FDA Bayesian Statistics Guidance for Medical Device Clinical Trials—Application to Process Validation

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"Statistical Viewpoint" addresses principles of statistics useful to practitioners in compliance and validation. We intend to present these concepts in a meaningful way so as to enable their application in daily work situations.

The comments, questions, and suggestions of the readers are needed to help us fulfill our objective for this column. Please contact our coordinating editor Susan Haigney at shaigney@advanstar.com with comments, suggestions, or manuscripts for publication.

KEY POINTS

The following key points are addressed:

- On February 5, 2010, the US Food and Drug Administration Center for Devices and Radiological Health and Center for Biologics Evaluation and Research issued a final *Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials*.
- The guidance furthers FDA'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.
- The generality of Bayesian approaches suggests an increasing number of applications throughout the pharmaceutical and medical device industries, including process validation.
- The Bayesian approach offers a rigorous way to quantify prior information and to combine it with confirmatory validation results to obtain better estimates of critical process characteristics and more informed decisions about process fitness.
- A simple example is provided to illustrate the intuitive nature of the Bayesian approach.
- Bayesian approaches have the potential of reducing the size of a validation qualification (process validation stage 2), but may require additional resources in planning the trial, analyzing the results, and interpreting and reporting the conclusions.
- Great care is needed in the selection and justification of prior information to be included in the analysis of confirmatory results.

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)-

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sponsored process analytical technology (PAT) (2), process validation (3), and International Conference on Harmonisation (ICH) *Q8*, *Q9*, and *Q10* guidance (4) before it, this CDRH 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.

FDA has 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 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 manufacturing site within the corporation.

This commentary briefly discusses the FDA Bayesian statistics guidance. Brief histories of clinical trials and the new guidance are discussed. The application of Bayesian statistics to pharmaceutical process validation is proposed. This approach integrates prior information and thus enables better decisions. Other clinical and pharmaceutical applications of the Bayesian approach are discussed.

Why Validation and Quality Assurance Professionals Should Care About Clinical Trials Regulatory Guidance

Just as the qualification phase of a process validation is the culmination of a significant scientific effort to design a quality process, the clinical trial phase is the apex of a significant scientific effort to design a safe and effective intervention (e.g., pharmaceutical, medical device, diagnostic) against a medical or related problem. Both designs are expected to incorporate elements of prior knowledge, sound science and engineering, risk assessment, and specification control. The execution of both phases should be based on a prospective experimental design. The choice of accepting or rejecting the process or intervention should include a consideration of the statistical risks. A decision to accept will be followed, in both cases, by continuous monitoring, knowledge building, and improvement throughout the lifecycle. Clinical trials may carry a greater burden to assure human safety than process qualification, and so regulatory guidance and oversight of clinical trials has a longer history. However they share a similar statistical pedigree and an appreciation of these parallels may give quality assurance professionals insight into how their own efforts are regulated and what future direction regulations might take.

A BRIEF HISTORY OF CLINICAL TRIALS

A brief review of clinical trial history is helpful to appreciate the magnitude of the shift. 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., Nuremburg Codex, 1947 and the Declaration of Helsinki, 1964-2001).

Clinical trials have evolved into a standard decision tool, focusing on patient safety, informed consent, rigorous statistical, prospective design and analysis, 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.

GUIDANCE OVERVIEW

This FDA Bayesian 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 as primary
- 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 document 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. FDA 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.

CONTENT OF THE NEW GUIDANCE

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 guidance.

Incorporated into the guidance are the following lessons drawn from the FDA's experiences with Bayesian approaches:

- There is a need to educate industry and 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.

Table: Comparison between stages for process validation and clinical trials.

Process Validation Stage	Process Validation Stage Description	Clinical Trials Description
1. Process design	The commercial process is defined based on knowledge gained through development and scale-up activities.	The medical intervention is defined based on preclinical, safety, phase I pilot studies, clinical data on very similar products or other populations, or patient registries.
2. Process qualification	The process design is confirmed by qualification trial(s) as being capable of reproducible commercial manufacturing.	The medical intervention is confirmed by controlled clinical trial(s) as being able to meet the desired safety and efficacy endpoints with high probability.
3. Continued process verification	Ongoing assurance is gained during routine production that the process remains in a state of control.	The safety and efficacy of the market product is actively monitored through post-market surveillance, pharmacovigilance, and phase IV studies.

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 2010 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. FDA recognizes that while Bayesian approaches may often offer a lower clinical burden, they may require a greater statistical or computational burden.

COMPARISON OF PROCESS VALIDATION AND CLINICAL DEVELOPMENT

According to the 2010 FDA guidance (3), process validation consists of three stages as shown in the Table. Clinical trials share an analogous sequence.

The process design stage (Stage 1) is critical for both process validation and clinical development. This is where a firm foundation of process knowledge must be acquired.

Stage 2 is the formal "process transfer to production" for routine use. As with clinical trials, Stage 2, process qualification (PQ), is where the "safety and efficacy" of the manufacturing process is rigorously demonstrated to all stakeholders. This stage can be viewed as just another step in the knowledge-building continuum. However, it is unique in being a decision and communication point and cannot be eliminated. FDA calls Stage 2 an "important milestone" in the process validation lifecycle. Traditionally, Stage 2 has consisted of manufacturing three product batches. However, the "burden of proof" required in Stage 2 may depend on the amount of prior knowledge already available from Stage 1 design and development and from other sources. If a large body of relevant scientific or theoretical knowledge is available along with a well documented and successful development history, some abbreviation of Stage 2 may be justified. If the prior knowledge from Stage 1 is meager, three successful PQ batches may not be sufficiently convincing. Increased testing post PQ in Stage 3, continued process verification, may be warranted.

To properly judge the risk of transferring the process to routine production we need to quantify the Stage 1 prior process knowledge and combine it in a rigorous way with the new data produced in Stage 2. How can this be done? The Bayesian paradigm of knowledge building gives us the proper statistical framework to accomplish this task.

Continued process verification (Stage 3) is essential for both process validation and clinical development. There are several reasons for the continuous monitoring. Products and their manufacturing processes may drift over time. Stage 2 PQ is truly a "snapshot in time" and cannot guarantee continued good performance throughout the product lifecycle. It is important to assure that safety, efficacy, and fitness-for-use are maintained within the required control allowances. The process of knowledge building must not stop when the process is transferred or the new intervention is approved. Clinical trials may have limited numbers participants relative to the expected

product use after commercialization. Validation PQ lots may be manufactured under increased scrutiny by technical staff, management, and under most favorable manufacturing conditions. More realistic routine production occurs after PQ has been completed, including exposure to the full range of conditions that will be experienced after introduction. Due diligence dictates continued vigilance. In addition, active monitoring offers the opportunity to continuous improvements and process optimization.

APPLICATION OF BAYESIAN STATISTICS TO PHARMACEUTICAL PQ: A SIMPLE ILLUSTRATION

To illustrate a Bayesian approach to process qualification, we will take a very simple example. In this example the single qualification criterion for a batch "run" will be a binomial outcome (pass or fail). In any real qualification, there would likely be multiple criteria and some would be based on continuous measures such as mean lot potency. The Bayesian approach can certainly be applied to these more complex situations, but this simplified example serves to illustrate the key elements of the Bayesian learning process.

Consider the validation of a new process using the traditional "three runs" approach. For our hypothetical process, there is only one key quality characteristic and it has only two possible outcomes (pass or fail). The process is costly and we've never made a run at this scale before. We make our three runs and they all pass our validation criteria.

The key question we want to address is: "What evidence do these three validation runs provide about the true failure proportion of the process?" We will refer to this proportion as the "failure rate" and note that it takes on values between 0 and 1. If we knew the true failure rate exactly we would be able to assess the risk of moving the process to production. If the evidence supports a low failure rate, then a transfer to production is justified. If the evidence cannot support a low failure rate, then redesign may be required.

In the Bayesian paradigm, knowledge about a characteristic is quantified by its probability distribution. The tighter the distribution, the more knowledge we have about its true value. In this example in which the parameter of interest (failure rate) is a proportion, the beta probability distribution gives us a very natural and intuitive way of quantifying information about the failure rate and of combining prior information with data from confirmatory trials. The beta distribution has two parameters, as follows:

A = number of failed trials
B = number of successful trials

Where the total number of trials = A + B.

First we need to quantify our prior knowledge about the failure rate. Usually, a process will not get to the stage of qualification unless there is already a strong indication from the design stage that the failure rate is low. However, we will take a conservative approach regarding prior knowledge in this example. A conservative approach will give the greatest weight to the data actually obtained from the qualification trials.

Let us agree that prior to observing the qualification outcome, we have no opinion regarding the failure rate—in other words, we consider any failure rate between 0 and 1 to be equally likely. This opinion is illustrated by the red uniform probability distribution in Figure 1 (the "before validation" distribution). From a sampling perspective, the amount of knowledge in this uniform distribution is equivalent to having made 2 "prior runs" with 1 passing and 1 failing. Thus, the "before validation" uniform distribution in Figure 1 is a beta (Aprior, Bprior) distribution where,

Aprior = number of hypothetical "prior" runs that failed = 1
Bprior = number of hypothetical "prior" runs that passed = 1.

Now if we have made 3 qualification runs and all 3 resulted in a "pass," our qualification data can be summarized as:

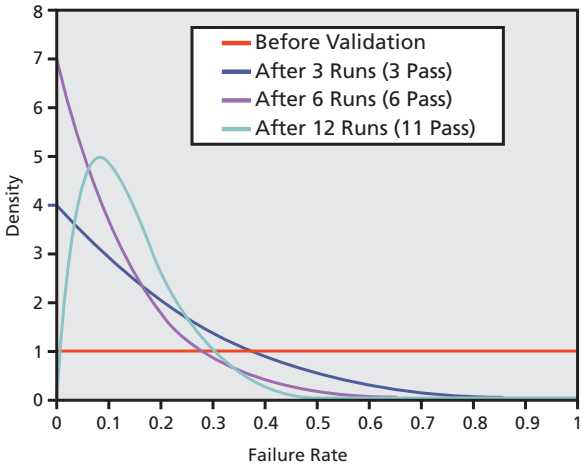
Aqual = number of actual runs that failed = 0
Bqual = number of actual runs that passed = 3

The Bayesian rule for combining prior information with the qualification data in this case is very simple. The amount of knowledge we have about the failure rate, after considering both prior knowledge, and new data will be expressed as a beta (A,B) distribution with parameters:

$$A = Aprior + Aqual \qquad [1]$$
$$B = Bprior + Bqual$$

This distribution is known as a "posterior distribution" and it is shown in Figure 1 by the "after 3 runs (3 pass)" black curve. Notice how this probability distribution gives higher likelihood to lower failure rates.

Figure 1: Knowledge building using distributional estimates.



Two other possible confirmation outcomes are considered in Figure 1 for comparison. Both of these assume the same amount of prior knowledge as for the "after 3 runs (3 pass)" scenario (Aprior = Bprior = 1). The "after 6 (6 pass)" and "after 12 (11 pass)" indicate posterior distributions that result from confirmatory trials of 6 or 12 runs in which 6 or 11 runs, respectively, pass. Notice that as the number of confirmatory runs increases, the amount of knowledge (tightness) in the beta distribution increases. The appearance of one failure in the last scenario (blue curve) reduces the likelihood that the failure rate is very close to zero.

The beta distributions given in Figure 1 provide informative visual summaries of the state of knowledge of the failure rate for a given scenario. Useful numerical summaries can also be obtained from the beta distribution and these are illustrated in Figure 2. For instance, the expected failure rate is often taken as the best point estimate for the failure rate of future runs and is obtained simply as,

Expected failure rate = A/(A + B) = (Aprior+Aqual)/(Aprior+Aqual+Bprior+Bqual).

Often, Bayesian estimates are given in the form of a 95% credible interval. The upper and lower limits for this interval estimate can easily be calculated using the MS Excel function BETAINV as,

Lower = BETAINV(0.025, A, B, 0, 1)
Upper = BETAINV(0.975, A, B, 0, 1)

The expected failure rate and the upper and lower 95% credible bounds are given in the table and plot of Figure 2.

The Bayesian methodology here is not limited to simple failure rates. Similar Bayesian approaches are available for all types of data (i.e., categorical, ordinal, count, and continuous). In general it would be preferable to use continuous scales of measurement that are more informative. This methodology is also not a recent development. It is just not well known within the validation field. It is used in other areas of risk management such as reliability, medical diagnostic predictive value, survival analysis, pharmacovigilance, and airport security screening. An introductory text that describes Bayesian approaches is given in reference 7.

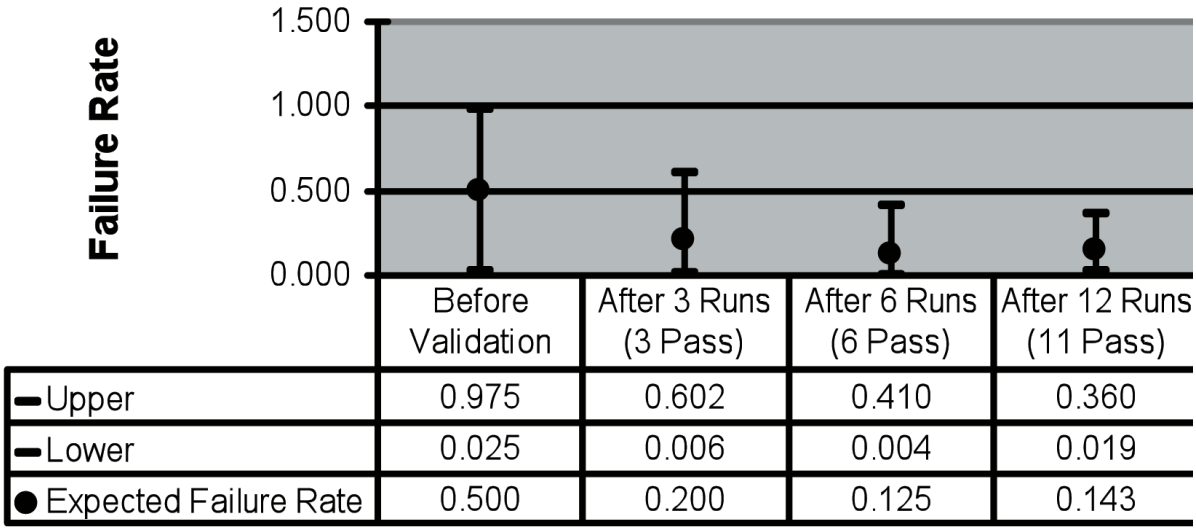
Often industry does not make complete use of development knowledge acquired during the design phase. Failure to properly document, justify, and utilize prior information may unnecessarily increase the cost of stage 2 confirmatory trials. The use of prior knowledge as part of the stage 2 confirmatory assessment will add robustness to the analysis and ensure a better decision. Rather than solely a "check box" exercise, stage 2 can also be leveraged as part of knowledge building. Had we been justified in assuming a more informative beta prior distribution in our example, we could easily have captured this knowledge using a beta distribution with an appropriate choice of Aprior and Bprior, then combined this knowledge with our confirmatory trial data using the above Bayesian updating rule (1).

As a more complex example of how prior information could be utilized, often the stage 2 validation runs are weakest in their estimates of variance. However, if reliable and relevant development information is available about (say) analytical variance, informative priors on this variance could provide a quantitative link to this history. If this can be scientifically justified, it could allow a better or more efficient decision regarding the capability and validation state of the process.

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 incor-

Figure 2: Knowledge building using point and interval estimates.



	Before Validation	After 3 Runs (3 Pass)	After 6 Runs (6 Pass)	After 12 Runs (11 Pass)
Upper	0.975	0.602	0.410	0.360
Lower	0.025	0.006	0.004	0.019
Expected Failure Rate	0.500	0.200	0.125	0.143

rectly concluding treatment efficacy (also known as the Type 1 error). FDA believes that keeping this Type 1 error probability low (0.05 is typical 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 (8). 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, this 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 FDA 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

The Bayesian approach enables integration of prior information into statistical decision making. What are the sources of prior information?

Medical Devices

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 (e.g., 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 legal
- The control group cannot be used a source of prior information for the new device, especially if the objective is to show the new device is non-inferior.

Pharmaceutical Development

Experimental work conducted during pharmaceutical development provides experience that also contributes to judgments regarding process performance. Process trials in the laboratory, at pilot-plant scale, and partial commercial-scale runs are all valuable sources of process data that may be utilized in a Bayesian treatment. The formulation and manufacturing process for a new product may be a minor variation from a similar product or process with a long and successful manufacturing history. For example, formulation and process for a product containing a few milligrams of active pharmaceutical ingredient (API) and a new colorant may be equivalent to another commercial marketed product. In this case, manufacturing experience with the marketed product is directly applicable to the new product and could be utilized in a Bayesian analysis.

BAYES BEYOND MEDICAL DEVICES

As it stands, the guidance refers to medical devices (not drugs or combination drug or 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" (9)
- 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) (10).

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.

The use of Bayesian approaches to pharmaceutical trial design also has a long and successful history. M.D. Anderson Health Science Center in Houston has participated in over 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 (11, 12, 13, 14), 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 one to two 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 (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.

OTHER PHARMA APPLICATIONS OF BAYESIAN STATISTICS–CLINICAL AND PHARMACEUTICAL

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 (15).
- **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 16.
- **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 (18). 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 (19). 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 (20).

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 new guidance.

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ARTICLE ACRONYM LISTING

API	Active Pharmaceutical Ingredient
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	US Food and Drug Administration
ICH	International Conference on Harmonisation
IDEs	Investigational Device Exemptions
PAT	Process Analytical Technology
PMAs	Pre-Market Approvals
PQ	Performance Qualification