CDER Perspective: Challenges in Clinical Trials and the Path Forward

Pharmaceutical Compliance Congress and Best Practices Forum
November 3, 2011

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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

Systemic errors can render trial data unreliable

- Poorly designed protocols and ancillary documents
  - Inadequate attention to study feasibility
- Poorly executed protocols
  - Inability to verify critical efficacy and safety data
  - Missing data for critical endpoints
- Inadequate internal processes to ensure
  - Integrity of critical study activities (e.g. randomization)
  - Study and vendor oversight
  - Data quality control

Analysis of OSI Reviews of Marketing Applications1 Indicates Opportunities for Improvement Remain

1. *Meeker-O'Connell and Ball FDLI Update 2011;2: 8-12*

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

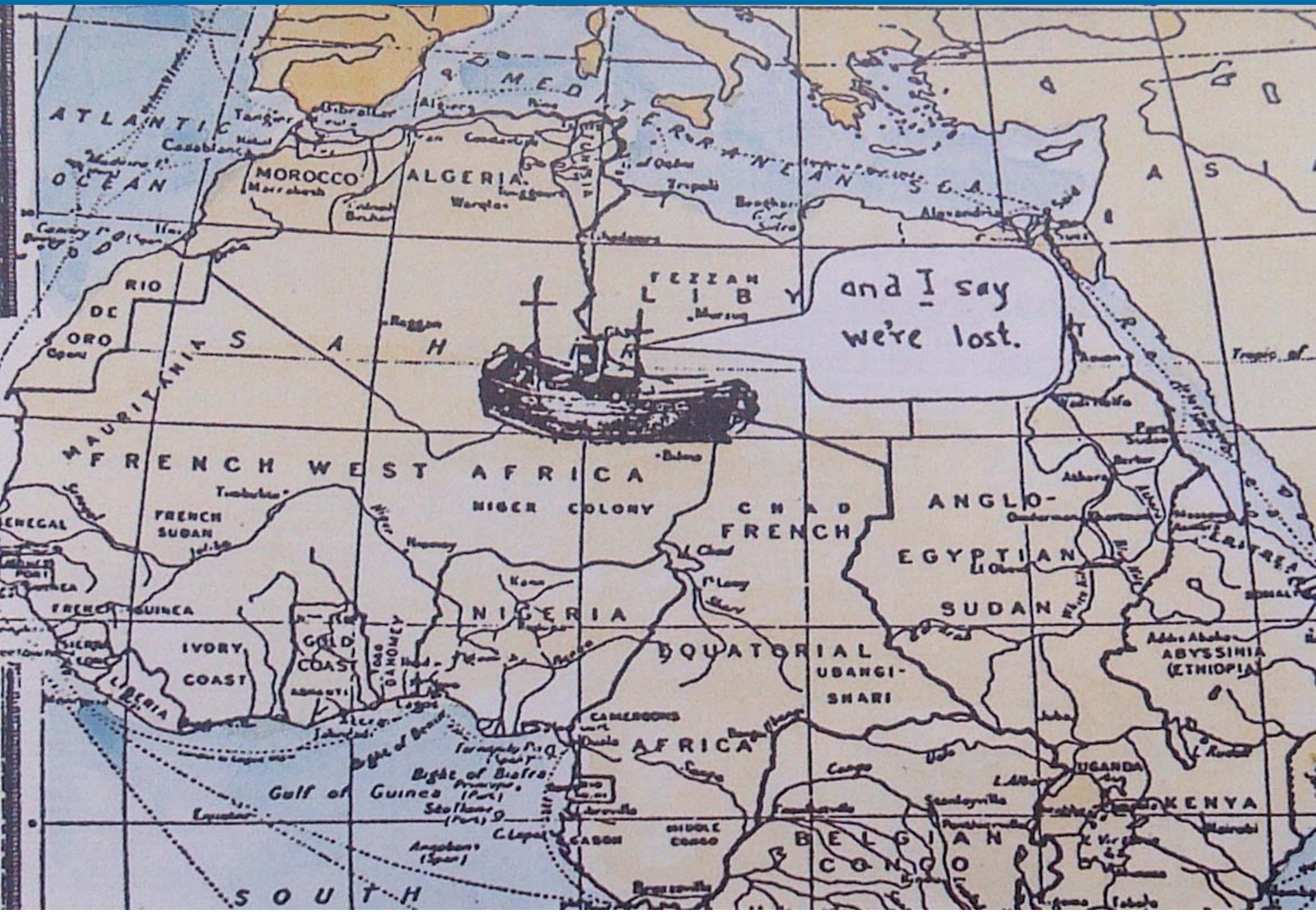
- Rejection of data for 4% of clinical investigators inspected in association with the related NDAs and BLAs
- Significant data integrity concerns affected 5 inspected applications (5%)
- Some systemic errors persisted due to deficits in sponsor monitoring, but had a **root cause in study design and planning.**
- For 2/5 applications, concerns arose from ***internal processes*** at the sponsor and CRO, unrelated to clinical investigator activities

