

DATE: August 19, 2006

TO: Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments about FDA's Guidance on the Use of Bayesian Statistics in Clinical Trials

BY EMAIL TO: <http://www.fda.gov/dockets/ecomments> or greg.campbell@fda.hhs.gov.

ACTION: Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS), a biomedical consulting firm, comments on Federal statistical analyses of products for clients. As such, CTRAPS has standing to comment about Federal statistical policy. CTRAPS submits these comments in response to (the Food and Drug Administration's) FDA's call for public comments about a proposed guideline, Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials [Federal Register 71: 29651 (May 23, 2006)]. Please note that CTRAPS staff attended a public meeting about the proposed policy on July 27, 2006, as announced in the Federal Register 71(125): 37084 (June 29, 2006). CTRAPS appreciates the opportunity to comment on the proposed guideline.

SUMMARY: The FDA Center for Devices and Radiological Health's (CDRH's) proposed Bayesian statistical procedures appears to be a strange mixture of Bayesian and frequentist approaches, which requires much additional statistical work. The point of view that CTRAPS adopts in these comments is intuitive. Dr. Ron Howard once commented about the rarity of seeing elephants on your property, unless you know that a circus has camped near your property, in which case you will not feel surprised to see one. This view is intuitively Bayesian.

In summary, CTRAPS has the following comments: FDA's has written clear guidance about the use of Bayesian methods, but the guidance is a strange mixture of Bayesian and frequentist approaches.

(A) Previously, FDA (and the regulated community) wanted to know whether random chance produced the data from a clinical trial. The answer to this question required much calculational work and difficult decision making. The decision required some assumptions that were inconsistent with data. The proposed guidance does not clarify how FDA proposes to use Bayesian methods in demonstrating that two data sets differ. (A new device outperforms one used previously.) Bayesian methods often become identical to frequentist methods in this application.

Reviewers found these calculations useful. Now, FDA seems to propose to use a more Bayesian approach to interpret the meaning of a clinical trial.

(B) The result has been a strange mixture of Bayesian and frequentist approaches. FDA has explained the false-positive, false negative perspective that the Agency adopts in the guidance,

using a frequentist approach. Instead, the proposed implementation of a Bayesian approach will require more calculations. Applicants will have to submit calculations that use both methods.

(C) In the proposed guidance FDA makes much of the necessity for an uninformative prior distribution for use with a Bayesian approach to clinical studies. CTRAPS found this guidance difficult to understand unless CDRH intends to cease using animal data about medical devices. Admittedly, nonhuman data are difficult to acquire with medical devices. However, widespread adoption of a Bayesian statistical approach in FDA, which CTRAPS advocates, will prove difficult unless CDRH explains how to use animal data to form a prior distribution. For food additives, as regulated by the Center for Food Safety and Nutrition (CFSAN), the standard is already set before a firm designs an initial clinical trial. [Also see 7//06//05, Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Center for Drug Evaluation and Research (CDER).]

(D) To cope with the difference between frequentist and Bayesian approaches, CTRAPS suggests that CDRH emphasize initial assumptions about sample space and entropy. For example, frequentist methods often assume that someone has drawn data from an infinite space, whereas Bayesian methods assume that the existing data are all anyone ever gets to see. Similarly, entropy acquires a different meaning (Chen and Rosenfeld, 1999; Ratnaparkhi *et al.*, 1994).

(E) CTRAPS hopes that FDA will persist in writing understandable prose and will continue with its focus on regulation.

(F) A public health dimension or perspective exists to the implementation of Bayesian methods in clinical trials. Bayesian methods hold out the prospects of fewer subjects and shorter durations in clinical trials. Thus, a Bayesian approach means fewer subjects at risk per information gained. It is not a matter of cost.

CTRAPS thought that dating the change in statistical methods to 1997 was disingenuous. Perhaps 30 years have elapsed since the advent of Bayesian methods. Thus, CTRAPS suggests that FDA look to the statistical literature to rationalize a change in methods, not to revisions in the Federal Food, Drug and Cosmetics Act..

(G) The choice of a model will prove crucial in FDA's guidance. Indeed, the guidance explains FDA's preferred model, which is a good fit to CDRH's mission. The problem resembles one common to decision analysis. Uncertainty is not symmetrical between the known and the unknown. Neither CDRH, nor a petitioner, can know what is unknown.

Sincerely yours,

Karen L. Engdahl, B.F.A.
President,
Consultants in Toxicology, Risk Assessment and Product Safety

Literature cited:

Stanley F. Chen and Ronald Rosenfeld, A Gaussian prior for smoothing maximum entropy models. **(In)** [*Technical Report CMUCS-99-108*] Carnegie Mellon University, Pittsburgh, PA (1999).

Adwait Ratnaparkhi, Jeff Reynar and Salim Roukos, A maximum entropy model for prepositional phrase attachment. **(In)** *Proceedings of the ARPA Human Language Technology Workshop*, pp. 250 (1994).