EUROPEAN MEDICINES AGENCY
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Methodology Working Party (MWP)

Concept Paper for the Development of a Reflection Paper on the use of Bayesian methods in clinical development

Agreed by MWP	November 2025
Adopted by CHMP for release for consultation	19 January 2026
Start of public consultation	30 January 2026
End of consultation (deadline for comments)	30 April 2026

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Keywords	Bayesian statistics, clinical trials, medicine development

1. Introduction

The purpose of the proposed guideline is to address key considerations for studies that utilise Bayesian statistics in clinical development.

2. Problem statement

Frequentist methods have traditionally been the standard approach to data analysis in drug development and regulatory submissions. Nevertheless, ICH E9 guideline [1] states that Bayesian methods may be used "*when the reasons for their use are clear and when the resulting conclusions are sufficiently robust".* Further guidance that discusses Bayesian methodology include ICH E11A on pediatric extrapolation [2], draft ICH E20 on adaptive designs [3], and the ACT EU Q&A on complex clinical trials [4]. Also, the use of prior beliefs is mentioned in the CHMP Guideline for investigation of small populations [5].

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Specific potential applications of Bayesian methods mentioned in the above guidelines include:

- Combining knowledge from previous data with newly generated study data in small populations
- Interim analyses, adaptations, pooling, incorporating external controls data (ACT EU Q&A)
- Extrapolation from adults to paediatric populations or between paediatric populations

In a clinical study using Bayesian statistics, a *prior distribution* needs to be specified for the statistical analysis to express the belief about the possible values of the quantity of interest. The prior distribution is subsequently combined with the data from the study to form the *posterior distribution*, which represents the updated belief about the values of the quantity of interest. Statistical inference is based on the posterior distribution, which reflects the uncertainty on the quantity of interest given the prior information and the study data.

In recent years, there has also been an increasing number of proposals in submissions to the EMA that used Bayesian methods for borrowing of historical or external data to enrich trial data to draw conclusions in the same or a related population or to draw conclusions in populations where adequately powered trials are not possible.

The use of Bayesian methods is also well-established in many other areas of development where the aim is not to generate confirmatory evidence but instead to generate supportive evidence, or in early phase clinical trials to generate evidence for internal decision making. Even if only intended for internal decision making, such methods nevertheless are part of scientific advice submissions, and may also be the subject of Marketing Authorisation Application assessment. Examples would be the use of Bayesian methods to fit pharmacometrics models and Bayesian approaches to early-phase dose-finding.

Currently, there is lack of clarity on the regulatory position on when Bayesian methods can be accepted in the confirmatory setting and the methodological requirements needed to address potential regulatory concerns. More specifically:

- Under what circumstances is it necessary to provide a justification for the use of Bayesian methods and which topics should such justification address in light of the regulatory impact?
- How to deal with increased methodological complexities associated with the use of Bayesian approaches in clinical trials, particularly when leveraging external data:
    - What criteria should define 'technical success' in a clinical trial using Bayesian analysis to ensure that conclusions are robust for regulatory decision-making?
    - How are the data that inform the prior distribution generated, collected and interpreted, and how is the prior distribution constructed and justified based on the data?
    - How much prior information is being incorporated into the posterior distribution and how much weight is carried by this prior information relative to the data generated within the study using Bayesian analyses?
    - What sensitivity analyses are required with respect to prior distributions and model choices?
    - How to assess error control for both primary and secondary endpoints in the absence of frequentist inference?
    - What information (analytical and simulation results) should be provided to assess the potential risk of bias in estimates?

- What operating characteristics (beyond error control and bias) of a design using Bayesian analyses should be investigated at the design stage?
- If Bayesian methods are considered in adaptive trials, what information (analytical and simulation results) should be provided at the design stage to show that the risks of erroneous conclusions are adequately controlled, e.g. in trials with Bayesian stopping and success criteria?
- For studies considering the use of informative priors to borrow information from external data, how to deal with lack of control of type I error rate? What other error rate metrics could be acceptable and what needs to be shown for this?
- What information regarding Bayesian analyses including computational methods should be included in the Marketing Authorisation Application dossier and what level of details should be prespecified in study protocol or statistical analysis plan?

- The overall aim of the proposed reflection paper will be to clarify when Bayesian methods may be considered appropriate in the regulatory setting and to describe the information and justifications required for their use to support regulatory decision making. It will also emphasise the importance of engaging early with regulators if Bayesian analyses are intended to be used in a clinical trial

3. Discussion (on the problem statement)

Topics to be addressed may include

- Terminology and key concepts of the Bayesian paradigm:
  - Definition of probability in Bayesian statistics, where parameters are treated as random quantities
  - The Bayesian toolbox: prior, posterior and predictive distributions
- Considerations at the design stage of trials using Bayesian methods
  - Use of decision criteria based on posterior probability statements
  - Sample size calculation
  - Recruitment and allocation strategies
  - Strategies to handle multiplicity with a co-primary or multiple endpoints
  - Designs with adaptive elements
    - Early stop for futility and efficacy at interim analyses using Decision rules based on the posterior distribution or the end-of-study predictive distribution
    - Multiplicity control for interim analyses
    - Adaptation of other elements of the study design at the interim analyses, e.g. the sample size.
    - Dose escalation
  - Prior distributions

- Regulatory scrutiny given its influence on the posterior distribution
- Pre-specification and characterisation, if applicable
- Considerations when using so-called *non-informative* priors reflecting very little or no information on the quantity of interest:
    - Improper vs proper priors
    - Priors specified on the scale of the quantity of interest (e.g. a rate ratio) versus a transformed scale of the quantity of interest (e.g. the logarithm of the rate ratio)
    - Understanding impact of the prior on the posterior distribution through sensitivity analyses under alternative non-informative priors or hyperpriors
- Considerations when using informative priors reflecting available information:
    - Clinical rationale and context of use
    - Sources of external information used to elicit the prior, including aspects related to comparability and estimands
    - Methods used to construct the prior distribution
    - Pre-specification and characterisation of the prior distribution, including simulations to understand operating characteristics under different scenarios
    - Prior-data conflict and the use of robust priors
    - Sensitivity analyses

- Data analysis and reporting of studies using Bayesian analyses
    - Pharmacometric analyses such as population PK, PK/PD, exposure-response, and disease progression modelling
    - Data Analyses
        - Pre-specification of Bayesian analysis models, likelihood and prior distributions for model parameters and hyperparameters
        - Missing data assumptions and handling
        - Alignment with the estimand
        - Posterior distributions with and without closed analytical expressions
        - Considerations when using numerical simulation techniques to obtain a sample from the posterior distribution
        - Pre-specification of sensitivity analyses depending on the type of prior (so-called non-informative vs informative)
    - Reporting results from Bayesian analyses
        - Convergence diagnostics of methods used to obtain a sample from the posterior distribution, if applicable
        - Graphical and numerical characterisation of the posterior distribution of model parameters and the posterior of the quantity of interest on the scale relevant for regulatory decision-making

- Results from sensitivity analyses depending on the type of priors:
  - If non-informative priors are used, posterior distributions under different non-informative priors
  - If informative priors are used
    - Quantification of the prior information on the posterior distribution
    - Credibility analyses to understand the influence and plausibility of priors leading to posteriors for which the decision criteria are met (e.g. "tipping point" type analyses)
    - Use of results derived from Bayesian analyses in a meta-analysis and potential for multiple uses of the same prior information

4. Recommendation

The Methodology Working Party recommends drafting a reflection paper on the use of Bayesian statistics in clinical trials to support regulatory decision-making taking into account the points identified above.

5. Proposed timetable

The present concept paper will be released for public consultation. The feedback received will be considered when developing the reflection paper. The proposed tentative timelines are as follows:

- March 2026: Release of the present concept paper for public consultation for 3 months.
- July 2026 to June 2027: Reflection paper development, including multi-layer review by relevant EMA scientific committees and working parties.
- September 2027: Release of the draft reflection paper for public consultation for 3 months.
- June 2028: Publication of final reflection paper.

6. Resource requirements for preparation

A drafting group consisting of members from the MWP and the European Specialised Expert Community (ESEC) representing different areas of expertise. It is anticipated that it will take 12 months to draft the reflection paper, including endorsement of relevant EMA scientific committees and working parties. A workshop was held on the topic in June 2025, to gather further examples of how Bayesian methods are currently being used in practice.

7. Impact assessment (anticipated)

The proposed reflection paper will give reviewers clear direction on the potential issues to identify during assessment when Bayesian methods are used. It will also provide medicine developers, marketing authorisation applicants and holders with guidance on the suitability and key principles of regulatory interest of certain trial designs, as well as the scope and extent of information that needs to be provided for assessment.

8. Interested parties

The Scientific Advice Working Party (SAWP), Paediatric Committee (PDCO) and Committee for Medicinal Products for Human Use (CHMP) will be consulted before the publication.

The views from industry, academia, patients and health care professionals will also be taken into consideration through the public consultation phase.

9. References

[1] ICH E9 Statistical principles for clinical trials, published in 1998.

[2] ICH E11A Pediatric extrapolation, published in 2024.

[3] ICH E20 Adaptive designs for clinical trials, step 2b, published in 2025.

[4] HMA-EMA ACT EU Complex clinical trials – Questions and answers (Reference number: EMA/298712/2022), published in 2022.

[5] Guideline on clinical trials in small populations (Reference Number: CHMP/EWP/83561/2005), published in 2006.

[6] ICH E17 General principles for planning and design of multi-regional clinical trials, published in 2017.

[7] ICH M15 Guideline on general principles for model-informed drug development, published in 2025.