Effective Use of the FDA Pre-Submission Process: An Industry Viewpoint

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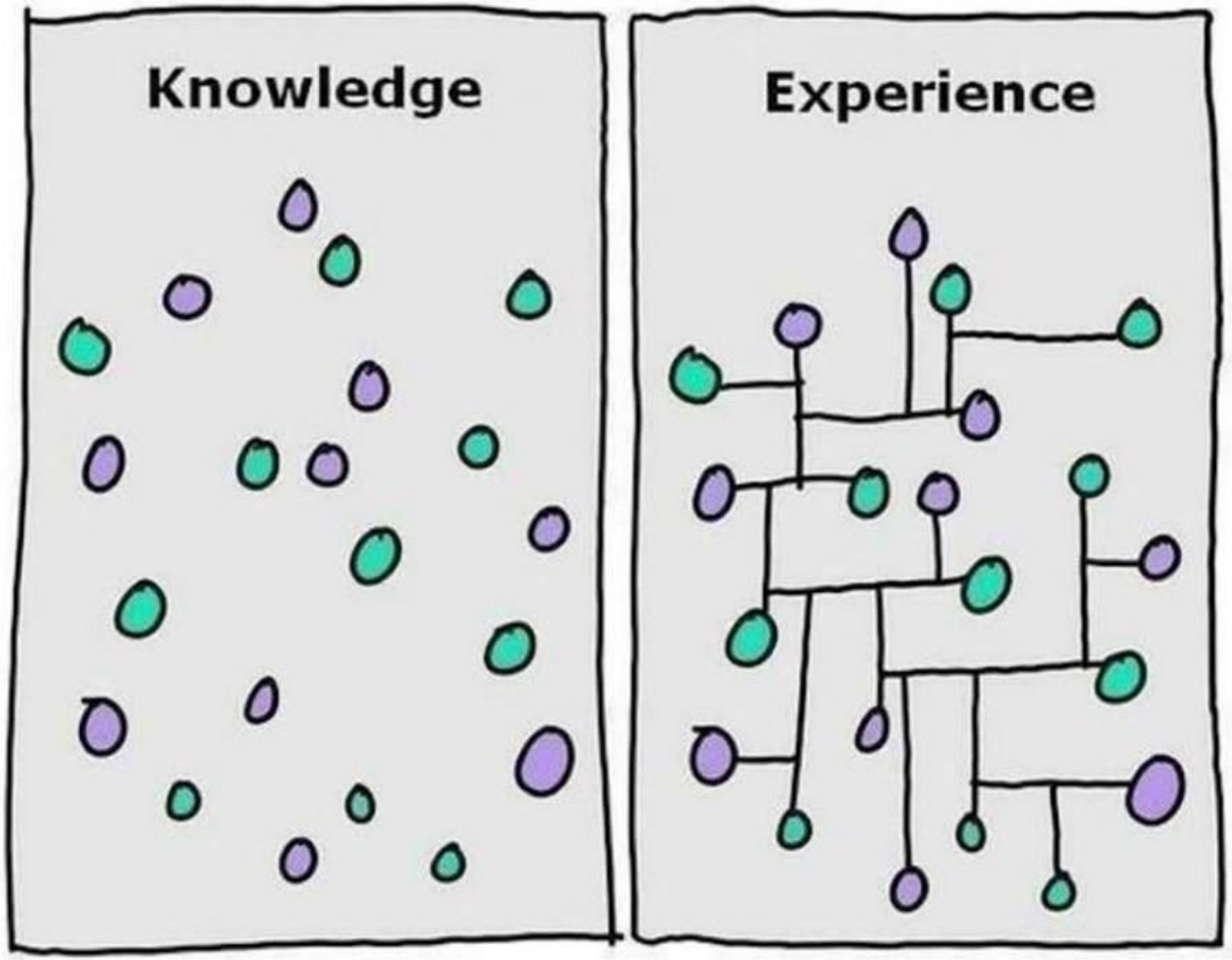
Knowledge
Experience

Agenda

- Why add an FDA Pre-Submission to your development timeline?
- When to add an FDA Pre-Submission to your development timeline…
- Points to Consider
- Pre-Submission Content and Questions
  - Regulatory Pathway, Meeting, Device Description
  - Intended use / Indication for use, Pre-analytics, Software
  - Analytical and Clinical Performance Studies
- The Meeting
- Afterward
- Case Studies
- Questions?

