CDER and CBER Experience

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Acknowledgments

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- Dr. Issam Zineh, Director, Office of Clinical Pharmacology, OTS, CDER

Background

Levels of FDA policy

- Statutes are laws enacted by Congress
- Regulations are binding interpretations of the law
- Guidance documents are non-binding descriptions of FDA's current thinking on a topic

1962 Amendment to FD&C Act

- Substantial evidence was defined in Federal Food, Drug, and Cosmetic Act, section 505(d) as:

  "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."

- Traditional interpretation in CDER is that 2 confirmatory (phase 3) trials with p-value<0.025 (one-sided) required to demonstrate effectiveness

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

- Published in 1998
- Quantity and quality of evidence
- Importance of independent substantiation
- Single-study submissions with supportive evidence

Clinical Pharmacology and Evidence Guidance

- Provides supportive evidence of effectiveness:
  - Extrapolation of findings for an approved product to a new population, e.g., pediatrics
  - Extrapolation to different dose, regimen, or formulation
  - Extrapolation to untested settings, e.g., adjunctive to monotherapy
- Provides evidence for a new drug:
  - As one of two A&WC trials (e.g., phase 2 dose-finding study)
  - Mechanistically supportive of a single trial, e.g., via PD biomarker
  - To identify subsets of patients with more favorable benefit-risk, e.g., when drug is toxic
  - With exposure-response modeling
  - To determine contributions of components of a combo therapy

Bayesian Statistics in CDER/CBER

- 2004 FDA Conference on Bayesian Methods → special issue of *Clinical Trials*
- 12 years later—What's happened since then?
  - Endorsed for exploratory phases of drug development
  - Use in confirmatory trials is mixed
  - Reasonably active research area in CDER/CBER Biostatistics

CDER/CBER Experience

Preponderance in oncology/hematology (both Centers)

- 2013 snapshot (CDER): 8 trials using Bayesian methods
  - 3 phase 3 trials
  - 15 phase 1/2 trials
- 2006-2013 survey (CBER): 4 trials using Bayesian methods
  - 2 phase 2 trials
  - 2 phase 3/4 trials
- Designs/methods proposed (examples):
  - Dropping an arm or restricting population based on conditional probability, or predictive and posterior probability
  - Adaptive Bayesian logistic regression model with escalation overdose control (single-arm dose-finding study)
  - Modified continual reassessment methods (CRM), modified toxicity probability interval with adjustment based on DLT

CDER/CBER Experience

Platform trials in oncology

- I-SPY II – phase 2/exploratory
  - Common biomarker screening platform
  - Response-adaptive randomization
  - Candidate therapies 'graduate' to phase 3
- I-SPY III -- phase 3/confirmatory
  - Brookings meeting held to discuss trial designs for accelerated approval in curative disease settings, e.g., neo-adjuvant breast cancer
  - Design incorporating Bayesian adaptations based on a biomarker assessed at interim that is predictive of clinical endpoint

CDER/CBER Experience

Anti-bacterial drug development

- CTTI Statistics Think Tank meeting August 2012 to discuss innovative approaches to non-inferiority trials (follow-up meeting in 2015)
- Proposals (with subsequent publications for most)
  - Bayesian meta-analysis with down-weighting of observational study data relative to RCTs
  - Bayesian NI trial with historical data as prior for control arm; credible intervals/Bayes rule for decision
  - Proposed alternative to single-arm studies of resistant pathogens (critical unmet medical need) incorporates unbalanced randomization (2:1, 3:1, or higher) with leveraging of historical control data to increase power
  - Multiple infection sites studied in single trial with Bayesian hierarchical modeling
- Potential master protocol discussed at FDA/NIH meeting (2014)

CDER/CBER Experience

Safety analyses

- Methods for handling multiplicity due to multiple hypotheses in safety trials (research and application)
- Avandia AC background package: Statistical review includes our use of Bayesian methods to analyze data from several studies, some of which had zero events of interest. The use of Bayesian methods here served as a sensitivity analysis, supporting the conclusion from the frequentist meta-analysis, presented at the 2010 AC meeting.
- Cardiovascular safety trials --- see next slide

Bayesian Methods for Large Safety Trials

- FDA has required large safety trials in several therapeutic areas
  - Type II diabetes, weight loss, asthma (LABAs)
  - Large number of high risk patients required, e.g., >600 events in diabetes trials
- Bayesian and other methods are being explored to provide comparable information with less patients, more timely
- CDER critical path funding supports a graduate student working collaboratively with thesis advisor and CDER statisticians to explore Bayesian methods for safety trials
- Proposal to incorporate prior information on control drugs into Bayesian model in a robust and transparent manner
  - Control data provide prior info on piece-wise exponential baseline hazard model
  - Power priors may be used to down-weight discrepant prior information

