

Review Considerations for Bayesian-Informed CMC Submissions

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Purpose

The Objectives of This Presentation Are to:

- Share BRDD's current and evolving perspectives on reviewing Bayesian-informed CMC submissions
 - Encourage transparent scientific exchange among industry and regulatory colleagues
 - Support shared learning and more effective submission review
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Roadmap

Part I What Makes a Bayesian-Informed CMC Submission Clear and Reviewable?

- Core information supporting statistical review
 - Additional Bayesian-specific considerations
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Part II Practical Lessons from Two Bayesian-Informed CMC Submissions

- Case Example 1: Establishing a Bayesian lower tolerance bound for post-thaw cell viability
 - Case Example 2: Supporting acceptance criteria by integrating process and stability information
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Part I: What Makes a Bayesian-Informed CMC Submission Clear and Reviewable?

Core Information Supporting an Effective Statistical Review

- Clear definition of the CMC question, analytical objectives, and estimand
- Description of the study design and data sources
- Assessment of data quality, relevance, representativeness, missingness, exclusions, and limitations
- Statistical methods and key assumptions
- Appropriate quantification and interpretation of uncertainty
- Model evaluation and sensitivity analyses
- Analysis-ready data, programming code, and analytical outputs supporting reproducibility

Part I: What Makes a Bayesian-Informed CMC Submission Clear and Reviewable?

Additional Considerations for Bayesian Analyses

- Prior specification, scientific justification, and influence on posterior results
 - Interpretation and practical relevance of posterior estimates, probabilities, and predictions
 - Potential conflict between prior information and current data
 - Sensitivity to alternative priors and model assumptions
 - Model adequacy, computational reliability, and MCMC convergence
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When Is Prior Information Appropriate?

Key Considerations

- Scientific, biological, and manufacturing relevance
- Source, quality, representativeness, and traceability
- Comparability with the current product, process, manufacturing conditions, quality attributes, and analytical method
- Influence on the posterior results and degree of borrowing
- Potential conflict between prior information and current data
- Sensitivity of conclusions to reasonable alternative priors

Prior information should be scientifically relevant, transparently specified, and statistically evaluated.

Part II: Case Example 1 – Establishing a Bayesian Lower Tolerance Bound for Post-Thaw Cell Viability

CMC Objective

- Establish an in-process action limit for post-thaw cell viability
- Reliably characterize the lower tail of the viability distribution

Study Data

- More than 160 manufacturing lots
 - Viability measured between 0% and 100%
 - Most observations concentrated near the upper boundary
 - Relatively few observations in the lower tail
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Case Example 1: Proposed Bayesian Approach

Proposed Model

- Model lot-level viability using a Beta distribution
- Use a prior intended to be diffuse
- Generate the joint posterior distribution of the model parameters

Lower Tolerance-Bound Calculation

- Construct the posterior distribution of the target quantile
- Select a specified lower percentile of that posterior distribution as the lower tolerance bound

The Beta model represented the bounded, asymmetric data, while posterior simulation propagated parameter uncertainty into the lower-tail estimate

Case Example 1: What Were the Main Focus Areas of the Review?

Review Focus

- Representativeness of the included lots
- Scientific justification for data exclusions
- Comparability and pooling across the different types of lots
- Adequacy of the Beta model, particularly in the lower tail
- Influence of prior choices on the tolerance bound
- Computational reliability and model diagnostics

Relevant data, justified assumptions, and transparent implementation made the analysis reviewable. process knowledge supported a constructive review.

Case Example 1: What Supported the Review?

Information Supporting the Review

- Clear CMC objective and statistical estimand
- Detailed and relevant lot-level information
- Scientific rationale for the Beta population model
- Specification and justification of the prior distributions
- Pooling supported by statistical assessment and process knowledge
- Transparent methodology, analysis-ready data and programming code
- Prior-sensitivity analyses and MCMC diagnostics

Relevant data, justified assumptions, and transparent implementation made the analysis reviewable. process knowledge supported a constructive review.

Case Example 2: Integrating Process and Stability Information

CMC Objective

- Support stability-based acceptance criteria for four quality attributes
- Predict expected quality-attribute ranges at release and throughout shelf life

Three Components of the Assessment

- Manufacturing-process variability
- Change and variability in drug-substance quality attributes over storage
- Change and variability in drug-product quality attributes over shelf life

The assessment integrated manufacturing-process variability and drug-substance and drug-product stability information

Case Example 2: Integrating Process and Stability Information

Study Data

- Approximately 18 lots for process-variability modelling
- Approximately 15 lots for stability modelling
- Development, clinical, engineering, and process-validation lots
- More than 30 process parameters across multiple manufacturing steps
- Hierarchical variability associated with blocks, bioreactors, and manufacturing units

The integrated framework linked manufacturing-process variability and stability information to the proposed acceptance criteria.

Case Example 2: Integrating Process and Stability Information

Analytical Framework

- Fit Bayesian MCMC mixed-effects response-surface models at relevant manufacturing steps
- Evaluate relationships between process parameters and quality-attribute variability
- Include hold time as a process input, where applicable
- Reflect hierarchical sources of manufacturing variability
- Integrate step-specific posterior distributions to characterize overall process variability
- Combine process predictions with drug-substance and drug-product stability information

The integrated framework linked manufacturing-process variability and stability information to the proposed acceptance criteria.

Case Example 2: What Supported the Review?

Information Included in the Submission

- Scientific rationale for the modelling approach and description of the hierarchical model structure
- Specification and justification of informative and intended-to-be-vague priors
- Selected MCMC and computational diagnostics
- Posterior predictive distributions
- Interpretation informed by product and manufacturing-process knowledge

The framework was reasonable; more complete reporting would facilitate a smooth review.

Case Example 2: Information That Would Have Strengthened the Submission

- Analysis-ready datasets and complete, executable programming code
- Complete documentation of key analytical steps and model implementation
- Comprehensive diagnostics for key model parameters and derived quantities
- Effective sample sizes and Monte Carlo standard errors
- Focused sensitivity analyses for prior and model assumptions
- Documentation and validation of sponsor-developed programming packages

The framework was scientifically reasonable, while more complete reporting would have strengthened confidence, reproducibility, and review efficiency.

What Can Support a Successful Bayesian-Informed CMC Submission and Effective Review?

- Early scientific dialogue on the CMC question, prior selection, and Bayesian analysis plan
- Clear analytical objective and estimand
- Meaningful scientific or practical value from the Bayesian approach
- Fit-for-purpose data, model, assumptions, and prior
- Demonstrated model adequacy, computational reliability, sensitivity, and robustness
- Transparent documentation, analysis-ready data, and executable code supporting reproducibility
- Interpretation within the totality of relevant CMC evidence

Success depends on making the complete analytical pathway transparent, robust, reproducible, and scientifically interpretable.

Questions, Comments, and Perspectives

YOUR HEALTH AND SAFETY... OUR PRIORITY.

