ASSOCIATION OF MEDICAL DIAGNOSTICS MANUFACTURERS ANNUAL MEETING

"EIGHT MORE TIPS FOR IVD MANUFACTURERS"

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1. Be Prepared

- Prepared for inspection
- Prepared for product problems
- Prepared for OIR meetings
- Prepared to defend your position
- Prepared for public scrutiny
- Prepared by looking for failure modes before failure
  - Pre-mortems

"Plans are nothing; planning is everything" – President Dwight D. Eisenhower

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2. The Law is an Ass/The Law is not Mocked

- The FDCA was not written with IVDs in mind
  - Exceptions: The definition of "device," including the word "condition"
- The regulations don't always fit well, e.g., MDRs
- Common complaint: the law makes no sense
- Sometimes, square peg/round hole

BUT

- The FDCA is the law
- Failure to comply is subject to range of sanctions
- Failure to comply may mean no 510(k)/PMA

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3. We Are a Nation of Laws, Not Men

- FDA regulatory regime highly legalistic
- Hierarchy: Constitution/FDCA/Regulations/Guidelines/Informal guidance
- Ultimately, any FDA decision must be based on the law

NB: Most FDA decisions do not reference law/regulations

But

- The law is ambiguous
- There is plenty of room for discretion
- Different FDA officials will have different perspectives
- Need to keep your audience in mind

NB: Communication of today, e.g., investigator, may have different ultimate audience, OIR compliance personnel, who will view the words differently

NB: Even in front of the U.S. Supreme Court, lawyers tailor arguments to individual justices

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4. A Word Means Just What I Say It Means

- The meaning of words is an under-appreciated source of confusion and error
- Regulatory success or failure can hinge on words
- Need to be sure you and OIR mean the same thing when you say the same thing

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4. A Word Means Just What I Say It Means (cont'd)

- Terms have elastic definitions, e.g., "safe," "effective," "substantial equivalence," etc.
  - Even with definitions, there is still room for interpretation
    - The word "manufacturer" is defined differently in different places
  - Length of definition does not guarantee clarity
    - ASR regulation one of the longest definitions but source of much confusion
  - Some terms may have elaborate guidance but still subject of debate, e.g., RUO
  - Some important terms not well-defined, e.g., LDT

Who gets to decide what words mean?

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5. What You See Is (Not) All There Is[1]

- Tendency to see what is there, rather than what is not there
- FDA will look for omissions, both in QSR inspections and submissions
- Beware of blind spots in datum or analysis or assumptions
- Group think is dangerous – perspective needs to be challenged
  - What about the precedents you don't cite?
  - Are there contrary articles?
  - Is there another statistical analysis with a different result?

It's easier to focus on editing what is in a document, e.g., a pre-sub, than to identify what is lacking.

[1] Daniel Kahneman, *Thinking, Fast and Slow*

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6. The Chances of Anything Coming From Mars are A Million to One

- IVD companies can underestimate the risk of an adverse outcome
  - Important for HHEs/recalls/MDRs
- Will multiply probabilities of seemingly independent events and calculate a vanishingly low probability
  - The observed frequency is higher
  - If the calculated frequency is one-in-a-million, and the observed frequency is much higher, reassess the calculation

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6. The Chances of Anything Coming From Mars are A Million to One (cont'd)

- Examine assumptions that go into estimates of probability
- Opposite problem: overweighting low risks[2]
  - Can cause companies and FDA to lose sight of overall benefit/risk

[2] See *Thinking, Fast and Slow*

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7. Punctuated Equilibrium

- Regulatory patterns can persist, until they suddenly don't
- There can be gradual evolution, e.g., slowly changing expectations for submissions
- There can also be sudden changes; new de novo procedures; appeal process; pre-sub requirements
  - LDT guidance?
  - Guidance on troponin assays
- Beware of regulatory analogue of earthquakes
  - Be alert for tremblors
- IVD companies need to be adaptable
  - Be able to change to fit into changed regulatory environment

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8. Money Talks

- Regulatory issues often affect commercial transactions
- Make sure regulatory/quality/clinical are involved at the right stages
  - Due diligence for acquisition/partner
  - Licensing agreements, e.g., milestone payments
  - Distribution agreements properly address relevant regulatory clauses
    - Recalls
    - MDRs
    - Marketing
    - Submissions
    - FDA interactions
- Regulatory considerations need to be addressed before agreements are signed/about to be signed

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