American Course on Drug Development and Regulatory Sciences

Substantial Evidence in 21st Century Regulatory Science
Borrowing Strength from Accumulating Data

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WELCOME !

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Why are we here?

"*Substantial Evidence*"

- **1962: "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to *evaluate* the *effectiveness* of the drug involved, on the basis of which it could fairly and responsibly be *concluded* by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.**

- **1997: If the Secretary determines, based on relevant science, that data and evidence from *one adequate and well-controlled clinical investigation* and *confirmatory evidence* (obtained *prior* to or after such investigation) are sufficient to establish effectiveness**

Statistical Evaluation of Substantial Evidence

- **Traditional "frequentist" requirements: demonstration of a *low probability* ($p < 0.05$), assuming non-effectiveness, based on data from each of two phase III clinical trials.**
  - **Ignores pre-phase III evidence of *effectiveness*** from **randomized, blinded trials** trials, including ***dose-*** *and* ***exposure-response trials***
  - **Ignores prior causal evidence of effectiveness** by testing the null hypothesis, assuming of ***non-effectiveness***, leading to inefficient and weakly informative phase 3 hypothesis testing
- **For discussion today: demonstration of a *high probability of effectiveness* (> 90% ?) utilizing evidence of all reliable sources of effectiveness data.**

21st Century Cures Act

(proposed)

Section 2061(BROADER APPLICATION OF BAYESIAN STATISTICS AND ADAPTIVE TRIAL DESIGNS

-encourages FDA to issue guidelines and policy for ***"the use of adaptive trial designs and Bayesian methods in clinical trials, including clinical trials proposed or submitted to help to satisfy the substantial evidence standard under section 505(d) of the FD&C Act.***

Workshop Agenda

Session 1: ***Introduction and Motivations***

Session 2: ***Stakeholder Perspectives on the Use of Bayesian Methods in Drug Development and Regulatory Science (DD&R)***

Luncheon talk: "*Reverend Bayes Goes to Washington*"

Session 3: Opportunities to Advance the Use of Bayesian Methods for DD&R

Session 4: Substantial Evidence through a Bayesian Lens