21st Century Drug Development: The Road to Consistency and Transparency

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Transparency and Consistency

2012

2009 FDA Transparency Initiative

2008 Emerging Science of Safety

2007 FDAAA

2006 Critical Path Opp List

2006 Drug Safety IM report

2004 Critical Path Initiative

1997 FDAMA amended definition of substantial evidence of effectiveness (based on a single study)

1982 Tamper Resistant Packaging Regulations

1970 First patient package insert with risks and benefits

1964 Declaration of Helsinki - protection of subjects health and rights

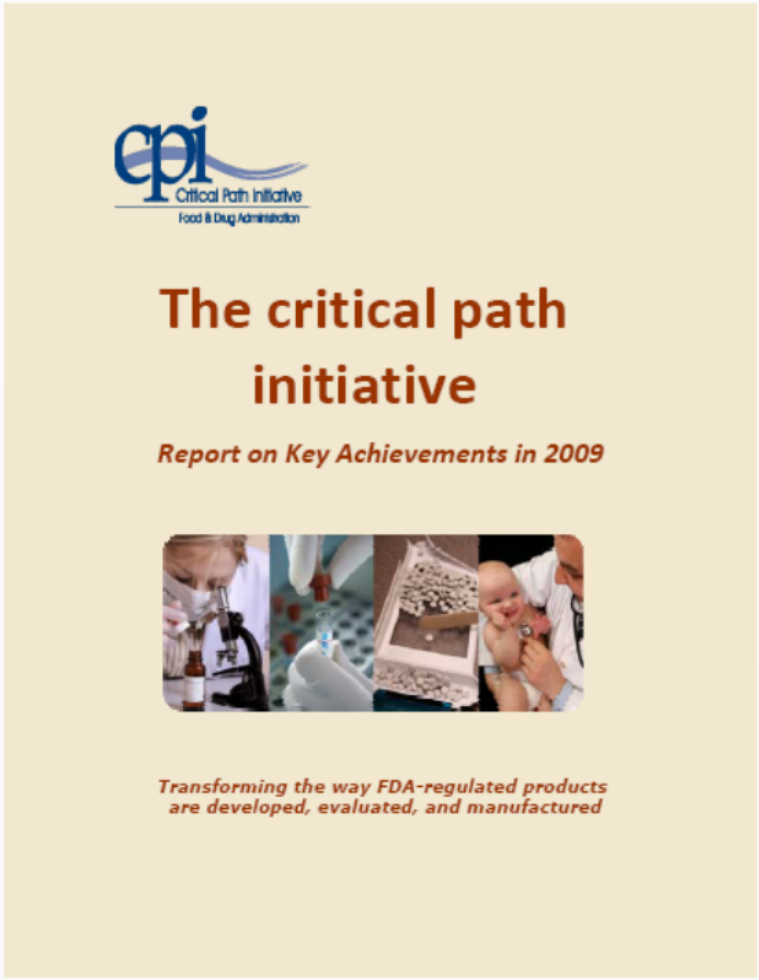
1962 Kefauver-Harris Amendment to FFDCA - proof of efficacy and safety before marketing

1938 Federal Food, Drug and Cosmetic Act - proof of safety

1906 Food and Drug Act - outlawed mislabeled food and drugs

US Regulatory Highlights

Critical Path Initiative (CPI)



- Launched in March 2004
- Landmark report - 'Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products' -> diagnosed reasons for widening gap between scientific discoveries and innovative medical treatments
- Conclusion: action was needed to modernize scientific and technical tools as well as harness information technology to evaluate and predict the safety, effectiveness, and manufacturability of medical products.
- Action: national effort to identify specific activities all along the critical path of medical product development and use to transform critical path sciences.

http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm

Critical Path Initiative

- March 2006 - FDA's Critical Path Opportunities List
  - Specific areas where the sciences of product development had the greatest need for improvement
  - Listed 76 specific examples where new scientific discoveries could be applied during development to improve the accuracy of tests that predict the safety and efficacy of potential medical products.
  - Divided among 6 topics