Moving Forward

- Barriers to broader acceptance -- internal
  - Education (methods and software) for reviewers
  - Getting buy-in from clinical colleagues
  - Subjective nature of priors
  - Type I error control
  - Concern with bias from 'borrowing information'
  - Resources (reviewer's time required for extensive simulations)
- Barriers – external
  - Skepticism of regulators' acceptance
  - Lack of consistency across therapeutic areas/divisions in what is accepted
  - Lack of examples that can be publicly discussed

Moving Forward

Areas that seem particularly ripe for innovation through application of Bayesian methods

- Rare diseases
  - Patients are scarce resource; difficult to enroll
  - Randomization may not be feasible
  - Most in need of borrowing information/leveraging other data sources
- Pediatric diseases with adult trial data available
  - Bayes hierarchical modeling – CDRH guidance
  - Formal priors based on adult data -- discussed at 2004 conference
  - DIA working group on Bayes methods for pediatric trials (Tiwari, Thompson, Price, Gamalo, others) – position paper forthcoming

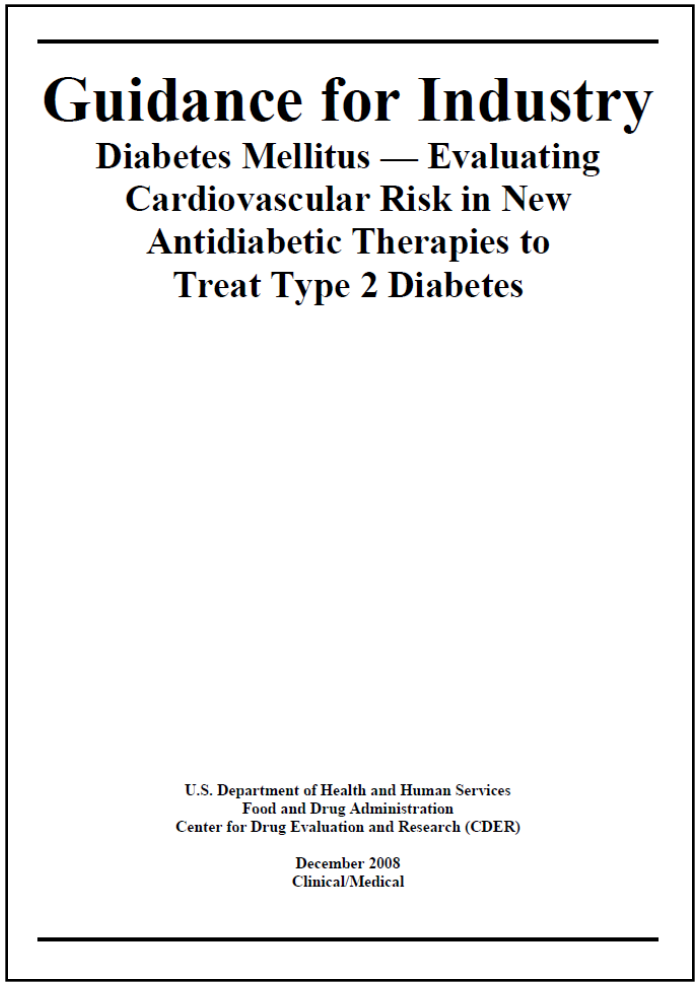
Bayesian Research in CDER

Selected topic areas

- Non-inferiority trials
- Meta-analysis
- Drug safety analysis
- Active and passive drug surveillance
- Benefit-risk
- Bayesian subgroup analysis

BACK-UP SLIDES

T2DM Guidance (2008)



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Establishes Regulatory Thresholds for Evaluating Cardiovascular Risk

- **Stage 1**: H_0: HR ≥ 1.8
- **Stage 2**: H_0: HR ≥ 1.3

Adaptive designs in CBER

DIA DEVELOP INNOVATE ADVANCE

Analytical Report

Therapeutic Innovation & Regulatory Science
1-10

DOI: 10.1177/2168479015604181
tirs.sagepub.com

CBER's Experience With Adaptive Design Clinical Trials

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Abstract

There is considerable interest among pharmaceutical and other medical product developers in adaptive clinical trials, in which knowledge learned during the course of a trial affects ongoing conduct or analysis of the trial. When the FDA released a draft Guidance document on adaptive design clinical trials in early 2010, expectations were high that it would lead to an increase in regulatory submissions involving adaptive design features, particularly for confirmatory trials. A 6-year (2008-2013) retrospective survey was performed within the Center for Biologics Evaluation and Research (CBER) at the FDA to gather information regarding the submission and evaluation of adaptive design trial proposals. We present an up-to-date summary of adaptive design proposals seen in CBER and provide an overview of our experiences. We share our concerns regarding the statistical issues and operational challenges raised during the review process for adaptive design trials. We also provide general recommendations for developing proposals for such trials. Our motivation in writing this paper was to encourage the best study design proposals to be submitted to CBER. Sometimes these can be adaptive, and sometimes a simpler design is most efficient.

