Comment on FDA Draft Guidance Document Entitled "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials"

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I would like to congratulate the FDA Center for Devices and Radiological Health (CDRH) on the excellent draft guidance document entitled "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials." The document clearly represents the product of substantial work and an appropriate compromise between statistical innovation and a recognition of the strengths of traditional statistical approaches to device trials.

The guidance document wisely stresses the importance of sound clinical trial design and conduct, with the specific goal of minimizing sources of bias. Appropriate emphasis is also placed on meetings with the FDA with the goal of agreeing on prior information to be used during both the design and analysis of the proposed pivotal trial. *Nonetheless, I believe the document could be strengthened by explicitly mentioning the value of conducting sensitivity analyses to changes in assumed prior information during trial simulations, to account for the diversity of priors which may represent the beliefs of the sponsor, clinical and engineering experts, and the regulatory agency.* Such Bayesian robustness assessments can be valuable in ensuring that the proposed study design will yield evidence that is convincing to a wide range of important stakeholders who may hold different prior beliefs regarding the effectiveness of a device.

At the public meeting held July 27, 2006 in Rockville, Maryland, FDA presenters stressed the FDA's commitment to avoiding the conduct of trials with a high likelihood of falsely suggesting a device is safe and effective or, conversely, a high likelihood of being inconclusive or falsely concluding that a device is ineffective or unsafe. The latter concern is motivated by a desire to avoid placing research subjects at risk without the likelihood of substantial contribution to knowledge and/or the welfare of future patients. It is with this apparent motivation--avoiding trials with high false-positive or false-negative risks-- that the agency is requesting simulations to determine traditional frequentist error rates for proposed Bayesian designs, conditioned on single point assumptions regarding the parameter of interest. While I understand and acknowledge that such trial characteristics are useful when comparing proposed Bayesian designs to traditional frequentist trials and may therefore provide important benchmarks, the best measure of the potential of a trial to yield an erroneous conclusion is not an error rate conditioned on a point assumption regarding the parameter of interest but, alternatively, one conditioned on a true prior belief or the set of possible prior beliefs held by divergent stakeholders.

For these reasons, *I would strongly encourage the FDA to revise the guidance document to explicitly request that the primary simulations of a planned trial to determine false positive and false negative error rates be conditioned on realistic prior distributions for the parameter of interest, especially for those situations in which the sponsor and the Agency are able to agree in pre-trial meetings on the prior information to be utilized.*

When no agreed-upon prior information exists, these simulations should generally consider a range of plausible priors.

These Bayesian error rates will generally be much smaller than the traditional frequentist type I and type II error rates, since they appropriately incorporate the contributions of parameter values that fall some distance from the point null hypothesis or the point alternative hypothesis. Thus, the Agency's comfort with different levels of these Bayesian error rates will require recalibration, hence the continued importance of also defining the traditional frequentist error rates for the proposed trial designs. Nonetheless, the draft guidance should also be revised to explicitly mention that, while traditional frequentist error rates need to be determined, no specific targets for these rates is implied for a Bayesian trial design.

Again, I would like to congratulate CDRH on this excellent draft guidance. I believe it will be of substantial use to sponsors, clinical trialists, and regulators alike in defining recommended practices for the Bayesian design and analysis of medical device trials.