Review of the CDRH/CBER Bayesian Guidance

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"Global Regulatory Viewpoint" addresses various regulatory and compliance topics including newly published regulations. This column discusses regulatory information from a global perspective. The content in this column is useful to those who deal with pharmaceutical development, expectations for CMC sections of regulatory dossiers, and guidance for manufacturing, validation, and CGMPs.

Reader comments, questions, and suggestions are requested to help us fulfill our objective for this column. Please contact column coordinator Richard Poska at richard.poska@abbott.com or coordinating editor Susan Haigney at shaigney@advanstar.com for further information.

KEY POINTS

The following key points are addressed in this article:

- On February 5, 2010, the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) issued a final Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials
- The guidance furthers the US Food and Drug Administration’s efforts to foster innovation, efficiency, and sound science in the industry
- The guidance joins, after two and a half centuries, two seminal concepts: scientifically rigorous, prospective clinical trials and Bayes rule
- The appearance of the guidance represents a paradigm shift in allowing the objective use of data-based prior information to better inform the interpretation of clinical trial results
- Bayesian approaches have the potential of reducing the size of a clinical trial, but may require additional resources in planning the trial, analyzing the results, and interpreting and reporting the conclusions
- The guidance is based on the substantial experience the agency has had with Bayesian clinical trials as well as more than three years’ worth of input from industry and academia
- Great care is needed in the selection and justification of prior information to be included in the analysis of trial results
- Despite a history of many successful pharmaceutical Bayesian clinical trials, the Center for Drug Evaluation and Research (CDER) was not a sponsor of the new guidance
• The generality of Bayesian approaches suggests an increasing number of applications throughout the pharmaceutical and medical device industries, including, perhaps, process and method validation.

INTRODUCTION
On February 5, 2010, the US Food and Drug Administration’s Center for Devices and Radiological Health (CDRH) issued its Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (1). The appearance of this guidance represents another milestone in the agency’s efforts to foster innovation, science-based development, and knowledge building. Like the Center for Drug Evaluation and Research (CDER)-sponsored process analytical technology (PAT) guidance (2), process validation guidance (3), and International Conference on Harmonisation (ICH) guidances (4) before it, this new document is consistent with the agency’s efforts to get safe and effective products to market faster. Also, in the spirit of these earlier efforts, it represents a paradigm shift toward a continuous learning approach to planning, monitoring, interpreting, and reporting clinical research.

A Brief History Of Clinical Trials
To appreciate the magnitude of the shift, it is helpful to review some history. British naval surgeon James Lind was a pioneer in the application of a rigorous clinical trials approach that included a hypothesis to be tested (e.g., dietary acids could cure scurvy) and a systematic experimental design (e.g., Lind used six parallel groups each receiving a different supplement including a “sea water” control). His trial (performed in 1747) demonstrated that citrus fruits cure scurvy.

From 1800 onwards, clinical trials proliferated and more attention was paid to statistical design and interpretation. Placebos were first used in 1863. In the 1920s, R.A. Fisher introduced randomization and the p-value (<0.05) as a measure of statistical significance. The first trial using properly randomized treatment and control groups as well as blinding to remove bias was carried out in 1948 by the British Medical Research Council to test the treatment of tuberculosis by streptomycin. Since 1945, the ethical impact of clinical trials has become increasingly important, resulting in strict regulation of medical experiments on human subjects (e.g., Nuremberg Codex, 1947 and the Declaration of Helsinki, 1964-2001).

Clinical trials have evolved into a standard decision tool, focusing on patient safety, informed consent, prospective design, rigorous statistical analysis, and promoting evidence-based medical practice. The statistical approaches in clinical studies have used prior information from previous studies only at the design stage, not as a part of formal decision making at the data analysis stage. However, FDA is mandated to consider the least burdensome and appropriate means of evaluating effectiveness of a device that would have a reasonable likelihood of resulting in approval. The agency thus walks a difficult tightrope, balancing medical progress with patient safety.