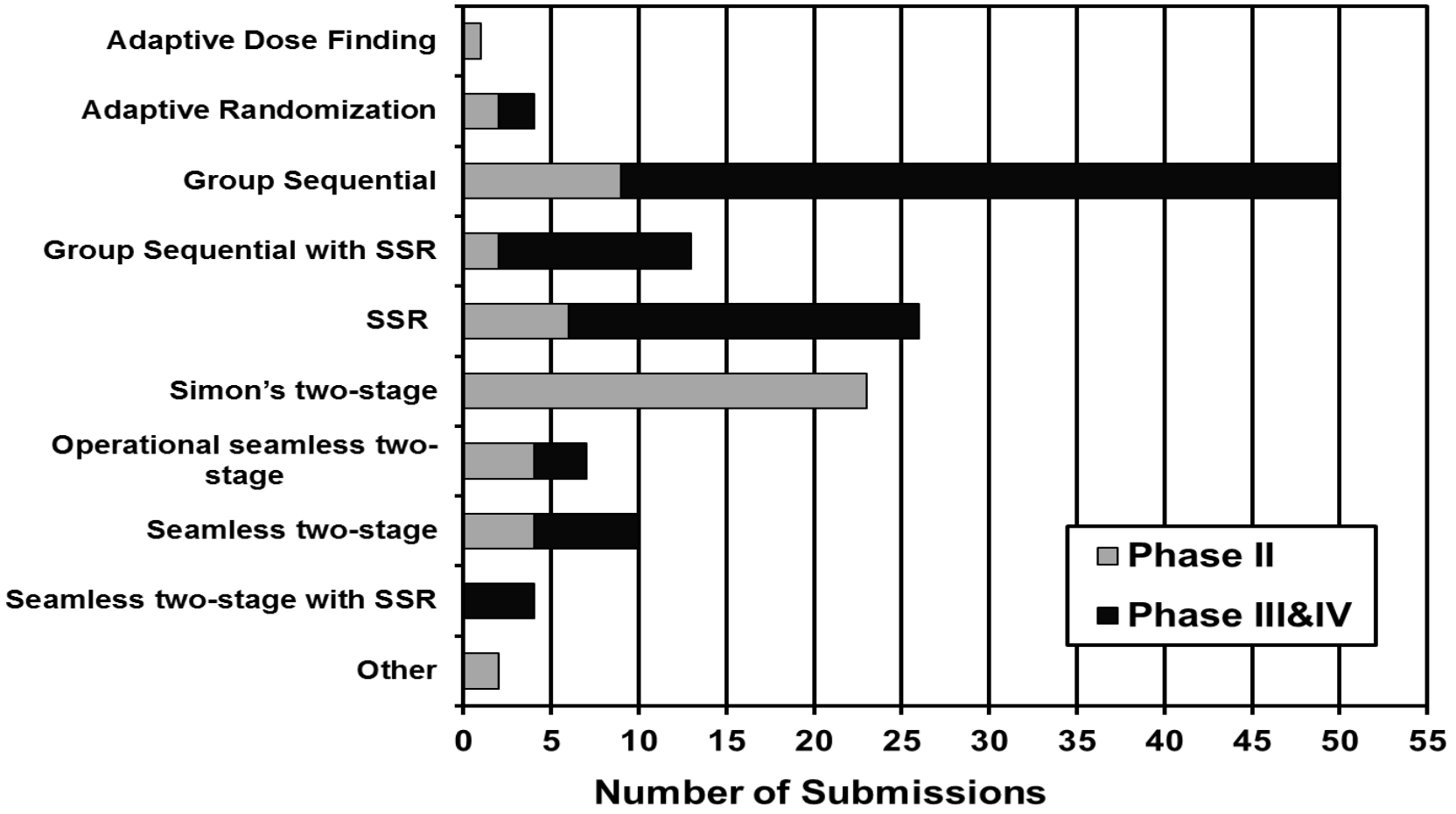
Keywords

adaptive design, FDA, clinical trial, survey, biologics

CBER AD survey

- Survey of IND and IDE statistical reviews from 2008-2013
  - Phase II - IV
  - Number of submissions assigned: 12,095
  - Number of review memos screened: 1,225
  - Number of submissions involving AD components: 140
- Results broken down by CBER product office:
  - Vaccines (OVRR)
  - Blood (OBRR)
  - Cell, tissue, gene therapy (OCTGT)

