

Comments from PSI (Statisticians in the Pharmaceutical Industry Limited) on FDA Draft Guideline on Use of Bayesian Statistics for Medical Device Clinical Trials

Generally, the draft guideline was very well received by PSI members who thought that it would be a very helpful document when planning a trial intending to use Bayesian methods. Members were also encouraged that Bayesian methods were being addressed in much more detail (and more explicitly) than in previous documents – such as ICH E9. Some reviewers felt that the document contained too much background/tutorial type information and that in some case there was too much repetition. A clear distinction in this respect between Bayesian methods and regulatory requirements would be helpful, as would more references.

The first set of comments below are major comments for consideration, the next set of comments are secondary comments for consideration, and the final set of comments summarise typographical and/or style comments.

Major comments

Section	Issue or Concern with the Guideline	Proposed Solution or Amendment
3.9	“A change in prior information or the model at a later stage... may imperil the scientific validity”. Typically new information will add to our knowledge and should be viewed in a positive manner – in terms of learning.	Suggest that the section either explains why new information is viewed as a potentially negative development or state that new data arising during the course of trial has a potentially positive benefit and its use should be encouraged. Although dialogue with the regulatory agencies would of course be expected.
5.5	Non-informative priors Uniform distributions may be uninformative for some models and some model parameters but may be informative for some other model parameters (e.g. hierarchical models, generalised linear models).	Some discussion is required in this respect. In particular it should be highlighted that careful consideration needs to be given to the choice of uninformative prior and an assessment should be made regarding how the posterior inference changes with different choices of prior / different choices of parameterisation
9.1	Frequentist power tables	Can the author provide clarification on how these can be produced in cases where we have used prior data, unbalanced randomisation, mid-course changes in trial design etc. Are we being asked to provide frequentist “backup” to Bayesian design?

Secondary comments

Section	Issue or Concern with the Guideline	Proposed Solution or Amendment
General	The guideline provides a short overview / tutorial of Bayesian methods (Section 4.). We would expect any Sponsor considering a Bayesian trial / submission would be familiar with the basic concepts and techniques.	Introduction to Bayesian statistics could easily be placed in an appendix, omitted or shortened.
3.	A subsection on foundation would be helpful, since in various places the guideline states that the Bayesian approach is coherent, consistent and scientifically valid. Its strength is in sound foundations.	Add subsection on Foundations
3.3	MCMC is now a well developed area and should have more emphasis.	Add more references and emphasize how well developed this is now.
3.5	Bayesian analysis software is often considered to be validated to a lesser degree compared with SAS, say.	Some reference to 21CFR Part 11 requirements might be appropriate in terms of using software such as WinBUGS.
3.7	Many of the design issues around using Bayesian techniques stated in the guidance are not unique to the Bayesian paradigm – for instance, concurrent controls, randomisation, the importance of covariate information.	Could the guidance reference (perhaps in Section 3.7) which design / analysis requirements carry over from other guidance and highlight those that may be different?
3.8	“The Bayesian methodology can allow for augmentation... if the observed variability of the sample is higher than that used to plan the trial.”	Further clarification would be helpful in terms of augmentation. Perhaps an illustration could be provided, or some reference made to adaptive designs and mid-course changes.
3.8	Frequentist methods can also be used to stop a trial early.	This point should be acknowledged.
3.8	The meaning of “Exact analysis” is unclear.	“Exact” analysis typically has a frequentist connotation – for instance in terms of small cell frequencies. Please clarify what is mean in terms of Exact in this context.
3.9	Bullets 2 and 3 are used in the frequentist approach also. The main difference is the pre-specification of the prior.	Suggest this point is emphasised.
3.9	Device labelling	Illustrations of how the results of the Bayesian analysis can be expressed in device labels would be helpful.
3.9	“In some cases, we recommend you perform sensitivity analyses to check robustness of models and priors”. When would FDA see checking robustness as unnecessary?	Please provide an example
4.	Terms are defined in section 4 that have been referred to earlier.	A re-ordering of the document might help the flow.
4.1	The word probability is uses frequently when what is really meant is probability distribution over quantities of interest.	Highlight that the outcomes of Bayesian inference are probability distributions (posterior, predictive)
4.2	Use of the term endpoint may be ambiguous. Suggest retain parameter since it is explicit and relates to a model.	Suggest delete the term endpoint
4.2	‘Suppose x is the rate of a serious adverse	Replace rate with probability

	event....' A 'rate' would not necessarily lie between 0 and 1, as would a probability.	
4.2	The notation x for parameter is unusual.	Suggest use the standard Greek letter θ for parameters, and X or Y for the data.
4.2	A figure might help.	Please add a figure.
4.4	Bayes theorem does not appear in the guideline in its mathematical form	Suggest Bayes theorem is explicitly stated in mathematical terms
4.5	It would be nice to illustrate how simple and straightforward the Bayesian approach is when it comes to predictions.	Include the derivation of the predictive distribution as the weighted average of the sampling distribution of the future data (weighted over the posterior)
4.6	A reference for exchangeability would be helpful	Add a reference, if possible
4.7	Add an example	Use the binomial example with fixed sample size vs. negative-binomial to illustrate the principle.
4.8	The sentence 'Another way of saying this is that Bayesian inferences are based	Change to... 'Another way of saying this is that Bayesian inferences are based on the "parameter space" (the posterior distribution) as introduced through the prior whilst frequentist inferences are based on probabilities over the "sample space" (the set of possible outcomes of a trial)'
5.5	It is unclear what would constitute an unacceptably high prior probability of a successful trial. Indeed if the prior information is genuinely strong then perhaps a study is not necessary.	Some guidance on what considerations are made in terms of judging whether a prior probability of success is too high would be helpful.
5.6	'If the results of the study.....borrow negatively'. There is some debate as to what should be done if the prior and study information conflict.	Alternative wording might be 'If they agree you gain power, if they disagree then the prior acts as a brake on over-interpretation of the specific data' – may be better than 'borrowing negatively'
6.1	Summaries of the posterior distribution	Suggest that the median and credible interval are added to the list to summarise the posterior. Are Bayes factors an option?
6.2 & 9.4	Hypothesis testing / Operating characteristics	Type I and Type II errors are best related to decision criteria which could be numerical superiority, clinical non-inferiority etc.
9.1	Prior information	Suggest include a bullet in relation to choice of model for prior data, since prior distributions are for given models / likelihoods.
9.1	Additional items	For the effective sample size calculation (ESS) what prior should be used for $V1$ (without borrowing)? This should presumably be an uninformative prior, but which? A formal "reference prior"?
9.2	Model selection Is this referring to the "Bayes Factor"	Can the author please provide clarification / references for this approach?

	approach or “Bayesian Model Averaging”?	
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Typographical / stylistic comments

3.2	“informative prior information” sounds a little strange	Suggest states state simple as “prior information”
3.2	Use of the ‘good’ in the phrase ‘When good prior information is available ..’ and similar could be seen as subjective	Replace ‘good’ with ‘reliable’
3.7	Title is a little odd. Since it is sound science it is not clear how it could be viewed as pushing aside sound science	Perhaps change to “The Bayesian approach and sound science.”
4.1	“For Bayesian trials, hypotheses are tested with decision rules”	Suggest change to: “For Bayesian trials, hypotheses are assessed with decision rules that are based on posterior probabilities”
8.	Gamerman, D. (1997).	Gamerman, D. (1997). Markov
8.	Gelman, A., Carlin, J. B., Stern, H. S. & Rubin, D. B. (2004).	Should it be (2003)?