Regulatory Options for Novel Markers

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Definitions and Assumptions

- Novel marker = analyte that has not been actively classified by FDA (assigned a class and product code), and was not in commercial distribution prior to May 28, 1976.
- Some novel markers are “close” to existing markers/analytes from the physiological point of view (lipoproteins, markers of glycemic metabolism, coagulation factors).
- FDA practice >10 years ago was to try very hard to find a suitable predicate vs assigning de novo status; more recently, de novo encouraged.

Background-
Review of "non-novel markers"-
Class I or Class II*

* (Class III IVDs on a separate PMA track)
  - Traditional 510(k) (Class I or Class II) for the same product code, same intended use, and where differences in technology do not introduce new issues in safety or effectiveness.
  - If Class I 510(k) exempt (almost all Class I), or selected Class II 510(k) exempt, then no premarket notification is needed, and FDA requirements confined to QSR, registration, and listing.

Novel Markers

Options and Decisions To Be Made

- Regulatory
  - "Close enough" predicate/product code usually based on same intended use (paper predicate / legal predicate)
  - The de novo route
- Clinical Trial Design(s)
  - "Head-to-head" with "close predicate" (value or pos/neg); low likelihood of a numerical match (see next slide)
  - Head-to-head with validated research or academic method for numerical match (Traditional [if paper predicate] or de novo if no paper predicate)
  - Use outcomes data, often non IVDs (clinical status, x-rays, ultrasound, expert panels, Traditional or de novo)

Clinical Trial Designs-1

Head to Head with Close Predicate

- Compare numerical number (low likelihood) or pos/neg
- Compare clinical interpretations based on individual cutpoints; example: new assay has a cutoff of 10 between normal and affected, and established assay has a cutoff of 30.
  - » Cannot use routine statistical tests such as Deming regression
  - » Use 2 x 2 tables, instead, that categorize normal and affected cases according to the assays' cutoff values
- This will support a Traditional 510(k) even if novel marker

Clinical Trial Designs-2

Head to Head with a Validated, but not FDA Cleared Method

- Need to get FDA buy-in (through Q-Sub process) of the validated method.
- Most common examples (in my experience) are mass spec and other well established research methods.
- Will compare new test results head to head with the validated method.
  - » If there is a strong correlation, use the routine statistical tests.
- If there is a paper predicate, then Traditional 510(k)
- If no paper predicate, then de novo

Clinical Trial Designs-3

Novel Marker vs Outcomes Data

Development studies and pilot studies will determine the optimal comparator method(s)/outcomes.

- Simply stated, “how do you know the novel marker is providing the right answer?”
- The novel marker will express results as pos/neg, an arbitrary score, e.g., 1-5, or as a quantitative output with clinical units, e.g., mg/dL.
- The comparator method which may require an expert panel or an amalgam of results.
- These data support a de novo.

Traditional 510(k) vs De Novo- 1

- **Biggest submission differences are:**
  - No substantial equivalence discussion for 510(k)- minor effort
  - Risk/benefit discussion for de novo- major effort

- **Time commitment: 90 days vs 150 days (de novo)**

- **Huge difference in User Fees (2023)**
  - **510(k): Routine- $19,870 Small business- $4,967**
  - **De novo: Routine- $132,464 Small business- $33,116**

Traditional 510(k) vs De Novo- 2

- **Major Similarities**
  - Same forms and administrative information
  - Same intended use statement
  - Same device description
  - Same analytical and clinical validations
  - Same software validations (as applicable)
  - Same labeling requirements

Recap

- Bringing a Class I/II novel marker through FDA is a bit of a puzzle.
- Must consider the inter-relationships between submission options (510(k) or de novo) and clinical trial designs
- If a Traditional 510(k) is not an option, the de novo route is largely the same, but takes longer and is much more costly.

Thank You

Questions ????