ASSOCIATION OF MEDICAL DIAGNOSTICS MANUFACTURERS ANNUAL MEETING

"TEN TIPS FOR IVD MANUFACTURERS"

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1. The Times They are A-Changin' – or Changed

- Statute - FDASIA
- Regulations - Registration
- Policies – A flurry of new and proposed guidance documents
- FDA's expectations – Regularly evolving, often without notice

The past is not necessarily prologue

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2. Be Careful Out There

- Details matter
  - Credibility is key in FDA interactions
- Errors undermine credibility
  - Internal inconsistencies within documents
  - Inconsistency between statements in submission and study reports
  - Faulty assumptions – or making assumptions
  - Mathematical errors
  - Ambiguous or confusing writing

Haste makes waste – and creates delays

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3. What are Your Intentions?

- Intended use is fundamental to submission and strategy
  - PMA/de novo/510(k)?
  - How much data?
  - What kind of data?
- Study design and intended use must match
  - Particularly tricky for banked specimens or retrospective studies
  - An intended use/study design mismatch can doom the submission
- Intended use must be established at early stage

Words matter, and the words of intended use may matter most of all

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4. Be Analytical

- OIR puts a great emphasis on analytical tests
- Good clinical performance necessary but not sufficient
- Make sure do necessary analytical studies and do them correctly
  - Keep up with changing standards, e.g., new CLSI guidelines or FDA expectations

Analyze your analytical plan and execute it properly

5. Avoid IVD Isolationism

- IVD regulatory regime unique in many ways
- But IVDs are a subset of devices and subject to device regulatory requirements
  - Enhancement/Improvement draft guidance
  - Changes to 510(k)'d devices
  - Refuse to Accept/File
  - Risk/Benefit for PMA/de novo

Think locally (IVD), act globally (devices)

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6. Listen Up

- OIR does give advice
  - Conferences, e.g., AMDM
  - Pre-submission meetings
  - Written feedback
  - Review memoranda
- Do not ignore it
  - Reduce chance of success
  - Can irk OIR, e.g., "As we previously advised, we recommend that you [*fill in the blank*]"

What we have here is a failure to communicate

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7. Be Appealing?

- OIR is not always right
- FDASIA + Guidance Document = faster appeals
  - Appeals had been impractical because of delays; now rapid
- Changes affect timing, not biases built into system
- Appeal to Division Director and then OIR Director
- Dilemma: Little time (30 days) to decide to appeal or work together

Know when to hold 'em and when to fold 'em

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8. Kwality Counts

- Quality matter at all stages
  - Analytical
  - Clinical
  - Submission
  - Manufacturing
  - Meeting presentation
  - Regulatory Decision-making
  - Health Hazard Evaluations
  - Consultants
- There are multiple ways in which quality shortcomings can hurt

8. Kwality Counts (cont'd)

- Bad Advice: "Make it as perfect as possible consistent with the rapidity of construction demanded." – Central Pacific Railroad, 1866
- More Bad Advice: "I thought we had better take *high ground* and confine ourselves to the law until we are where we can make more to break it than keep it." – Collis Huntington

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8. Kwality Counts (cont'd)

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9. Statistically Speaking

- Statistics play a large role in many submissions
- Statistical issues can preclude clearance/ approval
- Get statistical help at an early stage
- Use someone who speaks "statistics"
  - Statistical debates arcane, complex, and critical

99% of people (CI 97%-101%) don't really understand statistics

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9. Statistically Speaking (cont'd)

- "But perhaps the bigger problem is the way that Fisher's statistical philosophy tends to conceive of the world. It emphasizes the objective purity of the experiment – every hypothesis could be tested to a perfect conclusion if only enough data were collected. However, in order to achieve that purity, it denies the need for Bayesian priors or any other sort of messy real-world context."

- Nate Silver, *The Signal and the Noise, Why So Many Predictions Fail – but Some Don't*, 2012

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10. Freedom of Speech

- Evaluation is First Amendment law
- Washington Legal Foundation – reprints
- Sorrell – information
- Caronia – off-label promotion
- Tobacco labeling
- Off-label speech may be constitutionally protected
- But: false or misleading speech is not
  - Material omissions can be false or misleading
  - Not affirmatively stating what is off-label?
- Bigger topic: IVDs = Information (sort of)

Think before you speak

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