CDER Perspective: Challenges in Clinical Trials and the Path Forward

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Current Oversight Models for Clinical Trials May Be Outmoded

• Reactive and premised on retrospective detection of errors
• Lack of proportionality
• Resource intensive
• May not optimally address significant risks to trial integrity, particularly systemic error
Analysis of OSI Reviews of Marketing Applications1 Indicates Opportunities for Improvement Remain

104 original and supplemental NDAs/ BLAs reviewed by OSI from 1QFY10 to 1Q FY11

- Significant data integrity concerns affected 5 inspected applications (5%)
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a root cause in study design and planning.
- For 2/5 applications, concerns arose solely from internal processes at the sponsor and CRO, unrelated to clinical investigator activities

1. Meeker-O'Connell and Ball
FDLI Update 2011;2: 8-12
Inefficient practices may consume valuable resources and inadvertently detract from quality

**Case Study: Clinical Trial Monitoring**

- Millions of data points collected on a clinical trial; Not all used in regulatory decision-making.¹

- OSI focus: critical errors in endpoint and safety data

- Industry standard for monitoring:
  - 100% source data verification at the clinical site
  - “The flexibility in the GCP guidelines is not often utilized” ²

- FDA regulations permit a variety of monitoring approaches

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² Sensible guidelines for the conduct of large randomized trials. Clin Trials 2008 5: 38
Desired State for Clinical Development similar to Quality by Design in Manufacturing:

“Maximally efficient, agile clinical development programs that reliably produce high quality data* and protect trial participants without extensive regulatory oversight”

*Data that are fit for purpose
Systematic, proportionate approach to clinical development

- Emphasis on process control
- At the trial level, the protocol is the blueprint for quality
  - Prospectively identify the important risks to subject safety and data reliability
    - Risks may accrue from a variety of sources
  - Tailor the protocol and its delivery to eliminate or mitigate these important risks.
  - Monitoring and auditing become tools in a quality toolbox, with flexibility in approaches
CDER is fostering the development of risk-based approaches to clinical trial oversight

Examples

• Clinical Trials Transformation Initiative (CTTI) Project on Quality Frameworks: Making clinical trials fit for purpose

• Pilot prospective review of a sponsor’s risk-based integrated quality management plan

• OECD-GSF Working Group to Facilitate International Cooperation in Non-commercial Clinical Trials
  – Feasibility of a risk-based approach for multinational trials
Key Dependencies

- Recognition of differences in manufacturing and clinical development
- Broad engagement of stakeholders
- Effective communication: fundamental change in oversight
- Early identification of barriers
- Evaluation of different approaches and methodologies
- Changes in FDA oversight and inspectional processes
Corresponding Shift in CDER’s Approach

• Shifting inspectional resources to permit assessment of clinical trial oversight in real-time
• Risk-based inspection planning
• Enhancing external collaborations
  – EMA / FDA GCP Initiative
• Adopting an enterprise compliance intelligence approach
  – Using data analysis to identify risk concentrations and craft targeted solutions
  – Coordinating with other Offices within the Office of Compliance and across the Agency
Thank you!

Questions?