Substantial Equivalence Review of Medical Devices

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All devices reach the market based upon the same statutory finding of reasonable assurance of s/e

- Class I – mostly 510(k) exempt
- Class II / Preamendment Class III – mostly 510(k) required
  - Preamendment Class IIIs are a transitional problem that will be resolved in a few more years
  - They should not be part of the evaluation of the 510(k) process
- Class III – PMA approval
All devices reach the market based upon the same statutory finding of reasonable assurance of safety and effectiveness.

- Framework is risk-based
- FDA classifies devices based upon the premarket and postmarket controls necessary to provide reasonable assurance of safety and effectiveness

NB: The manufacturer does not make this choice!
Approximately 98% of devices requiring premarket review each year -- 510(k) pathway

- Approx 65% of devices are 510(k) exempt and proceed to market without any premarket review each year
- Approx 33% annually travel the 510(k) pathway to market
- Approx 2% annually travel the PMA approval pathway to market (or variants)
510(k) clearance is based upon FDA’s finding of substantial equivalence to a “predicate device”

- Basically, another Class I/II device
- Our office found that of the first consecutive 100 clearances this year, median age of predicate was 60.5 months (average 73.5 months; range 1 to 310 months)
510(k) clearance is based upon FDA’s finding of “substantial equivalence” to a predicate device

- Same intended use as the predicate; and
- the same technological characteristics as the predicate; or
- has different technological characteristics and the information submitted to FDA:
  - does not raise new (different) questions of safety and effectiveness; and
  - demonstrates that the device is at least as safe and effective as the legally marketed device
### Substantial equivalence decision necessarily implicates safety/effectiveness

- “510(k) review is both the mechanism by which a manufacturer seeks marketing authorization for a new device and by which FDA classifies devices into their appropriate regulatory category. Because devices are classified according to the level of regulatory control necessary to provide a **reasonable assurance of safety and effectiveness**, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues.” - Draft Substantial Equivalence Guidance at 3.

- Proposed device must be shown **as safe and effective** as predicate device – necessarily implicates safety/effectiveness review
FDA’s implementation of the statutory substantial equivalence definition

- Decision 1: Is the new device compared to a legally marketed predicate device?
- Decision 2: Does the new device have the same intended use as the predicate device?
- Decision 3: Does the new device have the same technological characteristics as the predicate device?
FDA’s implementation of the definition is more granular

- Decision 4: Do the differences in technological characteristics between the new device and the predicate raise different questions of safety and effectiveness?
- Decision 5a: Are the methods for evaluating the different characteristics’ effects on safety and effectiveness acceptable?
- Decision 5b: Do the data demonstrate equivalence and support the indications?
Substantial equivalence review controls the evolution of medium risk technology

- Each newly cleared device is an available baseline for future comparison
- This creates a chain of linked comparisons
- FDA effectively allows advances only far enough that likely clinical impact can be predicted
  - Novel devices shunted to PMA approval for a closer look (de novo if low risk)
Substantial equivalence allows FDA / industry to leverage FDA’s review experience

- Open regulatory architecture – similar to judge made common law
- Allows leapfrogging within industry sectors
- Avoids continually reinventing wheel

NB: PMA approval has closed regulatory architecture
510(k) allows appropriate focus on modifications

- Well characterized technology
- Incremental improvements
- Ground up s/e evaluation would be a waste of everyone’s time and money
510(k) allows appropriate focus on modifications; not a “loophole” or “abbreviated” review

- Class I/II devices almost always can be validly disaggregated as to elements of safety and effectiveness (e.g., biocompatibility, electrical safety, mechanical performance, and sterility)

- All elements can be analyzed using a combination of findings from
  - Comparison to similar technology FDA has already reviewed (predicate devices)
  - Conformance to FDA-recognized or other standards
  - Bench, animal, and/or clinical testing as needed (to bridge gaps)

- **Combined data set provides a solid, rational scientific basis for predicting the clinical performance of a proposed device**
510(k) process is stable/predictable but has flexibility to accommodate technological advance

- Similar to common law judging
  - FDA reviewers are constrained by prior clearances (=stare decisis)
  - But also have significant discretion to determine the applicability of prior clearance to the case at hand
    - E.g. Cytori Therapeutics
510(k) process easily accommodates device heterogeneity

- Each clearance adds richness to the body of potential baseline technology
  - Allows very fine comparisons in a wide variety of device types

- Baseline automatically incorporates latest technology in a self-sustaining fashion
  - Compare performance standards which are threatened by technological advance and variation
IOM’s call to scrap the 510(k) process is ill considered

- They admit it is not based on safety / effectiveness “crisis” (they deny a crisis)
- They admit basis is not a negative impact on innovation (they deny it can be measured)
- They do not cite empirical problems with the system that cannot be fixed
IOM’s call to scrap the 510(k) process is ill considered

- The problem? “The committee found that it was designed in 1976 to provide only a determination of the \textit{substantial equivalence} of a new device to an already marketed (predicate) device; it was \textit{not designed to determine whether a new device provides a reasonable assurance of safety and effectiveness}” (IOM report at xi)

- Actually the 510(k) system as we know it was not part of the 1976 design at all
IOM’s call to scrap the 510(k) process is ill considered

- They ignore the watershed Safe Medical Devices Act of 1990 (SMDA)
- They cite Lohr v. Medtronic – which involved a device cleared in the 1980s prior to the SMDA
- This is like criticizing the design of the federal government based upon the Articles of Confederation
IOM’s call to scrap the 510(k) process is ill considered

- IOM Finding 2.1: “The safety and effectiveness of individual preamendment Class II medical devices has not been systematically reviewed. Continued use in clinical practice, however, provides at least a level of confidence in the safety and effectiveness of preamendment Class II medical devices still on the market”

- What is the purpose of premarket review? 37 years later – does it really matter that there wasn’t a clinical trial or PMA process? Note grudging concession.
Alternatives to the 510(k) process?

- Performance standards for Class II devices was the key to the 1976 design – a complete flop
- Even in the 1970s, PMA approval was only practical for a small number of high risk devices – problem hasn’t gotten better 37 years later with even more sophisticated devices
- European-style CE mark system might work
Future of 510(k) Process

- I predict it will be around for a long time
- It works well – can always be improved – see my paper for a reform proposal
- Anyone who calls for replacement system should be prepared with a practical alternative – certainly not PMA approval
Thank You!

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