CPI Topics

1. BETTER EVALUATION TOOLS
   - Developing New Biomarkers and Disease Models to Improve Clinical Trials and Medical Therapy
2. STREAMLINING CLINICAL TRIALS
   - Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints
3. HARNESSING BIOINFORMATICS
   - Data Pooling and Simulation Models
4. MOVING MANUFACTURING INTO THE 21ST CENTURY
   - Manufacturing, Scale-up, and Quality Management
5. DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS
6. SPECIFIC AT-RISK POPULATIONS — PEDIATRICS
   - Unlocking Innovation in Pediatric Products

CPI TOPIC 2: STREAMLINING CLINICAL TRIALS
Creating Innovative and Efficient Clinical Trials and Improved Clinical Endpoints

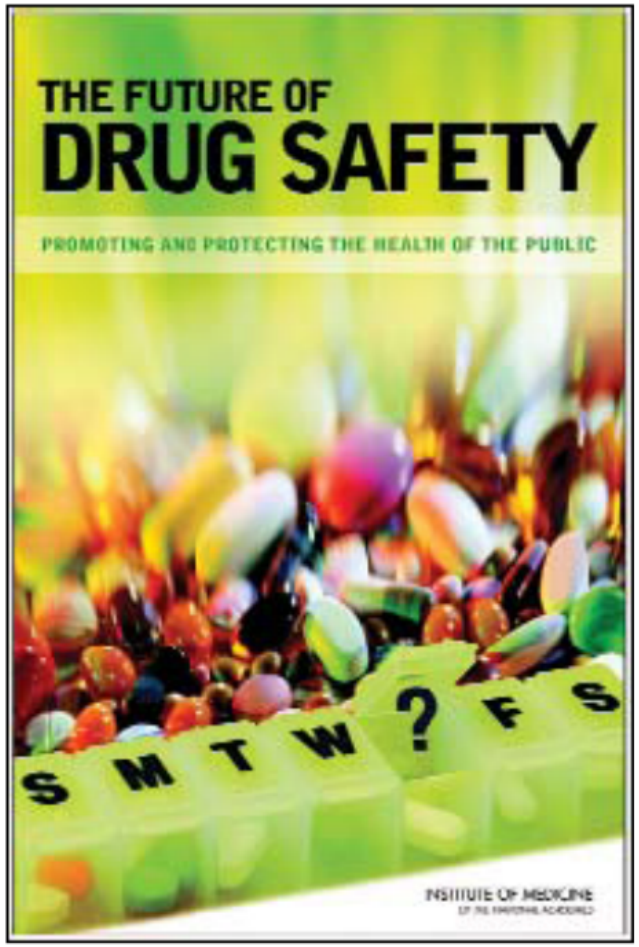
- Advancing Innovative Trial Designs
  - 34. Design of Active Controlled Trials
  - 35. Enrichment Designs
  - 36. Use of Prior Experience or Accumulated Information in Trial
  - 37. Development of Best Practices for Handling Missing
  - 38. Development of Trial Protocols for Specific Therapeutic Areas
  - 39. Analysis of Multiple Endpoints
- Improving Measurement of Patient Responses
  - 40. Measuring Disease-Related Symptoms
  - 41. Measuring Patient-Centered Endpoints
  - 42. New Trial Design in Oncology
  - 43. Improving Efficacy Endpoints for Infectious Diseases
- Streamlining the Clinical Trial Process
  - 44. Development of Data Standards ---> Will come back to this
  - 45. Consensus on Standards for Case Report Forms

Advancing Innovative Trial Designs

- 34. Design of Active Controlled Trials
  - Non-inferiority trials
  - Agree and clarify appropriate statistical methods and standards
  - New methods are needed for cases when prior data are insufficient to estimate the effect of a therapy
- 35. Enrichment Designs
  - Enriched trials (conducted in potential high response subgroup) have greater power and could result in therapies targeted at those most likely to benefit.
- 36. Use of Prior Experience or Accumulated Information in Trial
  - Adaptive trial design
  - Non-frequentist methods (Bayesian)
- 37. Development of Best Practices for Handling Missing Data
  - Alternatives to LOCF are needed.
  - Evaluation of different analytical approaches
  - Development of consensus on how to impute missing data in a variety of different situations
- 38. Development of Trial Protocols for Specific Therapeutic Areas
  - Consensus on trial designs that are tailored to specific diseases or conditions (e.g., how to select participants, structure of the trial, outcome and endpoint measures, duration)
- 39. Analysis of Multiple Endpoints
  - Key issues include the statistical implications of requiring success on more than one endpoint, appropriate statistical adjustment when endpoints are correlated, and handling of secondary endpoints.
  - Appropriate methods for sequential analyses of endpoints.

