

# Perspectives on Bayesian statistics in regulatory decision making

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*Views expressed are my own and do not necessarily reflect views of CBG-MEB or EMA*



**UMC Utrecht**

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# To start

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- EMA concept paper on Bayesian Statistics in Clinical Development (drafted, not yet approved)
- Stakeholder workshop at EMA next week (17 June)
- I will **not** present the concept paper
- Focus will be on current regulatory perspectives

# EU Legislation

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*Future directive 2001/83/EC and regulation (EC) 726/2004*

Reasons for refusal of marketing authorization:

- **benefit-risk (B/R) balance is not considered favourable**
- **quality, safety or efficacy is not properly/sufficiently demonstrated**
- qualitative and quantitative composition is not as declared
- assessment or addressing of environmental risks is insufficient
- proposed labelling and leaflet not in accordance with legislation

# Current practice in regulatory decision-making

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## Substantiation of therapeutic efficacy

- generally based on frequentist statistics
- with error control at the trial level (ICH-E 9)
- rejection of null hypothesis in trial as a severe test

Informs further B/R assessment and regulatory decision

# Bayesian methods in guidelines

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## **ICH: E 9: Statistical principles for clinical trials - Step 5**

Adopted

Reference Number: CPMP/ICH/363/96

Legal effective date: 01/09/1998

Use of Bayesian approaches may be considered when

- the **reasons for their use are clear** and
- when the **resulting conclusions are sufficiently robust**

# Bayesian methods in guidelines

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Other guidelines/documents mentioning Bayesian methods

- EMA Guideline on clinical trials in **small populations** (2007)  
*Incorporating previous data or prior beliefs*
- ICH E11A Guideline on **pediatric extrapolation** (2025)  
*Incorporating data from (adult or other pediatric) reference population*
- ACT-EU's **complex clinical trials** Q&A (2022)  
*Description and explanation of Bayesian approaches (Q3) – including clear reasons and purposes for use (ICH E-9)*

# Potential uses of Bayesian methods

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Many (recent/not so recent) developments in Bayesian methodology:

- **Extrapolation** (e.g adults to pediatrics or across formulations)
- Incorporation of external data/information (**dynamic borrowing**)
- Combining data from different sources (**evidence synthesis**)
- Borrowing across baskets or subgroups (**pooling**)
- Interim decisions using posterior/predictive distributions (**adaptive designs**)
- Bayesian **pharmacometrics** (PK) modeling
- Internal decision-making: **probability of success**

# Bayesian methods in regulatory decision-making

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Bayesian methods mainly seen in:

- Pediatric extrapolation (Paediatric Investigation Plan)
- Modeling and simulation (Pharmacometrics)
- Early-phase studies (Dose-finding)
- Exploratory phases of drug development

Applications in pivotal studies submitted for MAA limited

# Bayesian methods in regulatory decision-making

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Despite ICH-E 9 mentioning Bayesian methods already in 1998:

- Why have they **not made their way** to regulatory decision-making?

Based on formulation in ICH-E 9:

- What are **clear reasons** for using Bayesian methods?
- When are results of Bayesian analyses **sufficiently robust**?

# Justification of Bayesian methods

ICH – E9: ‘...when reasons for their use are clear’

No advantages	Operational advantages/ pragmatic reasons	Clearer advantages
<ul style="list-style-type: none"><li>• Bayesian t-test</li><li>• Bayesian MMRM</li><li>• etc</li></ul> all with non-informative/vague/weakly informative prior	<ul style="list-style-type: none"><li>• Estimation in small populations</li><li>• Adaptive designs using predictive distributions</li><li>• Pooling across small subgroups</li></ul>	<ul style="list-style-type: none"><li>• (Pediatric) extrapolation</li><li>• Borrowing external information in rare diseases</li><li>• Borrowing (external) data for underpowered secondary endpoints or small (sub)populations</li></ul>
<b>No external data/ assumptions</b>		<b>Incorporation or borrowing of external information</b>

# Justification of Bayesian methods

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- Standard basis for approval is self-standing evidence
- Each Bayesian element needs self-standing motivation (ACT EU Q&A)
- Can use be motivated in case of no advantage (but low complexity)?
- How should advantages and larger complexity be weighted?

# Additional complexities of Bayesian methods

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ICH – E9: *‘...when resulting conclusions are sufficiently robust’*

Additional choices (requiring justification) related to:

- Informative priors, external data sources, weight for external information
- Bayesian model, including hyperparameters
- Model used for pooling across subgroups or baskets

Other complexities

- Numerical methods often needed for estimation
- Type I error control not always possible (informative priors)

# Additional complexities of Bayesian methods

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We need to reflect on what is required in terms of:

- Sensitivity analyses showing robustness of conclusions to choices
- Prespecification of the analysis methods including:
  - What will serve as primary analysis
  - Detailedness of reporting

We also need to reflect on:

- How to ensure consistency of severity of testing among approaches
- How to deal with lack of type I error control

# Other considerations

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- Point estimate and interval **estimation**
  - How to report treatment effect in SmPC?
  - How to deal with bias and additional uncertainty?
- **Clinical context**
  - How to describe and justify assumptions in clinical context?
- **Transparency**
  - Prespecification/reporting of methods, tools and data sources
- **Efficiency**
  - More time needed for assessment and explanation to clinical assessors

# Next steps toward reflection paper

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- Stakeholder workshop at EMA next week (17 June)
- Final draft of concept paper
- Public consultation
- Writing of the reflection paper