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

1: Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: IOM Workshop Report 1999.
2. Sensible guidelines for the conduct of large randomized trials. Clin Trials 2008 5: 38


and I say we're lost.
ATLANTIC OCEAN
MOROCCO
ALGERIA
MEDITERRANEAN SEA
FEZZAN
LIBYA
RIO DE ORO
MAURITANIA
SAHARA
FRENCH WEST AFRICA
NIGER COLONY
FRENCH SUDAN
SENEGAL
FRENCH GUINEA
IVORY COAST
GOLD COAST
DAHOMEY
NIGERIA
CHAD
FRENCH EQUATORIAL AFRICA
UBANGI-SHARI
CAMEROONS
GABON
MIDDLE CONGO
BELGIAN CONGO
ANGLO-EGYPTIAN SUDAN
ABYSSINIA (ETHIOPIA)
UGANDA
KENYA
LIBERIA
Gulf of Guinea
Bight of Biafra
SOUTH

Challenges Cause Uncertainty for Both Drug Developers and Regulators

How do we find a clear path forward?

1. Greater dialogue with all stakeholders
2. Identify / address areas in which current regulatory framework may:
   - Inadequately reflect evolving models of trial conduct
   - Unintentionally introduce inefficiency
3. Standardize / harmonize where feasible
4. Return to first principles: focus on "what matters"
5. Build quality into trials

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

Building Quality into Clinical Trials

- Quality cannot be audited or inspected in retrospectively
- "The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol."

  FDA Draft Clinical Monitoring Guidance (published 29 August 2011)
- At the trial level, the protocol is the blueprint for quality
  - Prospectively identify the important risks to subject safety and data reliability
  - Tailor the protocol and its delivery to eliminate or mitigate these important risks.
- Monitoring and auditing become <u>quality tools</u>

CDER is fostering the development of risk-based approaches to clinical trial oversight

- Pilot prospective review of a sponsor's risk-based integrated quality management plan (IQMP)
- Clinical Trials Transformation Initiative (CTTI) Project on Quality Risk Management: Making clinical trials fit for purpose
- Draft Guidance on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

Clinical Trials Transformation Initiative (CTTI)

- Public-private partnership between Duke University and FDA
- Conducts projects that will generate evidence to inform regulators and other stakeholders about strategies and practices that will improve the clinical research enterprise
- Comprised of over 50 organizations
  - Government agencies
  - Industry representatives
  - Patient and consumer representatives,
  - Professional societies
  - Investigator groups,
  - Academic institutions,
  - Other interested parties

August 2011 CTTI Workshop on Quality Risk Management: Making Clinical Trials Fit for Purpose

- First in a planned series of workshops to:
  - Develop quality-by-design and quality risk management principles applicable broadly to clinical trials and development programs
  - Identify and share best practices for implementing these principles
- Presentations will be available at: http://www.trialstransformation.org
- Workshop summary in development

Draft Clinical Monitoring Guidance (published 29 August 2011)

- FDA regulations are not specific about how sponsors are to conduct monitoring of clinical investigations and, therefore, are compatible with a range of approaches to monitoring
- FDA last provided comprehensive guidance on appropriate monitoring of clinical investigations in 1988
- FDA recently withdrew this guidance

FDA Draft Clinical Monitoring Guidance (published 29 August 2011)

- Focus is on monitoring of clinical investigators
- Makes clear that sponsors can use a variety of approaches to fulfill their responsibilities related to monitoring
- "No single approach to monitoring is appropriate or necessary for every clinical trial."
- Recommends that sponsors develop a monitoring plan that is
  - Tailored to the specific human subject protection and data integrity risks of the trial.
  - Ordinarily, includes a mix of centralized and on-site monitoring practices.

FDA Draft Monitoring Guidance Recommendations

- Identify "what matters" – critical study data and processes

- Perform and document a risk assessment to identify risks to these critical data and processes
  - What could go wrong?
  - What would be the impact?
  - Could we detect it?

> "Before setting out to identify and mitigate risks it is first necessary to establish the priorities that need to be addressed .... It is the risks that are a significant threat to those priorities that most merit the allocation of resource in their mitigation."
>
> European Medicines Agency (EMA) Draft Reflection Paper on Risk-Based Quality Management in Clinical Trials (4 August 2011)

CDER Efforts – Risk-based Oversight

- Risk-based inspection models
  - Currently being piloted
    - Application-related (NDA/BLA) risk-based site selection tool
    - IRB inspection model
  - Under development
    - Bioequivalence Inspection Planning tool
    - Risk-based Sponsor and CRO inspection prioritization tool to facilitate real-time, surveillance inspections

Questions or Comments?

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References

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  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

- EMA Draft Reflection Paper on Risk-Based Quality Management in Clinical Trials (4 August 2011)
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf