# Bayesian Submissions to FDA and the Evidentiary Standard for Effectiveness: the CDRH Experience

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# Outline

- Evidentiary Standard for Medical Device Approval in the US
- A Little History
- FDA Bayesian Guidance
- Accomplishments
- Reporting results
- Concluding remarks

# Device Evidentiary Standard for PMAs: Valid Scientific Evidence

- Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use. (CFR 860.7 (c)(1))

# Evidentiary Standard for Device Effectiveness

- There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations. CFR 860.7 (e)(1)

# Contrast with Drug Regulation

- Valid scientific evidence not substantial evidence.
- Well controlled investigations not adequate and well controlled investigations
- For effectiveness, principally (not primarily) from well controlled investigations

- No advice in the law or in the regulation about the use of frequentist (or Bayesian) statistics, no advice about p-values and the use of Type I error probability as a success criterion

# International Harmonization and Bayesian Statistics

- ICH E-9 "Guidance on Statistical Principles for Clinical Trials" for pharmaceutical products
- "Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate; the use of Bayesian and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust."

# Why Did CDRH at FDA Launch the Bayesian Effort in 1998?

- Devices often have a great deal of prior information.
  - The mechanism of action is physical (not pharmacokinetic or pharmacodynamic) and local (not systemic)
  - Devices usually evolve in small steps whereas drugs are discovered.
- Computationally feasible due to the gigantic progress in computing hardware and algorithms
- The possibility of bringing good technology to the market in a timely manner by arriving at the same decision sooner or with less current data was of great appeal to the device industry.

# Secrets of Success

- Support at all levels in CDRH:
  - Bruce Burlington, David Feigal, Dan Schultz, Jeff Shuren, Larry Kessler
- The educational and outreach efforts
  - HIMA/FDA Workshop "Bayesian Methods in Medical Devices Clinical Trials" in 1998.
  - FDA internal course "Bayesian Statistics for Medical Device Trials: What the Non-Statistician Needs to Know" in 1999 and 2001.
  - Lots of short courses and seminars and one-on-one consults

# Bayesian Workshop

- "Can Bayesian Approaches to Studying New Treatments Improve Regulatory Decision-Making?" held May 20-21, 2004, at NIH
- Jointly sponsored and planned by FDA and Johns Hopkins University
- Presentations by Janet Woodcock, Bob Temple, Steve Goodman, Tom Louis, Don Berry, Greg Campbell, 3 case studies and panel discussions.
- August, 2005 issue of the journal *Clinical Trials* is devoted to this workshop

# Prior Information: Two Extremes

- Complete Prior Information
  - no data needed; data do not change the prior engineering understanding
- No Prior Information (***de novo*** trial)

- Medical device trials are often somewhere in between.
- Why is there prior information?
  - The physical mechanism of action of the device may be well understood and local as opposed to systemic.
  - In contrast, if a small change is made to a drug formulation, the change is usually systemic.

# Bayesian Approach: Different Decision Rule

- Companies (sponsors) deserve to understand what constitutes success in a clinical trial. For most trials this has been couched as a statistically significant result for the primary effectiveness endpoint using hypothesis testing, reported as a P-value.
- A Bayesian approach has a different decision rule, based on the posterior distribution.

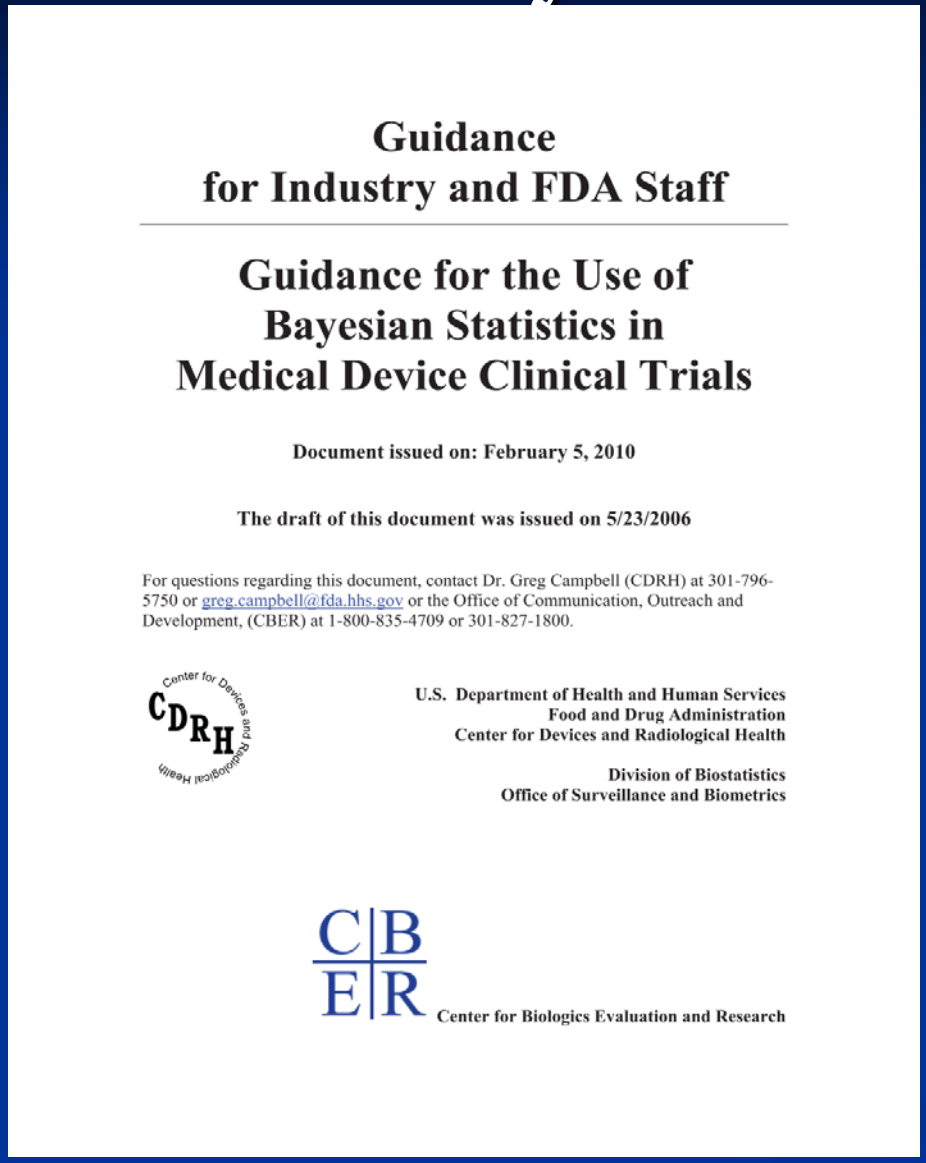
# What are the Differences?

- If you use a non-informative prior, you can get approximately the frequentist inference.
- But if there is prior information, if one company has a lot of good prior data and another company none, why should you treat them the same? Why would you ask companies with good prior information to behave as if they know nothing?
- When there is prior information, the decision criterion is adjusted accordingly, so the posterior prob. criterion is determined by the design and the simulations so as to ensure Type I error control (which helps to protect the US public from approving products that are ineffective or unsafe).

# The Choice of the Prior

- Emphasis at FDA is to rely on empirically generated priors, using data from clinical studies agreed upon in advance by the company and FDA
- The rationale:
  - Subjective priors can be based on all kinds of information.
  - Ability to evaluate a subjective prior within FDA without using other proprietary information is difficult.
  - Prior elicitation can be difficult and time-consuming.
  - Debate about priors could ensue at Advisory Committee Panel even if FDA and industry agree on subjective prior.
  - Worry about robustness to priors: enthusiastic, skeptical, reference
- Use simulation to understand the operating characteristics of the design (Type I error control and power)

# Bayesian Guidance



Guidance
for Industry and FDA Staff

Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials

Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

For questions regarding this document, contact Dr. Greg Campbell (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

Center for Biologics Evaluation and Research

- Finalized February 5, 2010.
- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf

# CDRH Guidance

- Guidance advocates that Bayesian trials are designed and analyzed prospectively (like all other trials) and that the prior is agreed to in advance.
- Guidance advocates two approaches:
  - Use prior information from agreed upon previous studies with patient-level data and "borrow strength" adaptively with a Bayesian hierarchical model
  - Use information during the trial to adapt the trial during its course. Usually no prior information outside the adaptive trial is employed (although it could be). The BIG advantage here is to model the primary outcome in terms of intermediate endpoints.

# Hierarchical Bayesian Modeling

- Use a hierarchical model and place usually non-informative priors at the highest level of the hierarchy
  - For example, consider a number of past studies and the current one, each with different numbers of patients and assume that the patients within a study are exchangeable and the studies are exchangeable among each other.
  - Place a (non-informative) prior to reflect the distribution of the studies. With no prior studies, one obtains results very similar to a frequentist analysis.
  - This model borrows strength adaptively from past studies to model the current study.

# Bayesian and Adaptive Designs


- Campbell, G. (2014). Similarities and differences of Bayesian designs and adaptive designs for medical devices: A regulatory view. *Statistics in Biopharmaceutical Research* **5**(4): 356-368.
- Draft Guidance for Industry and Food and Drug Administration Staff: Adaptive Designs for Medical Device Clinical Studies. Issued May 18, 2015. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446729.pdf

# Bayesian Statistics: Submissions to CDRH

- Many Original PMAs (or Supplements) have been approved and a number of IDEs (planned designs) have been approved for Bayesian trials as well as several applications for "substantial equivalence" (510(k)s).
- For all publicly available trials on FDA website as of 2011, see:

Campbell, G. (2011). Bayesian statistics in medical devices: Innovation sparked by FDA. *J. Biopharm. Statist.* **21** (5): 871-887.

# Bayesian Clinical Trial Publications

- Recent publications in the literature that are non-methodological but are scientific reports of confirmatory Bayesian device trials for marketing:
  - Holmes, D.R., Reddy, V.Y. et al (2009). Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* **374**: 534-542.
  - Stone, G.W., Martin, J.L. et al. (2009). Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. *Circulation Cardiovascular Interventions* **2**: 366-375.
  - Castro, M., Rubin, A.S. et al (2010). Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *American Journal of Respiratory Critical Care Medicine* **181**: 116-124.
  - Wilber, D.J., Pappone, C., et al (2010) Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* **303**: 333-340.

# Concluding Remarks

- An exciting time in the world of statistics and in medical devices.
- Bright future for Bayesian adaptive trials and for trials that use prior information
- An example of innovation at FDA

# Thank You

- "…the term "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." Food Drug and Cosmetic Act 21 USC § 355(d)

- There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed. (CFR 314.126 (a)(7))

- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. (CFR 314.126 (a))
- Substantial evidence was defined in section 505(d) of the Act 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."