A Brief History Of Bayesian Statistics
In 1762, James Lind’s “An Essay On The Most Effectual Means Of Preserving The Health Of Seamen” led the British navy to adopt his recommendations. Remarkably, one year later in 1763, the work of another British pioneer, Thomas Bayes, was published. “An Essay Towards Solving A Problem In The Doctrine Of Chances” showed how data from a new experiment can be supplemented with prior knowledge to make a more informed interpretation of experimental results. Bayes’ Rule is a probabilistic recipe for learning from evidence as it accumulates.

Bayesian statistical methods make it possible for companies to combine data and mechanistic knowledge from previous studies with data collected in a current trial. The combined information may provide sufficient justification for smaller or shorter clinical studies without sacrificing the goal of evidence-based medicine. Until recently, wide-scale use of Bayesian methods was infeasible because of the intractable mathematics. However, modern computing power and algorithms now make it possible to take advantage of Bayesian continuous knowledge building.
After 250 years, this new guidance reunites these two seminal concepts: a scientifically rigorous and safe experimental approach to clinical trials plus a statistically sound way of incorporating prior knowledge to make better decisions.

**History Of The New Guidance**

This new guidance grew out of the substantial experience the agency has had with Bayesian methodology in clinical trials. FDA has approved a number of medical devices whose submissions utilized Bayesian statistical methods, as follows:

- About 5-10% of CDRH submissions are Bayesian
- At least 20 original pre-market approvals (PMAs) and PMA supplements have been approved with a Bayesian analysis
- The PMA supplements include stent systems, a heart valve, and spinal cage systems
- Many investigational device exemptions (IDEs) have also been approved
- Several device applications for “substantial equivalence” (510(k)s)
- As of 2009, a number of device reviews are in process.

The draft version of this guidance was issued on May 23, 2006 for comment. A public meeting to discuss the document was held on July 27, 2006. FDA received several hundred specific comments on the guidance, many of which were incorporated into the final guidance. The agency has also held a number of joint workshops and internal courses on the use of Bayesian methods (5, 6). So the final guidance includes input from across the medical device industry.

**WHAT DOES THE GUIDANCE SAY?**

The final guidance describes use of Bayesian methods, design and analysis of medical device clinical trials, the benefits and difficulties with the Bayesian approach, and comparisons with standard statistical methods. The guidance also presents ideas for using Bayesian methods in post-market studies. The guidance indicates that a correct Bayesian approach could be less burdensome than a traditional statistical approach.

The guidance suggests the following information to be included in clinical trial protocols to facilitate Bayesian trial designs:

- Prior information to be used and the assumptions made
- A criterion for success of the study
- Justification of the proposed sample size
- Tables of the probability of satisfying the study claim
- Evaluation of the prior probability of the study claim
- Simulations of the trial at the planning (or IDE) stage.

These and other suggestions are explained in detail within the guide.

Incorporated into the guidance are the following lessons drawn from the agency’s experiences with Bayesian approaches:

- There is a need to educate industry and the FDA review staff on Bayesian approaches
- There may be a need for new decision-rules for clinical study success
- Bayesian trials need to be prospectively designed
- It is rarely a good idea to switch from traditional to Bayesian approach (or vice versa)
- Companies using Bayesian trial design need to meet early and often with CDRH because the entire FDA review team plays a prospective role
- Both the device label and the Summary of Safety and Effectiveness may need to change
- A successful company generally has a solid Bayesian statistician (or someone who really wants to learn) as an employee or consultant
- Computer simulation to anticipate the operating characteristics of a Bayesian design is recommended.

As with all FDA guidance, this new document represents the agency’s current thinking. It does not create or confer any rights for or on any person and does not bind FDA or sponsors, or disallow alternative approaches that satisfy the requirements of the applicable statute and regulations.
The new guidance does not mean that future submissions should employ Bayesian approaches. Most submissions received by CDRH use traditional statistical methods. Most statisticians in the agency are non-Bayesian. The mere use of Bayesian approaches in submissions will not, by itself, increase chances of approval. Whatever statistical approaches are employed in submissions should be appropriate to the study objectives and the availability of prior knowledge. The agency recognizes that while Bayesian approaches may often offer a lower clinical burden, they may require a greater statistical and computational burden.