Institute of Medicine Report (2006)

- FDA asked IOM to convene a committee to assess the U.S. drug safety system
- Recommendations include:
  - Labeling requirements and advertising limits for new medications
  - Clarified authority and additional enforcement tools for the agency
  - Clarification of FDA's role in gathering and communicating additional information on marketed products' risks and benefits
  - Mandatory registration of clinical trial results to facilitate public access to drug safety information
  - An increased role for FDA's drug safety staff
  - A large boost in funding and staffing for the agency



Food and Drug Administration Amendments Act (FDAAA) – Sept 2007

- Greatly increased the responsibilities of FDA
  - Reauthorized drug user fees, medical device user fees, and statutes affecting pediatric uses of drugs
- Ensured that clinical trials information is provided to the National Institutes of Health (NIH) ClinicalTrials.gov.
- Regarding Drug Safety:
  - FDA has new authority to require postmarket studies and clinical trials, safety labeling changes, and Risk Evaluation and Mitigation Strategies.
  - Requires increased activities for active post market risk identification and analysis particularly those related to tools and methods for data access and analysis.

Initiatives around Drug Safety

- FDA identified a series of management initiatives designed to strengthen drug safety based on 3 components:
  - Detection of risks
  - Analysis and evaluation of the risks
  - Management of risks, including risk communication
- CDER initiatives: Safety First (drug safety during pre and post marketing have equal focus) and Safe Use (reduce preventable harm)
- Sentinel initiative: a national integrated electronic system to monitor medicinal product safety - can query public and private databases
- Emerging 'science of safety' - using molecular information to predict patient risk, state-of-the-art systems for surveillance, and a life cycle approach
- Emerging 'science of quantitative safety assessment' - eg., use of clinical trials with safety as endpoint, meta-analysis, rare events, use of epidemiology and observational databases
- FDAAA Enforceable requirements, eg., Risk Evaluation and Mitigation Strategies (REMS)

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Guidances: Responding to the need for Transparency and Consistency

Suicidality: Prospective Assessment of Occurrence in Clinical Trials

- Draft Guidance for Industry
  - Posted for public comment in Sept 2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf
- Prospective assessment of suicidality now being routinely done in NS clinical trials at GSK

Adaptive Design Clinical Trials for Drugs and Biologics

- Draft Guidance for Industry
  - Posted for public comment Feb 2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf
- Topics such as
  - what aspects of adaptive design trials (i.e., clinical, statistical, regulatory) call for special consideration
  - when to interact with FDA while planning and conducting adaptive design studies
  - what information to include in the adaptive design for FDA review
  - issues to consider in the evaluation of a completed adaptive design study.
- Note also:
  - EMA Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design (2007)

Non-Inferiority Clinical Trials

- Draft FDA Guidance for Industry
  - Posted for public comment March 2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf
- EMA Guideline on the Choice of the Non-Inferiority Margin (2005):
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003636.pdf
- EMA PtC on Switching Between Superiority and Non-Inferiority (2000):
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf

The Prevention and Treatment of Missing Data in Clinical Trials

- Panel on Handling Missing Data in Clinical Trials;
National Research Council, Committee on National Statistics (146 page document)
  - http://www.nap.edu/catalog/12955.html
- Thorough discussion and 17 recommendations

EMA Guideline on Missing Data in Confirmatory Trials

- Effective January 2011
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Safety Data Collection

- Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations
  - Draft Guidance Posted 02/09/12
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf

Monitoring

Draft guidance – issued August 2011 – describes a risk- based approach to monitoring, including the use of central monitoring
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

E7 Studies in Support of Special Populations: Geriatrics

- Published guidance
- Q&A document posted February 2012
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM189544.pdf