Why add an FDA Pre-Submission to your development timeline?

- Regulatory strategies and potential pathways can drive marketing strategies
- Reduces the regulatory uncertainty
- Clearly defines your intent and feedback on that intent
- Opportunity to ask questions very specific to your proposed diagnostic
- Allows you to proactively address the risks and concerns early in the process
  - Address thru additional testing and other ways to mitigate risk (design improvements, etc)
- New technology and/or new indication
- Is a clinical study required? If yes, doing the right study $$$
- New intended use (de novo) vs comparison to predicate (510(k))?
- No recent similar clearances (no recent similar decision summaries)
- Reduction of redos, repeated studies, retests (ultimately saves additional $$)
  - early FDA input rather than during the submission review clock (additional information request)
- Bundling multiple devices together
- CLIA waiver considerations / dual submission
- Use of data generated outside the United States

When to add an FDA Pre-Submission to your development timeline…

- Age old question
- Balance – you need enough info (device, development plans, claims) to get a meaningful response while still having enough time to plan your studies

- Typical questions asked of an RA professional within an organization….

  - Is this a de novo 510k or a dreaded PMA?
  - Will FDA agree with our strategy / with our study?
  - What will FDA ask during the 510k?
  - How come this (competitor) can say this in their labeling, website, promotional material?
  - If I change x, y or z will this be a 510(k)?
    - Or (my fav), what change can I make before it's a 510(k)?
  - How long will the review be (total calendar days?)
  - "that presub process takes too long", can't we get a answer faster?

Points to Consider

- Clear introduction and purpose of the pre-submission
  - Be specific!
    - It depends on how much detail you can provide: if its early in the process, say so in the intro
- Keep the style the same throughout
  - Lots of folks writing different sections – one reviewer
- Vet! Get someone to read for content and readability
- Anticipate FDA questions
  - Answer in write up
- Be transparent: either you do it now or during the 510(k)….
- Questions, questions, questions. Present you proposal and ask if FDA agrees – be very specific in your questions to get specific responses
- Use the meeting time to only discuss controversial topics from the written FDA comments
  - Keep intros to a minimum/avoid recap of presub
  - If nothing controversial, cancel meeting! Everyone likes that

Pre-Submission Content and Questions
Regulatory Pathway, Meeting, Device Description

- Regulatory Pathway
  - Provide justification for your proposed regulatory path (include benefit/risk statements)
  - Clearly describe the predicate device
  - Q: Ask FDA if they agree with the regulatory path you have chosen and/or your choice of predicate is appropriate. Ask if you should consider other potential predicates

- Meeting
  - Indicate whether you want a face to face, teleconference, or just written responses

- Device Description
  - Present a clear and detailed device description, make sure all things required to generate the test result are identified (reagents, calibrators, instrument, software, instructions to run test (if available)
  - Include pictures, diagrams, if possible
  - Allows for understanding of risk and how your analytical and clinical studies will mitigate them

Pre-Submission Content and Questions
Intended use / Indication for use, Pre-analytics, Software

- Intended use / Indication for use
  - Be as clear as possible: match it to your clinical study population and/or your chosen predicate device wording
  - Include clinical interpretation (assumed).
  - Consider if your intended use needs to be very specific (population or setting of use)
  - Q: Ask FDA if they agree with the proposed intended use as written (understanding that is could depend on the outcome of your studies)

- Include and pre-analytical steps, specimen conditions and handling
  - Q: Ask if you study designs sufficiently incorporate pre-analytical steps and any variants of them.
  - Q: Ask if there are any risk that we haven't considered

- Software
  - Explain how your software impacts the test results, explain any known risks, present your validation plan, provide screen shots, if available
  - Q: Ask if FDA agrees with your proposal and if any other risks should be considered

