Understanding the FDA Guidance on Adaptive Designs: Historical, Legal and Statistical Perspectives

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Outline

Introduction - Past, Now and Future

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  - PhRMA working group
  - CHMP and FDA (draft) guidance

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- Wave 3, after 2015
  - New evidential paradigm
  - Cloud based interactive analytics
  - Peer networking

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- Two-stage design with sample size adjustment
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- Adaptive error spending approach
  - Error spending approach controversial and not well-understood
  - Analysis with unknown (random) maximum information
- Adaptive designs with changing population

Major Challenges

Statistical Foundation

- Conditionality, sufficiency, and likelihood
- Neyman-Pearson approach versus significance test
- Multiplicity versus p-value as evidence
- Effective design versus efficient analysis
- Bayesian adaptive designs as inefficient group sequential designs
- Dose-response to quantify therapeutic range

Approaches to Innovation

- Academic research and consensus
- "Elites" versus grass-root
  - Regulatory agencies
  - Industry

Legal and Regulatory Basis - Sample Size Adjustment

Section 355 (b)(5)(C) of the Federal Food, Drug and Cosmetic Act (FD&C Act), June 25, 1938

"Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except —

(i) *with the written agreement of the sponsor or applicant; or*

(ii) *pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."*

Legal and Regulatory Basis - Adaptive Designs Framework

21 CFR 312.23, prior to April 1, 1992 Revision

"In phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of non-responders to an alternative therapy."

- Adaptations with alternatives or contingencies
- Type of adaptations specified in the protocol
- No requirement for pre-specified algorithm leading to adaptations, consistent with practice in group sequential designs where boundaries are guidelines but the ultimate decisions depends on totality of data and clinical judgment

AD Guidance Statistical Issues - Modeling and Simulations

FDA AD Guidance (1321-1323)

"*Some modeling and simulation strategies lend themselves to a Bayesian approach, ..., the study design is still able to maintain statistical control of the Type I error rate in the frequentist design*"

Foundation of Clinical Trial Design and Analysis

- Controlling the SIZE of the test at a given type I error rate
- Properties of a procedure established on a solid mathematical foundation
- Assumptions clearly stated, and robustness against violations of the assumptions evaluated
- Theoretical and methodological work, independently verifiable and peer reviewed
- Mathematical Statistician (HHS Employee Directory)

AD Guidance Statistical Issues - Modeling and Simulations

Background

- FDA guidance documents are required by FD&C Act
- Long history of inter-agency conflicting philosophies
- Special interest groups, lacking a broader industry participation

Limitations of Modeling and Simulations

- Calibration of type 1 error rates with extremely limited simulation models
- Adaptation as rule rather than guidance, ignoring real time decision making with totality of accumulating efficacy and safety data
- Verifiability, partiality and robustness (e.g., NMAR)

Current Progress at the FDA

- Many IND examples across different therapeutic areas
- Seemly an agency wide consensus (e.g., public meetings)

AD Guidance Statistical Issues - Dose-Response

PhRMA Working Group Report on Dose-Finding

- Misleading report and presentations, lack of a broader industry participation
- Methodology issues from prior literature purposefully ignored
- Selective simulation settings to hide weakness of the procedures
- Lower probability for detecting the target dose, higher attrition to phase 3
- Partial reports of the totality of the research

Resolution

- 2006 JSM presentation, discussion paper by Liu and Chi (2010)
- FDA awareness of partial report since late 2011
- Upcoming manuscript

AD Guidance Statistical Issues - Error Spending Approach

Critique of the Error-Spending Approach by D.R. Cox (2004)

"Indeed, I believe that many statisticians approaching statistics from a broadly frequentist perspective are uneasy at notions such as "spending error rates", perhaps because these treat notions of error rates as more than just hypothetical concepts used for calibrating measures of uncertainty against performance in idealized situations. While in some situations there may be compelling quasi-political arguments, as well as cost considerations, pointing against too frequent an analysis, in principle it is hard to see an argument at a completely fundamental level."

Approaches to Innovation

FDA

- Many enthusiasts in early FDA regulatory research history
- One or two advocates at the FDA
- Supports from broad review divisions and therapeutic areas
- New generation of grass-root researchers

Industry Needs

- Innovative design driven by subject area experts
- Regulatory acceptable to achieve business objectives
- Effectiveness based on clinical development program

"Elites"

- Job hopping, communication and collaboration skills, etc.
- Statistical knowledge, technical and mathematical skills
- Subject areas, basic science and public health needs
- Practical trial experience in industry and regulatory settings

Closing Remarks

D. R. Cox (Chatfield, 1991)

"*Most real life statistical problems have one or more nonstandard features. There are no routine statistical question; only questionable statistical routines.*"

Reference

Liu, Q. and Chi, G. Y. H.(2010). Understanding the FDA guidance on adaptive designs: historical, legal and statistical perspectives. *Journal of Biopharmaceutical Statistics*, **20**, 1178-1219.