Current Industry Challenges in Conducting Clinical Studies & Trials

Scott Adams, Ortho Clinical Diagnostics,
a Johnson & Johnson company

Challenges Come in Many Forms

- Study Design
- Study Management
- Business Case
- Regulatory Strategy

Building the Sponsor-FDA Relationship

- Partnering with FDA is one of the most important things a Sponsor can do to ensure success
- Every interaction, whether verbal or written, is an opportunity to build this vital relationship
- FDA teams have proven willingness to provide constructive feedback

510(k) Confusion and Improvement

- Transparency, predictability, and adaptability
- Studies and submission must continue so we need to return to basics and share ideas with colleagues and the FDA
- The reality of most IVDs is that 510(k) works well; we must be careful not complicate the process with new regulations which add proportionally more burden to IVD development
- 04 August 2010 *510(k) Working Group Preliminary Report and Recommendations*

Inferior Predicate: What is Equivalence?

- As technology improves rapidly, new IVD assays become increasingly superior making "equivalence" difficult
- Predicate may be considered the "gold standard" even with poorer performance relative to a new test
- Discordance rate may raise concerns about performance
- Furthermore, changing standards of care and clinical guidance affect what seems appropriate for comparison purposes

Pre-IDE vs. submission review

- Pre-IDE meetings and correspondence often provides FDA guidance on significant clinical design issues that Sponsor implements
- Sponsors try to do the right thing and follow the guidance from pre-IDE even though it is not binding

Lab-Developed Tests

- LDTs began as a way to fill unmet needs such as low volume or highly specialized assays
- LDTs have become common and widely accepted, but concerns are rising about their scientific and clinical foundation
- Established IVD companies manufacture tests with clinical validation that supports a specific intended use(s) based on a business case to support development
- FDA meeting on 19-20 July 2010 first step toward a plan to regulate LDTs in a way that retains innovation and assures safety and efficacy

Outside Experts

- Experts and KOLs are vital to the success of both the FDA and the Sponsor
- How will FDA and Sponsors share experts?
- 04 August 2010 *510(k) Working Group Preliminary Report and Recommendations*

PMA vs. Class IIB

- 04 August 2010 *510(k) Working Group Preliminary Report and Recommendations*
- Products that have been around for many years with a large amount of clinical data independent of the approval studies could be candidates for 510(k) IIB route

Comparative Effectiveness Data

- CER provisions in recent healthcare reform legislation – Patient-Centered Outcomes Research Institute
- IVDs play an important role in most medical decisions and likely will play a vital role in personalized medicine
- How will CER apply to IVDs?
  - Study designs that assess value of IVDs to patients and payers
  - Use of cost-per-test data in appropriate ways to define value
  - Pre- or Post-market assessment of IVDs affects ability to prove value
  - Funding strategies with CER users to control costs of studies with IVDs

Risk-Benefit Analysis

- Negative aspects of a new product may be given more weight than known negatives of the standard of care
- Value of new tests may be dependent on a variety of factors including cost and complexity
- "Personalized" test based on biologic factors may motivate individuals better than established tests or algorithms
- 04 August 2010 *510(k) Working Group Preliminary Report and Recommendations (enhance science-based professional development of CDRH staff and establish a network of external experts to better inform the review of cutting-edge technologies)*

Statistical Concerns

- "Gold Standard" is not golden
- Positive is Positive, but Negative is not always Negative.
- Sponsors may not be able to use statistical methods to discuss effects or to adjust performance
- Verification bias is an inherent concern for IVDs, but none of the statistical methods are acceptable or well understood for general purposes

Patient Privacy Affects Sample Collection

- IRBs are cautious about the use of samples even though guidance is clear
- Donor centers and clinical laboratories also concerned
- Educating "leftover" sources may require Sponsor effort

IRBs

- IRB oversight is critical to IVD studies to protect human subjects
- IRB submission forms are not always IVD friendly
- Central IRBs allow Sponsor to educate and build relationships
- Local IRBs utilize PI's involvement to overcome obstacles
- IVD sites often have little or no experience with clinical studies or IRB submissions

Clinical Studies are Costly and Complex

- FDA and customers demand proof of safety and efficacy
- Sponsor wants broad intended use statements
- Global submissions may require multi-national enrollment
- Less dependence on US subjects would be efficient when the use of ex-US subjects can be shown to have no impact on quality
- Study designs are affected by future adoption by clinicians who need to follow their disease association guidelines
- Fair market value; finding the right collection sites; specific types of laboratories may be required for testing

Multiple FDA Contacts Adds Complexity

- HIV tests come under review by both CBER and CDRH
- 2 different sets of rules to follow during clinical studies, submission, and audits makes the process cumbersome in a single clinical program
- Sponsors may use the best parts of all applicable regulations, but may find that auditors prefer to follow the checklist of one center and do not appreciate attempts to provide the best merged version
- Pre-agreement is important in these cases

Post Approval Studies

- PAS rigor can be equal or greater than approval studies
- Risk of an expensive post-approval study is becoming part of the business case
- Statistical designs could end post-approval studies early once data confirms performance and safety
- Another option might be to accept post marketing data from outside post approval study

Thank you!