Responsible Sharing of Clinical Trial Data: An FDA Perspective

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Outline for today

- **The Landscape**
  - The call for transparency and access
    - Need for reproducibility and credibility
    - The promise vs. fear and loathing
  - What and why
  - The Critical Path Initiative
    - Need for new approaches to drug development
- **Data Sharing at FDA**
  - History
  - Impediments
  - A possible approach
- **Implications of data sharing**

Data Sharing

- **Why?**
  - transparency
  - Reproducibility, reanalysis
  - Identify new information: placebo effects, biomarkers, endpoints, trial designs
- **What?**
  - Summary reports
  - Patient or participant level data (how much?)
  - Unselected broad access vs. selected data release or managed analysis
- **For what purpose?**
  - Data dredging?
  - Answer specific questions?

Data Sharing – The Landscape

Critical Path Report and Opportunities List

- ***Need*: enhance the medical product regulatory science toolkit**
- ***Barrier*: addressing scientific hurdles to more effective and efficient medical product development and review often requires pooling of effort, data and resources**
- ***Opportunity*: leverage and analyze pooled clinical and pre-clinical data to (e.g.):**
  - Explore new or modified biomarkers or trial endpoints
  - Evaluate the predictability of pre-clinical safety data
  - Understand background rates of AEs in defined patient populations
  - Develop disease models and simulate clinical trials

Strategic Plan for Regulatory Science

- ***Priority 5* - Harness Diverse Data through Information Sciences to Improve Health Outcomes**
  - "Successful integration and analysis of data from … disparate sources would provide knowledge and insight not possible from any one source alone."

Data Sharing at FDA

- Analysis of multiple clinical and/or pre-clinical data sets provides an opportunity to advance the science of drug development
- It may be possible to combine or pool datasets in a way that provides a rich scientific resource, while preserving commercial interests of sponsors
- Building databases of pooled clinical data around specific disease indications is occurring in numerous consortia (e.g. CAMD)
- Process of gathering, pooling and curating datasets is extremely resource intensive – limited public and private resources should be focused on the most pressing regulatory science questions.
- FDA has historically applied knowledge gained from analysis of pooled data to improving drug development and review - this analysis could benefit from additional external expertise.

Creating Consensus through Consortia

Seven global consortia collaborating with 1,000+ scientists and 41 companies

CAMD	Coalition Against Major Diseases **UNDERSTANDING DISEASES OF THE BRAIN**
CPTR	Critical Path to TB Drug Regimens **TESTING DRUG COMBINATIONS**
CRITICAL PATH INSTITUTE MS	Multiple Sclerosis Outcome Assessments Consortium **DRUG EFFECTIVENESS IN MS**
PKD CONSORTIUM	Polycystic Kidney Disease Consortium **NEW IMAGING BIOMARKERS**
PRO CONSORTIUM	Patient-Reported Outcome Consortium **DRUG EFFECTIVENESS**
ePRO CONSORTIUM	Electronic Patient-Reported Outcome Consortium **DRUG EFFECTIVENESS**
PSTC	Predictive Safety Testing Consortium **DRUG SAFETY**

FDA

- Biomarkers
- Clinical Outcome Assessment Instruments
- Clinical Trial Simulation Tools
- Data Standards

CDISC

C-Path Online Data Repository

CRITICAL PATH INSTITUTE

CONSORTIUM	STUDY NAME	# OF STUDIES	TOTAL # OF PATIENTS/ SAMPLES (RANGE BETWEEN STUDIES)	STUDY DURATION (RANGE)	# OF DATA CONTRIBUTING MEMBERS
CAMD	ALZHEIMER'S DISEASE	22	6,172 (57-719)	12 WEEKS – 2 YEARS	9

FDA Experience – A Few Examples

Exploring modified clinical trial endpoints

Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology* 2013 Jun;144(7):1450-1455.e2

Quantifying drug efficacy and risks for a specific indication

Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. *J Clin Psychiatry* 2011 Apr;72(4):464-72

Evaluating the predictability of pre-clinical safety data

Predictivity of Non-Clinical Repolarization Assay Data for Clinical TQT Data in FDA Database. *Int J Toxicol* 2013 Jan-Feb;32(1):63

Understanding factors contributing to failure of pediatric trials

Pediatric Antihypertensive Trial Failures. Analysis of End Points and Dose Range. *Hypertension* 2008 Apr;51(4):834-40