Pre-Submission Content and Questions
Analytical and Clinical Performance Studies

- Describe in detail all performance studies including sample types used, use of contrived samples, testing site selection, levels to challenge analytical measuring interval and medical decision points, sample numbers, patient populations, statistical analysis plans
- Q: Ask FDA if they agree with your proposals and ask specific questions on any uncertainty of the above
  - If performing a method comparison to a predicate or reference method, ask FDA if this study is sufficient or if a clinical study is required
- Q: Ask if there are any other guidances, CLSI documents, and /or recent decision summaries you should consider when designing your studies
  - If referencing an older guidance, check with FDA if that guidance is still applicable

- If a clinical study is required, include detailed information on sample collection, inclusion/exclusion, clinical data required, stat plan, site selection, etc
- Q: Ask if the clinical study design will support the intended use as proposed?
- If using banked specimens, describe conditions in detail
- Q: Ask FDA if they foresee any risks that we need to consider?

The Meeting

- After you receive the written feedback:
  - To your team: Anything unclear? Controversial?
    - usually statistical approaches can have differing opinions
  - Face to Face? Teleconference? No Meeting?
  - Strategy! You only have an hour
  - Company attendees – who do you need?
  - Assign roles and minute taker
  - Agenda and what to prepare:
    - Don’t waste time on things your team agrees with
    - Slide decks
      - No need to give company history
      - Don’t’ prepare a slide deck that rehashes your pre-submission document, everyone has read it
      - Slides are good when you have a complex device and need to explain it
      - Slide decks could be used to describe a backstory if FDA was unclear on why you chose your approach that you didn’t cover adequately in the Pre-Submission
- Minutes should be a summary of discussion and key points – not a transcript!

Afterward

- Possible Pre-Sub supplements:
  - Follow-up question/actions may require a supplement particularly if it requires an in-depth cross functional review at FDA
  - Need to consider if any major design considerations need to be addressed internally to lessen the barrier to clearance (any trade-offs?) – discuss with R&D and marketing
- Minor follow ups could be handled interactively (without supplement)
  - This should be agreed upon during meeting
- Future 510(k)/PMA submission
  - Provide a summary of all Pre-Submission interactions
  - Explain any differences in device design since the Pre-Submission
  - Address any concerns identified during the Pre-Submission process
  - If you didn't follow FDA's advice, explain why

Industry Experience
Case Study #1

- Device company submitted a pre-sub to propose an alternative method to support substantial equivalence to a predicate instead of a prospective, multi-site clinical sample collection
- The predicate device uses similar technology, there are several similar products on the market
  - No known safety concerns with any on-market tests
  - No special controls guidance document
- Company proposed a method comparison study using samples from the intended use population
- Company proposed performing all the same studies as described in the most recent 510(k) decision summary
- Through discussion with FDA, the company agreed to use enough samples to cover the range and add a certain amount of samples to cover key medical decision points for the method comparison study.
- By going down this path and gaining FDA agreement, the company was able to save around $1MM in clinical study costs alone

Industry Experience
Case Study #2

- Device company submitted a pre-sub to determine appropriate classification for a novel cardiac marker.
- Company proposed de novo pathway finding only predicates with a diagnostic intended use. New marker is intended for monitoring.
- Through discussion with FDA, an appropriate existing regulatory classification regulation was identified which allows for a traditional 510k pathway, avoiding the more lengthy de novo process.
- FDA is requiring clinical data for the new device
  - a straight forward method comparison would not provide sufficient assurance of safety and effectiveness.

Industry Experience
Case Study #3

- Sponsor submitted pre-submission on a new analyzer with 5 new reagent assays.
- Initial feedback was sought on bundling, predicate options, and performance study plans.
- FDA accepted bundling and provided some helpful suggestions on predicates options.
- FDA feedback on analytical performance plans, clinical protocols (method comparison, reference range, reproducibility) was key to timely design of studies.
- A supplement was filed to seek input and clarification on use of the Replacement Reagent/ Instrument Family guidance for a next gen analyzer.

Thank you!!!

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