Assessment of Abuse Potential of Drugs

- Draft Guidance for Industry
  - Posted January 2010
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf
- Specifically, the guidance discusses the following:
  - The definition of abuse potential
  - Information on submitting an abuse potential assessment, including a proposal for scheduling
  - A description of what constitutes an adequate abuse potential assessment
  - Information for sponsors performing an assessment, including (1) the design and conduct of appropriate studies and investigations and (2) general administrative recommendations for submitting a proposal for scheduling

Draft Guidances CDER is Planning to Publish…

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf
- Highlighting a few…
  - CATEGORY — Clinical/Medical
    - Pregnant Women in Clinical Trials – Scientific and Ethical Considerations
  - CATEGORY — Clinical/Statistical
    - Multiple Endpoints
  - CATEGORY — Electronic Submissions
    - Electronic Submission of Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions
    - Providing Regulatory Submissions in Electronic Format

EMA: Subgroup Analyses in Randomised Controlled Trials

- Recommends drafting a guidance document on methodological issues relating to subgroup analyses
  - By the Biostatistics Drafting Group of EWP
  - Deadline for comments 31 Jul 2010 – unclear on status
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090116.pdf
- Guidance needs to be given on
  - Situations in which industry/applicants should present results from subgroups
  - How such comparisons should be made (using formal statistical methods or otherwise)
  - In what situations regulatory authorities should require to see subgroup analyses that companies have not otherwise submitted

EMA: Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population

- Presents an overview of applications for initial MAAs or extensions of indications, identifying several factors that could be of importance for extrapolation of data for different drug classes
- Identifies specific issues based on experience specific to the EU population and should be regarded as a reinforcement of the ICH E5
- To be used when deciding whether certain clinical trials conducted in a specific area of the world would be relevant to the EU setting or if there are reasons to perform additional clinical trials within the EU.
  - Effective May 2010
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013468.pdf

EMA: Draft Concept paper on extrapolation of efficacy and safety in medicine development
- June 2012

EMA: Need for active control

- Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available
- Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold-standard
- Where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application. The need for an active control must be considered on a case-by-case basis.
- Paper outlines a framework for the discussion and justification of the choice of control arms that is expected from an applicant in a marketing authorisation application.
  - Out for public comment – deadline for comments 31 Mar 2011
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/01/WC500100710.pdf

EMA Therapeutic Area Specific Guidance…

- Concept paper on proposed revision to the Guideline for the conduct of efficacy studies for NSAIDs (EMEA/CVMP/237/01)
  - Draft –consultation closed
  - Last updated 01 Sep 2010
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/06/WC500091532.pdf
- Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders
  - Effective August 2010
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070043.pdf

PMDA – 2 or more randomized controlled trials

- In order to ensure the reliability of the results, it would be desirable, in principle, for the efficacy to have been confirmed in "two or more randomized controlled studies."
- "Two or more randomized controlled studies" implies not only confirmatory studies, but also includes:
  - exploratory dose-finding studies with similar results to those of confirmatory studies
  - overseas clinical studies whose results can be extrapolated based on the results of a domestic bridging study

PMDA = Pharmaceuticals and Medical Devices Agency, Japan

PMDA - Differences caused by ethnic factors? (when foreign clinical data are submitted as the pivotal confirmatory data)

- Have an adequate number of Japanese cases been included?
- Have ethnic factors (intrinsic and extrinsic factors) described in the ICH E5 guideline been considered?
- Is the pharmacokinetic profile in the Japanese population similar to that in foreign populations?
- Is the dose-response relationship in the Japanese population similar to that in foreign populations?
- In the case where ethnic factors (intrinsic and extrinsic factors) are considered to be different, would the factors have any major impacts on the efficacy and safety?
- Have any specific risks been recognized in the Japanese population?

Multi-Regional Clinical Trials (MRCT) Seoul Workshop

http://www.pmda.go.jp/english/presentations/pdf/presentations_20100913-2.pdf

Biostatistics New Drug Application Review Template

- Establishes procedures for documenting the review of original NDAs in the Office of Biostatistics, Office of Pharmacoepidemiology and Statistical Science, CDER
  - http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM313814.pdf
- The following are examples of important statistical issues that may affect the results
  - Breaking the blind
  - Unblinded or unplanned interim analyses
  - High percentage of dropouts
  - Inappropriate imputation for missing values
  - Change of primary endpoint during conduct of the trial
  - Dropping/adding treatment arms
  - Sample size modification
  - Inconsistency of results across subgroups
  - Type I error inflation due to multiplicity

Where to look for other FDA Good Review Practices that might be of interest

- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm
- For example:
  - Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf

How can Industry respond?

