Common Regulatory Errors by IVD Companies – and how to avoid them – or Ten Rules for Dealing with FDA

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It Must be Nice to have White Oak on Your Side

- FDA is a primary audience for IVD companies
- Want their support and trust
- Something easily lost
  - Unnecessarily adversarial
  - Lack of candor – credibility is fragile
  - Sloppy submission
  - No pre-submission for novel IVD
  - Ignoring FDA guidance
  - Willful non-compliance with law
  - Bad facts that are not handled properly
- However, FDA is not your friend
  - Sometimes, challenges and appeals are necessary

Talk Less, Listen More

- IVD manufacturers know their product best
- May have a lot to say about them
- FDA also may have a lot to say
- Companies sometimes don't listen well
  - ("Children won't listen")
  - Defensiveness is not helpful
- Root cause can be lack of clarity by FDA; listening can help
- Ultimately need to understand and address FDA's concerns

NB: Significant problem when FDA will not describe issue clearly, e.g., rationale for new pharmacogenomic policy

Being in the Room Where it Happens

- Navigating FDA IVD regulation involves multiple disciplines
- Make sure the right people are there
  - Technical skills
  - Subject matter experts
  - Experience
  - Independent views – group think is dangerous
  - Making sure appropriate regulatory/clinical legal perspectives are included

- Avoid having the wrong people, e.g., sales dominating a discussion on whether to recall or if a 510(k) is needed for a product change

Running Out of Time

- Can be a lot of pressure to move swiftly
  - Commitments to shareholders or investors
  - Internal goals
- Can lead to unrealistic forecasts for achieving milestone
- Can lead to submission prematurely
- Once a mistake is submitted to FDA, it cannot simply be erased (See Slide 2)
- Being efficient is important, but a bad submission can haunt a company for years
  - OIR will sometimes reference submissions from several years earlier, e.g., "In your pre-submission on August 13, 2017, you stated . . ."

The Trap of Never Being Satisfied

- FDA process often involves negotiations, including but not limited to intended use and labeling
- Overreaching can mean not getting the clearance or delaying it substantially
- Need to figure out what is essential, very important, nice to have, etc.
  - "You can't always get what you want."
- Understanding relationship between FDA-reviewed labeling and promotional claims is important

NB: Not every claim has to come directly from labeling

Not Throwing Away Your Shot

- Generally not true IVD companies have only one shot
- If a 510(k) is NSE'd, not a permanent bar; if pre-sub strategy elicits objection, can refine and try again, or challenge
- However, refining and resubmitting takes time
- Optimize that first shot
  - Look at predicates/precedents, especially recent ones and guidances/draft guidances, e.g., draft blood glucose guidance
  - Carefully review work product
  - Avoid the avoidable mistakes
  - Challenge your work product
  - Get expert or independent feedback, e.g., outside biostatistician or disinterested reviewer
  - Explore counter-arguments, e.g., is sample biased, what are the risks of a false positive

Get a Lot Farther by Working a Lot Harder

- There are some brilliant IVD ideas
- Some compelling diagnostic needs
- Identifying a compelling need is helpful but not sufficient – wow factor is not enough
- Details matter, e.g., analytical testing, labeling, impeccable study, understanding the failures that do occur
- Responding quickly and accurately to FDA's questions
- Scrubbing the work product to avoid mistakes, e.g., discrepancies or missing tables, making sure it is clear to a third party, e.g., FDA.
- Writing clearly

And We Make Our Mistakes

- Despite everything, there will be mistakes and problems
- Can be minimized but rarely avoided, especially for novel IVDs.

Cf. "Mothers, fathers, they all make mistakes."

- How do you handle the mistake – or unexpected outcome
- Acknowledge it, address it, put it in context
- Don't double down or deny

Searching and Scanning for Answers in Every [FDA] Line – and Vice Versa

- FDA feedback is carefully parsed
- FDA comments can be Delphic or obscure
  - Sometimes written by different FDA team members
- Can be hard to decipher
- Sometimes, the best course is to ask
  - FDA has acknowledged that its words were unclear

NB: FDA parses company's words just as avidly

Winning Clearance Was Easy[ish], Governing Is Harder

- The focus tends to be on getting the IVD to market
- Can easily stumble if the company isn't prepared for the next phase
  - QSR
  - Supply chain controls
  - MDRs – can be tricky for IVDs
  - Capacity to do risk assessments, e.g., Health Hazard Evaluation
  - What changes trigger new applications
  - Infrastructure to control marketing materials