits outweigh the risks** for the intended patient population

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Study Design

- FDASIA Section 601 – Signed into Law July 9, 2012
  - **FDA shall not disapproved an IDE on the basis of FDA's belief that the study design is inadequate to support a future premarket approval (PMA) application, 510(k), Humanitarian Device Exemption (HDE) or De Novo Classification**
- **NOTE:** Concerns with the Study Design are communicated as Study Design Considerations (SDCs) and are **NOT** reasons for disapproval
  - SDC need to be taken seriously and addressed in a timely manner

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510(k) Premarket Notification

- **510(k) Premarket Notification**
  - "premarket submission that is intended to demonstrate that the device to be marketed is **at least as safe and effective as legally marketed device** that does not require PMA."
    - Section 510(k) of the Food, Drug, and Cosmetic Act
  - Totality of the information must show **substantial equivalence**
- **Marketing Submission Pathway for many Class II devices,** e.g.,
  - Many balloon catheters (non-drug coated),
  - Vascular embolization devices (control hemorrhaging due to aneurysms, certain types of tumors (e.g., nephroma, hepatoma, uterine fibroids), and arteriovenous malformations)

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510(k) Guidance

- 510(k) submission documentation should show that **subject device is as safe & effective as the predicate device & demonstrate substantial equivalence (SE)**
  - **Predicate Device:** A legally marketed device to which the subject device of a 510(k) submission is compared to
- **FDA Guidance**: Best Practices for Selecting a Predicate Device to Support a Premarket Notification 510(k) Submission
  - Select predicate device that was cleared using well-established methods (e.g., FDA recognized voluntary consensus standards, FDA guidances)
  - Predicate devices meet or exceed expected safety & performance
    - Consider device's safety and/or effectiveness information (e.g., adverse events/complaints) after being commercially distributed
  - Predicate devices without unmitigated use-related or design-related safety issues
    - Consider whether there are any emerging signals (causal association or new aspect of known association w/AE) and/or safety communications
  - Predicate devices without an associated design-related recall

No change to applicable statutory & regulatory standards; New guidances are intended to improve transparency, predictability, & consistency.

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510(k) Guidance

- **In many cases:** substantial equivalence is demonstrated through robust non-clinical safety and performance data (no clinical data needed)
  - e.g., technological characteristics & intended use are same/sufficiently similar as predicate device
  - Clinical data may be needed to show substantial equivalence (SE) to the predicate device
- **FDA Guidance**: Recommendations for the Use of Clinical Data in Premarket Notification 510(k) Submissions
- **Four Potential Scenarios**
  - Differences in the indications for use of the new device & predicate device
  - Differences in technological characteristics of the new device & predicate device
  - SE b/t new device & predicate device cannot be determined by non-clinical testing (e.g., analytical, bench, animal)
  - Newly identified or increased risk for predicate device suggests clinical data may be needed for new device

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Summary

- IDEs are generally disapproved due to inadequate Report of Prior Investigations, e.g., incomplete testing, insufficient discussion as to the totality of the data supports that the benefit outweighs the risks
- New FDA Guidances aim to further clarify the 510(k) process
  - **FDA Guidance**: Recommendations for the Use of Clinical Data in Premarket Notification 510(k) Submissions
  - **FDA Guidance**: Best Practices for Selecting a Predicate Device to Support a Premarket Notification 510(k) Submission
  - **Note -** No change to applicable statutory & regulatory standards; New guidances are intended to improve transparency, predictability, & consistency.

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Thank you!

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