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510(k) Delays: Is it FDA or Quality?

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FDA determined that it is a lack of quality

- A new Refuse to Accept program for 510(k) submissions is in effect.
  - The procedures and decision-making criteria are reflected in a guidance document[1]
  - "The goal of this guidance document is to clarify the content needed in … 510(k) submissions to allow FDA to conduct a substantive review, thereby enhancing the quality of received 510(k) submissions and improving overall review time."
- Poor submission quality can no longer contribute to lengthy FDA review times, just delayed clearance.

but, what is the answer to the question?

In the spirit of full disclosure …

- I contributed to the creation of the RTA policy and procedures in June 1993/May 1994 and allowed the program to "sunset" because I did not see the value of investing resources in RTA activities.
- I am of the opinion that the quality of 510(k)s has steadily improved through the years and the quality of today's 510(k)s is generally very good.
- I believe that the responsibility for delays in 510(k) decision-making is shared equally between FDA and industry.

When in doubt, conduct a study …

"To determine why total review time and the number of cycles have been increasing, FDA conducted an analysis of AI Letters. We found that the principal cause for sending AI Letters and for the increasing number of cycles was the poor quality of submissions – those that did not contain required information to complete a review – from companies and companies' failure to fully address these quality issues when raised in an AI Letter."[2]

FDA's Method

- Two separate analyses of AI Letters were conducted:
  - one to assess incoming submission quality (Cohort 1); and
  - one to assess the drivers of the increasing numbers of review cycles (Cohort 2).
- FDA employees "… familiar with the review process but not involved in the premarket review of the sampled submissions …" performed all analyses.

Cohort 1

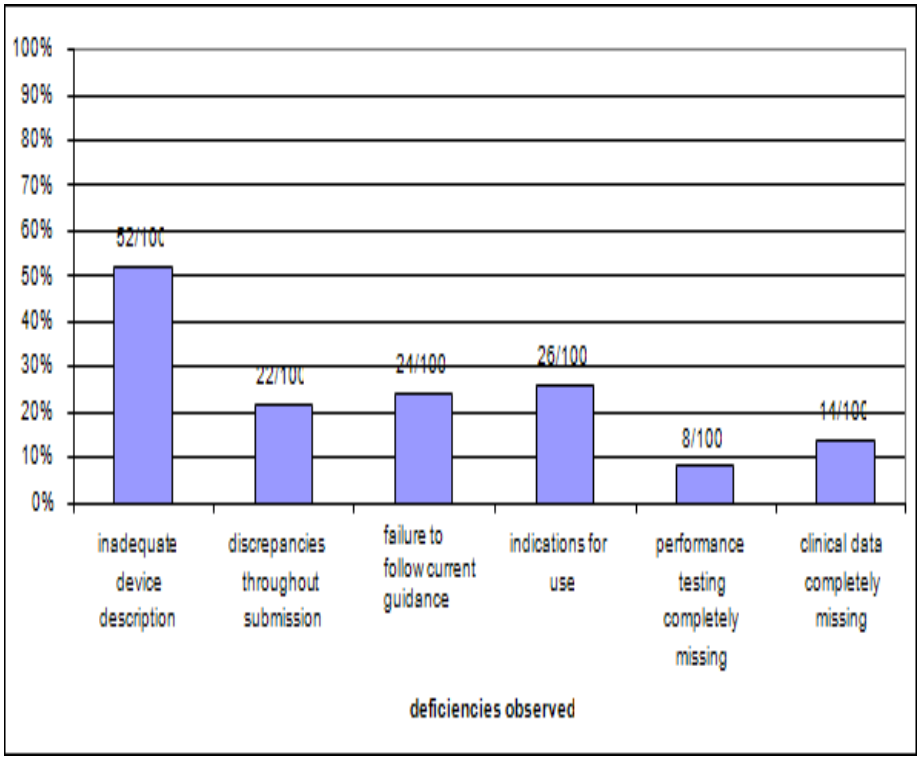
- AI letters from 100 510(k)s received between June 22 and September 14, 2010 (the "Cohort 1 Receipt Period").
  - 727 510(k)s received by ODE
  - 575 510(k)s (79% of receipts) received AI Letters.
  - 17% (100/575) of the submissions for which AI Letters were sent during this period.
- The 100 selected is a random sample (CI +/- 9%).
- The sample of submissions in Cohort 1 was comparable to the overall distribution of 510(k) applications received during the Cohort 1 Receipt Period.