Type of AD by trial phase



Trial characteristics by phase

		Study Phases		
		II	III&IV	Overall
		(N=53)	(N=87)	(N=140)
Trial design	Blinded	19 (35.8%)	58 (66.7%)	77 (55.0%)
	Parallel controlled	25 (47.2%)	84 (96.6%)	109 (77.9%)
	Randomized	25 (47.2%)	83 (95.4%)	108 (77.1%)
Methodology	Frequentist	45 (84.9%)	70 (80.5%)	115 (82.1%)
	Bayesian	2 (3.8%)	2 (2.3%)	4 (2.9%)
	Unclear	6 (11.3%)	15 (17.2%)	21 (15.0%)
Guidance category	Well-understood	36 (67.9%)	49 (56.3%)	85 (60.7%)
	Less well-understood	10 (18.9%)	22 (25.3%)	32 (22.9%)
	Unclear	7 (13.2%)	16 (18.4%)	23 (16.4%)
Review outcome	No comments	29 (54.7%)	23 (26.4%)	52 (37.1%)
	Need clarification	24 (45.3%)	64 (73.6%)	88 (62.9%)

Bayesian Research in CDER

Non-inferiority trials

1. Gamalo, M., Wu , R., Tiwari, R. Bayesian Approaches to noninferiority testing with binary endpoints. *Journal of Biopharmaceutical Statistics* **21**: 902-919
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3. Gamalo, M., Tiwari, R., LaVange, L. Bayesian Approach to the Design and Analysis of Non-inferiority Trials in Anti-infective Drugs, *Pharmaceutical Statistics*, 2014, 13(1): 25-40.
4. Pulak Ghosh, Farouk Nathoo, Mithat Gonen, Ram C. Tiwari; Assessing noninferiority in a three-arm trial using the Bayesian approach. *Statistics in Medicine* 30 (2011): 1777-1816

Bayesian Research in CDER

Non-inferiority trials (Continued)

5. Ghosh, S., Basu, S., and Tiwari, R. Bayesian approach for assessing non-inferiority in a three-arm trial with pre-specified margin, *Stat in Meth*, 2015, DOI: 10.1002/sim.6746

Bayesian Research in CDER

Meta-Analysis

1. Lin J, Gamalo-Siebers M, Tiwari R. Non-inferiority and networks: inferring efficacy from a web of data. Pharm Stat. 2015 Dec 7. doi: 10.1002/pst.1729

2. Muthukumarana, S. and Tiwari, R. Meta-analysis using Dirichlet Process. *Stat Methods Med Res* published online 16 July 2012.

Bayesian Research in CDER

Drug Safety Analysis

1. Bradley W. McEvoy and Ram C. Tiwari , Discussion of "Multivariate Bayesian Logistic Regression for Analysis of Clinical Trial Safety Issues" by W. DuMouchel *Statist. Sci.* Volume 27, Number 3 (2012), 340-343

2. McEvoy, B., Nandy, R.R., and Tiwari, R.C. Bayesian approach for clinical trial safety data using an Ising prior, *Biometrics*, 69 (2013), 661-672

Bayesian Research in CDER

Active and Passive Drug Surveillance

1. Lan Huang; Jyoti Zalkikar; Ram C Tiwari, Likelihood ratio test-based method for signal detection in drug classes using FDA's AERS database *Journal of biopharmaceutical statistics* 2013;23(1):178-200.

2. Na Hu, Huang, Lan, Tiwari, Ram C. Signal detection in FDA AERS database using Dirichlet process, *Stat in Med., 2015*

Bayesian Research in CDER

Benefit-Risk Analysis

1. Yueqin Zhao, Jyoti Zalkikar, Ram C. Tiwari, and Lisa LaVange, Bayesian approach to benefit: risk assessment (with Yueqin Zhao and Jyoti Zalkikar), *Statistics in Biopharmaceutical Research* 6 (2014), 326-337.
2. Shiqi Cui, Yueqin Zhao, and Ram Tiwari (2016), Bayesian approach to personalized benefit: risk assessment, *Statistics in Biopharmaceutical Research* , accepted.

Bayesian Research in CDER

Cluster Analysis

1. Man-Wai Ho, Wanzhu Tu, Pulak Ghosh, and Ram C. Tiwari; A Nested Dirichlet Process Analysis of Cluster Randomized Trial Data with Application in Geriatric Care Assessment, *JASA* 108 (2013): 48-68