Assessing tools for evaluating trial endpoints

Evaluation of Blinded Independent Central Review of Tumor Progression in Oncology Clinical Trials: A Meta-analysis, *Ther Innov Reg Sci* 2013 Mar;47(2):167-74

Development of disease models

Endpoints and Analyses to Discern Disease-Modifying Drug Effects in Early Parkinson's Disease., *AAPS J* 2009 Sep;11(3):456-64

Impediments to Data Sharing at FDA

- **Legal**
  - Data ownership
  - HIPAA/privacy
  - Proprietary information
- **Technical/Practical**
  - Format
  - Data standards, CDISC
  - Redaction
- **Resources**
  - Need to focus on FDA's key mission

Disclosure of Product Specific Non-Summary Safety and Efficacy Data

- **FDA laws and regulations already specify under which circumstances FDA can disclose product specific (unmasked) non-summary safety and efficacy data, including de-identified patient level data**
- **The criteria differ depending on the type of regulated product**
- **The circumstances under which FDA discloses this information and when EMA is contemplating disclosing this information are different.**

For example:

  - FDA generally discloses non-summary safety and efficacy data from a specific application only in response to a request under the Freedom of Information Act. EMA's proposal contemplates the proactive posting of certain non-summary clinical trial data from marketing applications.
  - EMA is contemplating disclosing the data after it makes a decision on an application, including a decision not to approve an application. FDA's regulations do not permit us to disclose information when we have issued a complete response letter, if the applicant is working on addressing the application deficiencies.

FR Notice: Masked and De-identified Non-Summary Safety and Efficacy Data

- The FDA is seeking public comments on whether certain study data could be made available after steps have been taken to remove information that would identify patients, as well as a specific product application or company, and whether any limitations should be put in place on its availability.
- Release of confidential commercial and trade secret information is not being considered under this proposal.
- Under this proposal, the FDA does not plan to make available any information related to a company's business arrangements contained within a product application (e.g. licensing agreements, supplier information)
- FDA does not plan to make available trade secret information under this proposal.
- *Such information will continue to be treated in a manner consistent with relevant statutory and regulatory provisions.*

FR Notice: Masked and De-identified Non-Summary Safety and Efficacy Data

- **FDA invites comments on the issues it should consider with respect to the availability of clinical and pre-clinical study data after steps have been taken to "de-identify" it by removing any personally identifiable information and "mask" it by removing data that could link it to a specific application or sponsor. Specifically, the agency is interested in comments from the public on the following topics:**
  - What factors should be considered in masking study data (e.g. should certain data fields be removed or modified; number of different products to pool within a class)?
  - Should there be any limitations on the agency's ability to make masked data available?
  - In addition to current FDA requirements to remove any names and other information that might identify patients, what other information should FDA consider when de-identifying the data?
  - Would regulatory changes facilitate the implementation of this proposal?
  - In what situations would disclosing masked data be most useful to advance public health?

FR Notice: Masked and De-identified Non-Summary Safety and Efficacy Data: **https://www.federalregister.gov/articles/2013/06/04/2013-13083/masked-and-de-identified-non-summary-safety-and-efficacy-data-availability.**

FR Notice: Additional Considerations

- **FDA's approach has been under development for several years – it is not linked to EMA proposal.**
- **FDA is not contemplating routine preparation and release of de-identified and masked clinical and non-clinical study data**
  - resource intensive - would divert scarce resources needed for the evaluation of urgently needed therapies
  - not a central focus of core regulatory mission
- **Emphasis: targeted opportunities to advance regulatory science**
- **Opportunity: focus limited FDA resources to address the most pressing regulatory science questions**
- **We encourage independently organized efforts to create, curate and share clinical trial datasets from all sources**

Other Efforts at Sharing Data

- **Industry**
  - GSK, Merck
- **Regulatory**
  - EMA
- **Journals**
  - BMJ
- **Institute of Medicine**
  - Forum and Study

Implications of Data Sharing

- **Structures and models**
  - Third party involvement?
  - Open source vs. requested data
  - Curation
  - Governance to access and analysis
  - Timing
  - Ownership/Donation?

Implications for Drug Development and the Clinical Research Enterprise

- **Cost**
- **Credibility**
  - Second guessing of results and regulatory decisions
- **Will trial design change?**
- **Competitive implications**
- **Impact on academics**