Cohort 2

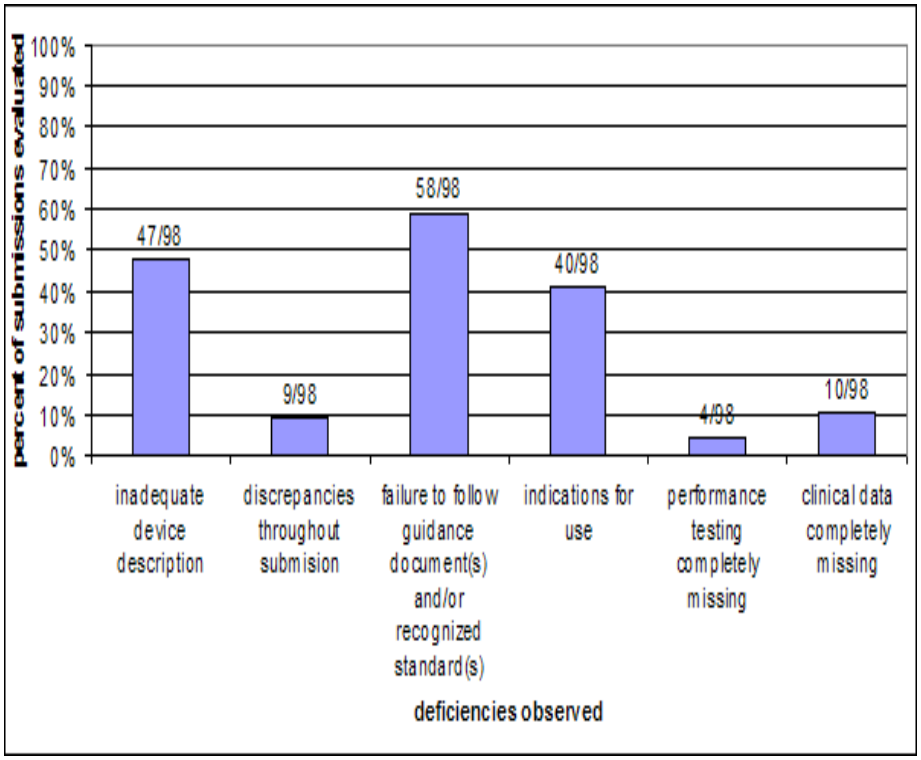
- 134 out of 930 submissions with a first AI Letter sent in 2010 and a second AI Letter sent before the analysis cutoff date (January 20, 2011).
  - 98 510(k)s received by ODE between October 13, 2009, and January 26, 2010
  - 36 510(k) submissions received by the Office of *In Vitro* Diagnostics (OIVD) between November 6, 2009, and July 9, 2010.
  - Only completed submissions with two or more AI Letters were selected.
- The most recent 134 510(k)s received of the remaining 633 submissions were selected.
- 297 of 930 submissions were excluded because they did not have a final decision as of the analysis cutoff date.

Types of Deficiencies Observed

Cohort 1



Cohort 2



Let's examine the types of deficiencies
FDA observed in a Point/Counterpoint fashion

Inadequate device description

- Point …
  - "Every 510(k) submission is required to have a description of what the device is intended to do."
  - "… if the reviewer can't tell from the submission what the device does, he or she cannot determine if the documentation included in the submission supports the device's intended use."
- Counterpoint …
  - Any 510(k) submitter not providing a device description deserves a RTA, but determining a device description to be "inadequate" is more than "administrative."