Protocol and study quality by design

Transparency

Sponsor transparency to FDA (protocol compliance, analyses)

Sponsor transparency to public: posting of results – US, EU

FDA transparency to public: transparency initiative and website

Data quality and traceability

More detail rather than less...

Building Quality into Clinical Trials - An FDA Perspective (May 2012)

Quality - characterized by the ability to effectively and efficiently answer the intended question about benefit:risk WHILE ensuring protection of human subjects {2008, Behrman}.

Elements of a quality clinical study:

- Scientifically valid and ethically sound experimental design [guidances, input from key thought leaders, FDA&IRB reviews]
- Adequate protection of subjects rights, safety and welfare [informed consent, protocol deviations, personally identifiable information]
- qualified personnel [training at investigator meeting, retraining, experience]
- 'adequate' monitoring [compliance w/investigational plan and regulations, review of AEs and impact]
- complete and accurate data [collect essential data]

Clinical Studies Will Need More Design Details
FDA presentation at DIA on 14 June 2010

- New emphasis in protocols:
  - "Quality by design" elements needed to explain operational merits in addition to traditional scientific merit
  - Operational merit is becoming the "deal breaker"
  - For example:
    - Why one hundred sites? Why these sites? Who's monitoring them? What are the metrics of monitoring them? Tell me about the Saturday-morning training of your 100 investigators
    - i.e., substantiate they are real investigators and aren't going to make a mistake and aren't inducing more noise
- Part of the quality control – a metric that measures whether you've followed what you said you were going to do
- FDA are looking toward more quality-by-design thinking, which will require having much more of this as part of the planning document, as well as the analysis and interpretation document.

Other Factors Impacting Sponsors

- Data privacy issues
  - Potential impact on how we write our documents (to protect PII)
  - Will impact the informed consent (to clearly allow the use of data in research, but with protection of PII)
- FDAAA - CTR summaries
- Publication Policies - rules for conduct and disclosure of human subject research
- Documentation of planning of analyses beyond study objectives (data re-use and data sharing)
- EU will require posting SOON….

Transparency about FDA transparency…

- Website for tracking
  - Agency-wide Program Performance
  - FDA-TRACK Program Areas and Dashboards
  - Completed Key Projects
  - Significant Accomplishments to Date
  - Quarterly Briefing Summaries
  - http://www.fda.gov/AboutFDA/Transparency/track/default.htm
- Can also track submissions they have received by clicking on:
  - Center for Drug Safety and Evaluation (CDER)
    - FDA-TRACK CDER Office of Translational Sciences Dashboard
      - Office of Biostatistics

Submitting the clinical trial data

- One of the purposes of providing the data are so that the reviewers can ascertain:
  - Did we do what we said we were going to do?
  - Did we do it in the manner we said we were going to use?
  - If we did not, then why and what instead?
- Regulatory reviewers will verify that they can replicate our results.

How can this be facilitated for the reviewer?

- Follow a standard (preferably the one they request)
- Ensure high quality of the data package
  - Algorithms and derivations are clearly defined
  - Can "easily" figure out what was done and what data were used
  - Ensure traceability (starting with the result and tracing back to the analysis data and raw data

FDA/CDER and CDISC

- CDER has been collaborating with CDISC, a standards development organization, in the development of standards to represent study data submitted in support of regulatory applications.
- Study data standards are vendor-neutral, platform-independent, and freely available via the CDISC website (www.CDISC.org).
  - SDTM (Study Data Tabulation Model) for representation of clinical trial tabulations ['raw' datasets]
  - ADaM (Analysis Data Model) for clinical trial analysis files
  - SEND (Standard for Exchange of Non-clinical Data) for representation of nonclinical animal toxicology studies tabulations.
- Have boilerplate language they provide to sponsors encouraging the use of the CDISC standards

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm