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Regulatory Perspective of the Diagnostics Manufacturer– Next-Generation Sequencing for Personalized Medicine

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Regulatory Perspective of the Diagnostics Manufacturer – NGS for Personalized Medicine

Agenda

- Joint Partnership
- FDA meetings interactions
- Claims
- Clinical sample testing efforts
- Considerations for schedule and timing to get to “IUO”
- Assumptions that can impact timeline
- Technology

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CDx Partnerships

- Should work as a collaboration
- All FDA communication Pharma company has had related to the need for a CDx, prior to the partnership, should be forwarded to the IVD partner
- During the partnership, joint preparation of the Pre submission packages and participation at FDA meetings/ TCs
  - Diagnostic manufacturer will facilitate
  - Diagnostic manufacturer RA team are the subject matter expects concerning the FDA assay interactions.
- Drug company to manage dialogue related to the therapy
- IVD company should be the subject matter experts concerning the requirements for IVD development and the analytical study designs.

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FDA Meetings/Interactions

- The earlier in the development process you can start your meetings the better.
- Each pre sub take time to prepare and for FDA review and comment. Build this into your timeline.
- It will take multiple interactions through out the program to obtain the feedback you need.
- Once you start to discuss the details of your analytical studies; this is where it gets complicated.
  - Obtaining feedback on your study designs and claims is key.
- Be sure your Pharma partners have the opportunity to pose questions specific to use of the assay for drug selection.
- Be sure you understand which type of questions go to CDRH and which go to CDER/ CBER.
  - The lack of understanding as to who should be asked can cause a delay to the feedback.
- FDA does prefer the modular PMA approach. If performing a modular submission;
  - start the shell dialogue sooner than the guidance calls out. FDA will probably prompt you as well.

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Claims

- What types of claims do you plan to make; analytical, clinical? Reporting of analytical markers where safety and effectiveness not established; example in EGFR - P120022
- Your testing effort must prove what you want to claim.
- NGS produces a huge amount of information, the more you want to claim and report out of the system, the larger your test effort will be.
- Use of clinical samples in analytical testing is required unless you can prove other wise.
  - Rare prevalence is considered 1% or less .
- Be prepared to provide study designs and data in order to support applicability of novel test approaches.
- Consider labeling limitations if needed.

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Clinical Sample Test Efforts

- New drugs or new indications for existing drugs
  - Prospective use of IVD or a CTA in a study
    - Bridging test effort required when CTA used
  - Retrospective testing of samples using a CTA or IVD.
    - Bridging test effort required when CTA used
  - Test samples prospectively using local tests and confirm prior to enrollment/ assignment using CTA or IVD
- "Me too" (currently exists on the market) assay development/ testing using samples from same "intent to treat population"
  - Retrospective testing of Phama banked samples or commercially available samples.
  - Prospective collection can be done as well.

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Schedule and Timing to Get to IUO

- If Pharma approaches you early, you have time to develop the IVD assay for use as an IUO within their registrational study.
  - This test and data will be used for the submission
- If Pharma has already started studies using a CTA
  - Single or Multiple CTAs may be in use
  - IVD development to be initiated in parallel
  - Incorporation of local test methods may be required in your test effort.
  - Bridging required once IVD completed; high level of concordance expected
  - Sample access required. Access to all positives when ever possible. If not available, rational must be stated. Statistical significance must still be met
  - If all, or a significant number, of positives cannot be retested an option may be to obtain positives from additional sources. (if FDA approves)
  - We need access to Negs as well. Either from the study or the same “intent to treat” population.
- Pharma schedule is aggressive, wants a fully validated/ IVD ready assay within a few months for use in a study.
  - Education required. Schedule may be adjusted to accommodate IVD development or you (or a partner lab) will develop a CTA for use in study.
  - Same issues noted above come into play

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Assumptions that can impact the timeline and effective dialogue

- Pharma believes that the assay path to market is simple and not very complicated. "Its just a test; its not a drug."
  - This can create issues in development of project schedule and initial FDA dialogue
- Pharma believes that it is easier to get what you want from OIRR vs the drug divisions. "Just tell them what you want."
  - This can create issues in development of project schedule and initial FDA dialogue
- It may take some time for Pharma to accept that the time required to develop the assays and the level of testing that is expected may be longer than they estimated.
  - Preconceived notions of a quick timeline can be difficult to re-ground

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Assumptions that can impact the timeline and effective dialogue

- IVD development and LDT development/testing are not the same
  - Pharma has access to many LDTs that are currently on the market. They may compare product concepts, claims and test efforts they see the LDT performed and assume that's all you have to do for an IVD.
  - This can be a difficult hurdle to get passed until your FDA meetings reveal this to them.

- Time required for IDE planning is not within Pharma initial schedule.
  - Time for risk designation request, design of testing requirements, specification development , pre IDE preparation and FDA dialogue need to be accounted for.
  - Analytical Validation of the IVD or CTA is required
  - Analytical validation of CTA is key to ensure successful bridging later on.

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Technology

- NGS analyzers are class II exempt; general consumables are class I exempt.
  - All the same documentation and testing is required to be on file; 510(K) submission not required
  - Requirements are noted within the Nov 19, 2013 De Novo clearance letter to Illumina. A special controls document does not exist.
- Be sure that FDA fully understands your technology; how it measures, what it measures, how the SW works, what you want to claim, etc
  - This is an absolute must.
  - All NGS systems do not work the same; utilize different consumables, etc. You could held accountable to test things that are not applicable.
  - Your testing effort will support what can be claimed.
  - You may have to circle back several times in order to ensure everyone is on the same page.
- Gold standard/ reference method testing is currently still required

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