**What About P-Values?**

Traditional clinical studies rely heavily on statistical methods that employ p-values as a decision making metric. From a traditional perspective, a clinical study is viewed as one instance of a series of repeated hypothetical trials. The design of the study is such that if in fact there is no medical benefit of the treatment, the p-value corresponds to the probability of incorrectly concluding treatment efficacy (also known as the Type 1 error). The agency believes that keeping this Type 1 error probability low (0.05 is typically required for “statistical significance”) protects the US public from approving products that are ineffective or unsafe. The use of p-values as a measure of evidence in clinical decision-making is not universally accepted, however (7). In any case, statistical significance alone should never imply clinical significance.

Bayesian methods do not rely on p-values. Instead, they consider the predictive value of the data, in light of prior knowledge, as a measure of evidence for or against efficacy. By focusing on the data in a particular trial, rather than on the expected outcome of a hypothetical series of trials, Bayesian methods are operationally less constrained. The study design can be more flexible and interim analyses can be employed to optimize sample sizes and treatment allocations as the study progresses.

However, just because Bayesian methods do not inherently rely on the hypothetical repeated trial p-value concept, does not mean that this metric is not available when Bayesian methods are used. Modern computer simulation allows us to evaluate the Type 1 error rate of any statistical decision making approach, including Bayesian approaches. So the agency recommends preliminary simulations to calibrate the Type 1 error (or some analog of it) and show that it is well-controlled. Simulations can also be of help in estimating the approximate size of the trial and the strategy of interim looks.

**Sources Of Prior Information**

Approval for devices often depends on a great deal of prior information. According to 21 CFR 860.7, valid scientific evidence for a PMA may come not only from well-controlled clinical studies, but also from case histories and reports of significant human experience, as follows:

- Company’s own previous studies: pilot studies, studies conducted overseas, very similar devices, data registries
- Permission legally obtained to use another company’s data
- Studies published in the literature
- Summaries of previous studies may not be sufficient to formulate apriori (e.g., patient-level data are often necessary).

Care is recommended to be sure that prior knowledge is used objectively. The guidance recommends the following:

- Prior information should be data-based to remove subjectivity
- Companies need access to good prior information to make it worth their risk
- FDA needs to work with the companies to reach an agreement on the validity of any prior information
- The prior information needs to be identified in advance as well as be agreed upon and be legal
- The control group cannot be used as a source of prior information for the new device, especially if the objective is to show the new device is non-inferior.
BAYES BEYOND MEDICAL DEVICES?

As it stands, the guidance refers to medical devices (not drugs nor combination drug/device products) regulated by CDRH or perhaps products such as blood screening tests jointly regulated by CDRH and CBER. Bayesian approaches lend themselves well to the following types of problems that often occur in medical device studies:

- Incorporation of data-based prior information into a current trial, allowing the data from the current trial to “gain strength” (8)
- More accurate or robust prediction models based on surrogate variables
- Analysis of multi-center trials (e.g., use hierarchical models to address variability among centers)
- Subgroup analysis
- Sensitivity analysis for missing data
- Need for trial design flexibility (e.g., to optimize trial treatment outcome or for early trial stoppage for success or futility, see reference 9).

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.

However, the use of Bayesian approaches to pharmaceutical trial design also has a long and successful history. The M.D. Anderson health science center in Houston has participated in more than 200 Phase I, II, I/II Bayesian trials. Examples of pharmaceutical products from industrial sponsors include ASTIN (Pfizer) and Pravigard PAC (BMS).

Despite these and other outstanding examples of pharmaceutical clinical trials that have benefited from Bayesian approaches (10, 11, 12, 13), CDER (which regulates pharmaceutical products) did not appear as a sponsor of this new Bayesian guidance. This may be because there is a perception that prior information for drugs is inherently more subjective or that the operating characteristics (Type I error and study power) are not as clear in the pharmaceutical trials setting. FDA has at times required Bayesian designs to employ more conservative Type I errors (e.g., 0.025) or to use analyses that employ “non-informative priors” (i.e., that take advantage of the flexibility of Bayesian approach without utilizing prior information).

