Session 2: Upcoming Guidance – Challenges and Opportunities

# EU Concept Paper on the use of Bayesian statistics in clinical development

*Peter van de Ven, PhD*

*Methodology assessor at the Dutch Medicines Evaluation Board*

*Member of the temporary drafting group*

# To start

- EMA concept paper on *Bayesian Statistics in Clinical Development* drafted
- This workshop is to **make sure that we do not miss important topics**
- Concept paper will be out this year, but after summer
- Comments on the concept paper will be considered when writing the reflection paper
- I will present regulatory perspectives on Bayesian methods in clinical development
- Any views expressed here do not necessarily reflect EMA or CBG's views

# EU legislation

*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

**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

**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

**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

**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**)
- Missing data handling (**multiple imputation**)
- Bayesian **pharmacometrics** (PK) modeling
- Internal decision-making: **probability of success**

# Bayesian methods in regulatory decision-making

**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 marketing authorization limited**

# Bayesian methods in regulatory decision-making

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** |
|---|---|---|
| • Bayesian t-test<br>• Bayesian MMRM<br>• etc<br>all with non-informative/vague/ weakly informative prior | • Estimation in small populations<br>• Adaptive designs using predictive distributions<br>• Pooling across small subgroups | • (Pediatric) extrapolation<br>• Borrowing external information in rare diseases<br>• Borrowing (external) data for underpowered secondary endpoints or small (sub)populations |
| **No external data/ assumptions** | | **Incorporation or borrowing of external information** |

# Justification of Bayesian methods

**Some principles**

- Standard basis for approval is self-standing evidence
- Use of Bayes needs to be motivated (ICH E-9)
- Each Bayesian element needs self-standing motivation (ACT EU Q&A)

**Some questions that we need to answer**

- 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

**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

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

- Sensitivity analyses to show 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 should we deal with settings where type I error control is not possible?

# But also some other considerations

- 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 of our assessments**
  - More time needed for assessment and explanation to clinical assessors

# Aim of planned reflection paper

Planned reflection paper should describe the **required information and justification** for use of Bayesian methods

- in order for them to be considered **suitable for regulatory decision** making and
- to **allow assessment of benefit and risks** of medicinal products

# Potential topics (non-exhaustive)

**Regulatory considerations on:**

- **Non-informative priors**: Prespecification, scale dependency, improper priors, impact on posterior and sensitivity analyses
- **Informative priors**: Prespecification, justification, sources of external information (comparability), methods for construction, characterisation, operating characteristics, prior-data conflict, robust priors, sensitivity analysis
- **Bayesian approaches to trials**, including adaptive elements not covered in other guidances
- **Prespecification and reporting of data analysis and reporting of results** (including pharmacometric analyses and disease-progression models)

Importance of **early engagement** with regulators

# To conclude

- There is a clear need for a reflection paper on Bayesian methods
- Your input is welcome
- We don’t want to miss important topics

**Thank you!**

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