FDA Perspective:
50 Years of Emphasis on Data Quality

Rachel E. Sherman, MD, MPH
Associate Director for Medical Policy
Center for Drug Evaluation and Research

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Substantial Evidence

- Substantial evidence is defined in the FD&C Act as:

  "*evidence consisting of adequate and well controlled investigations, including clinical investigations, by [qualified experts who could fairly and responsibly conclude that the drug will have the effect it purports or is represented to have in the labeling].*"

  (505(d) of the FD&C Act)

- Recent commentary on Kefauver-Harris Amendments see:

  [Greene, J. Reform, 2012, Regulation, and Pharmaceuticals – The Kefauver-Harris Amendments at 50, NEJM, 367:1481-1483.]

Applicable Regulations

- Adequate and Well-Controlled Studies are defined in FDA regulations at 21 CFR 314.126

- Clinical Holds and Requests for Modification:
  - FDA has the authority under 21 CFR 312.42(b)(4) to put on hold any trial that is not adequate and well controlled
  - FDA has the authority under 312.42(b)(2)(ii) to put on hold any phase 2 or phase 3 study clearly deficient in design to meet its stated objectives

International Guidances

- ICH-E8 General Considerations for Clinical Trials:
  - Describes internationally accepted principles and practices in the conduct of individual trials and overall development strategy for new medicinal products

- ICH-E9 Statistical Principles for Clinical Trials section 6.2:

  …the methods and measurements chosen to evaluate the safety and tolerability of a drug will depend on a number of factors, including knowledge of the adverse effects of closely related drugs, information from nonclinical and earlier clinical trials and possible consequences of the PK/PD properties of the particular drug, the mode of administration, the type of subjects to be studied…

U.S. Guidances

- Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations (AE Lite)
  - FDA is issuing this final guidance to help clinical trial sponsors determine the amount and types of safety data that should be collected during late-stage premarket and postapproval clinical investigations
  - AE Lite extends thinking that is present in ICH-E9

- Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring
  - Makes clear sponsors can use a variety of approaches to fulfill their monitoring responsibilities
  - Focus monitoring activities on important and likely risks to critical data and processes

Summary

Agency emphasis on data quality, not quantity and not proscriptive trial design

- Generalizability
- Labeling