By comparison with pharmaceutical submissions (e.g., new drug application [NDA]), medical device companies are more numerous and smaller. Innovation in medical devices is often evolutionary with incremental improvements every 1-2 years. Submissions for medical devices include IDE, PMA, and 510(k), rather than an NDA. Clinical studies for such devices may include only a single trial (two are usually required for drugs) in which blinding may be difficult. The Phase I-IV designations used for drug trials usually don’t apply. The mechanism behind such devices (e.g., drug eluting stents, pacemakers, joint replacements) may be based on non-biological, well-known mechanical processes with localized effects.

While the characteristics of medical device clinical studies may make them good candidates for Bayesian approaches, it would be a mistake to conclude that Bayesian methods should not be applied more broadly. When one strips away the safety and ethical issues associated with any clinical trial (device or pharmaceutical), it is no more than a prospective scientific experiment whose objective is to test a hypothesis and/or estimate some underlying parameter. Regardless of the phenomenon under study (e.g., mechanical, physical, chemical, or biological), it is in this more general experimental setting that Bayesian approaches apply. A decision whether to consider Bayesian approaches should not be based solely on the field of application, but more generally on the experimental objectives and applicability of prior knowledge in a specific situation.

BAYES BEYOND CLINICAL TRIALS?

Bayesian approaches are appearing at an ever increasing pace in all areas of regulated industries. Some examples include the following:

- **Coverage decisions.** Healthcare payers are contemplating the role Bayesian methods could play in making coverage decisions. In a June 2009 public meeting, the Medicare Evidence Development & Coverage Advisory Committee encouraged Medicare policymakers to consider
Bayesian approaches when reviewing trials or technology assessments during the national coverage analysis process (14).

- **Health outcomes research.** Bayesian approaches lend themselves to probabilistic and risk-based decision theory so that risk and benefit can be judged in public health terms. A readable account of the pros and cons of Bayesian approaches in this field is available in reference 15.

- **Quality by design.** Bayesian approaches offer a predictive probabilistic metric for process optimization and design space identification for drug products (16). This is particularly appropriate for manufacturing risk assessment when multiple quality characteristics must be controlled.

- **Process monitoring and control.** Bayesian approaches have been used to advantage in manufacturing lifecycle management (17). Certainly when the sponsor organization wants to make internal quality decisions based on the results of prior experiments, Bayesian approaches may allow more informed decisions.

- **Pharmacovigilance.** Safety assessment is one area where traditional strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise (18). The guidance states that the Bayesian approach is also good for surveillance purposes. Information may be updated as provided by a pre-market clinical trial with post-market data if exchangeability between pre- and post-market data can be justified (19).

- **Process or method validations.** FDA has recently emphasized the importance of statistical methods with respect to process validation (3). Aside from the human and safety aspects, the process qualification (validation stage 2) may be viewed as a prospective experiment much like a clinical trial with prior information available from the process design stage, or from previous experience with similar processes. Thus Bayesian approaches may be appropriate if prior knowledge can be justified and/or if Bayesian approaches offer a more informed assessment of risk. As an example, substantial prior information may be available when revalidating a process or method at a new location.

**CONCLUSIONS**

Conventional statistical approaches to clinical trials work are widely accepted, and for many problems, are well documented. Bayesian methods, on the other hand, hold great promise for making more informed and more economical clinical decisions because they can incorporate prior knowledge. With its probabilistic foundation Bayesian thinking offers greater power and flexibility and provides results in a more natural and intuitive form. We expect its use to become well established not only in clinical trials of all types, but in other areas of pharmaceutical and medical device development, lifecycle, and health outcomes management. FDA is to be commended for taking the initiative and introducing this guidance.

**REFERENCES**

6. Clinical Trials 2(4) (volume 2 August 2005 issue is devoted to the application of Bayesian methods in clinical trials).


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