Discrepancies throughout submission

- Point …
  - "discrepancies … most often related to device description or indications for use."
    - "Differences in device description can have a substantial impact on the review of a device."
    - "When the indications for use statement is inconsistent in a submission … we cannot determine if the device has the same indications for use as a predicate or if any differences alter the intended therapeutic/diagnostic effect of the device when compared to the predicate."
- Counterpoint …
  - "discrepancies" are never good, but differences are not always "discrepancies"[3] and differences can be revealing.[4]

Problems with Indications for Use

- Point …
  - … quality issues related to indications for use include:
    - lack of identification of any predicate for the indication,
    - the indication requires a Premarket Approval (PMA) and for which a PMA already has been approved, and
    - the indication for use for a device that uses a drug is inconsistent with the drug labeling.
- Counterpoint …
  - None of the identified issues relate to quality
    - Predicates must have the same "intended use", not the same "indications for use."
    - Indications that requires a PMA ≠ poor quality, it = "NSE."
    - Device labeling that recommends off-label drug use is not an indicator of poor submission quality.

Failure to follow or address guidance document(s) or recognized standards

- Point …
  - "If a manufacturer fails to follow current guidance (i.e. that which is up-to-date) for a certain device type or a recognized standard, and offers no explanation for its failure to do so, FDA would consider that submission to be of poor quality …"
- Counterpoint …
  - Guidance documents are not binding*, there is no requirement to state that one was not followed, and no means to know which are "up-to-date";
  - FDA recognized standards are voluntary[5]; and
  - the Agency's use of guidance and standards are to reduce regulatory burden.[6]

*21 CFR 115.(d)

Performance testing … is completely missing

- Point …
  - "Performance testing is required for all traditional 510(k)s."
    - "… for our analysis, we only determined that a submission had this deficiency if no performance testing information was provided at all. Without performance testing, we cannot evaluate whether a device's performance is substantially equivalent to that of a predicate."
- Counterpoint …
  - Performance testing is not a requirement for all traditional 510(k)s, "descriptive data" is always required.[6,7]

Clinical data required for certain device types is completely missing

- Point …
  - "For some device types, FDA requires clinical performance data to demonstrate substantial equivalence. FDA considers a submission to be of poor quality when such testing is clearly outlined in a device-specific guidance document or in a pre-IDE, but is completely omitted from a 510(k) submission."
- Counterpoint …
  - Guidance documents and "pre-IDEs" do not establish requirements and there is no device type where FDA always requires clinical data.[6]

FDA's findings

Submission Quality

- 83% and 82% of the submissions in Cohort 1 and Cohort 2, respectively, a deficiency related to quality
- 66% of all 2nd AI Letters resulted from inadequate response to the 1st AI letter (Cohort 2)

FDA Reviewers Changing Expectations

- 63% of responses to the an initial AI Letter caused the reviewer to raise a new issue (Cohort 2)
- In 12%* and 4%** of 2nd AI Letters (Cohort 1 and 2 respectively), FDA asked a new question that should have been raised in the 1st AI Letter

*8% were appropriate/4% inappropriate
**2% appropriate/2% inappropriate

My conclusions

- FDA has overestimated the contribution of poor submission quality to delays in 510(k) clearance and underestimated their own contribution.
- While the criteria for identifying poor submission quality is flawed, FDA has identified many issues that can lead to review efficiency.
  - Industry can take steps to improve submission quality.
  - Guidance documents can be more effectively leveraged.
  - Conformance with voluntary standards can reduce review times.
  - The circumstances that establish the need for clinical data can be identified.
- RTA will reduce FDA review time, but is not an effective means to achieve the Agency's objectives.

What is the future for the RTA program?

I hope to see another sunset!

Resources

1. FDA. *Refuse to Accept Policy for 510(k)s*. December 12, 2012. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014.pdf
2. FDA. *Analysis of Premarket Review Times Under the 510(k) Program*. July 19, 2011. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm263385.htm
3. FDA. *General/Specific Intended Use*. November 4, 1998. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm
4. FDA. *Indications for Use*. February 6, 1996. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080275.htm
5. FDA. *Use of Standards in Substantial Equivalence Determinations*. March 12, 2000. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm
6. FDA. *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles*. October 4, 2002. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm
7. FDA. Blue Book Memorandum K86-3. *Guidance on the CDRH Premarket Notification Review Program* . June 30, 1986 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm