EMA
EUROPEAN MEDICINES AGENCY

ICH E20 – a regulatory perspective

EMA workshop on the use of Bayesian statistics in clinical development, 18 June 2025

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The presenter has no conflict of interest.

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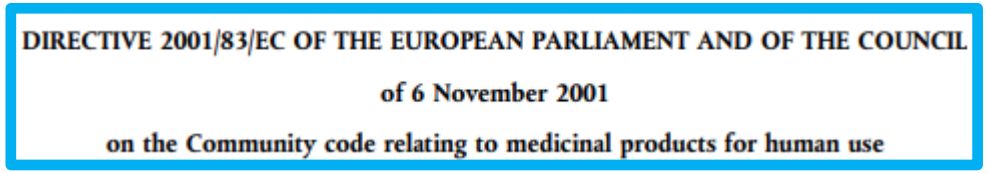
- Role of an EMA guideline
- Scope of adaptive designs using Bayesian methods in E20
- How to link E9 and E20
- Use case on historical borrowing
- Conclusion

Role of Guidance: Status in the EU system

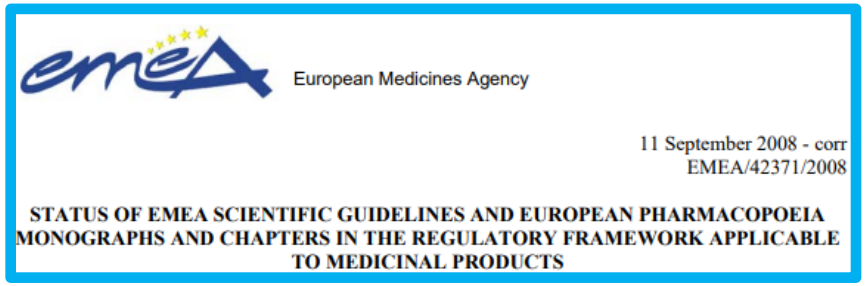
- ICH Guidelines are implemented in the EU as Scientific Guidelines
  (For example, ICH E9 is CPMP/ICH/363/96).
- The role of guidelines is defined in EMEA/42371/2008 directly referencing the Introduction of Annex I of Directive 2001/83/EC
  - "(4) In assembling the dossier for application for marketing authorisation, **applicants shall also take into account the scientific guidelines** relating to the quality, safety and efficacy of medicinal products for human use as adopted by the [CPMP] …"


DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

  - scientific guidelines **do not have legal force**,
  - **alternative approaches** may be taken, provided that these are **appropriately justified**,
  - scientific guidelines are to be considered as **harmonised Community positions**,
  - if they are followed by relevant parties (…), will **facilitate assessment, approval** and control of medicinal products.


European Medicines Agency

11 September 2008 - corr
EMEA/42371/2008

STATUS OF EMEA SCIENTIFIC GUIDELINES AND EUROPEAN PHARMACOPOEIA MONOGRAPHS AND CHAPTERS IN THE REGULATORY FRAMEWORK APPLICABLE TO MEDICINAL PRODUCTS

EMA

Role of EU guidance: Efficient guidelines

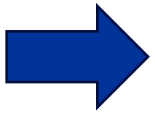
- Same recommendations on the EMA Website:
- "The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines. Applicants need to **justify deviations from guidelines** fully in their applications at the time of submission. Before that, they should seek scientific advice, to discuss any proposed deviations during medicine development".
- How guidance can be most **efficient** and enables **transparent** stakeholder interaction, within the regulatory system (EMA and NCAs) and with applicants / MAHs?

- It states **accepted standards**
  i.e. the agreed community positions
- It is **clear about conditions** for accepting proposals
  e.g., a certain design aspect
- It **explains how to argue** if one wants to deviate.

Scope of adaptive designs using Bayesian methods in E20

- **Definition** in *Section 1 Introduction and scope*

  - (…) “an adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial.”
  - It means that any pre-planned interim analysis makes a trial *‘a trial with an adaptive design’*.
    - Including when stopping a trial for futility (lack of efficacy).
  - **E20 scope is broader** than that in the EMA Reflection Paper
    - (…) “’adaptive designs’ allow much broader design modifications (sample size, randomization ratio, …) at an interim analysis of an ongoing trial, whilst still fully controlling the pre-specified type I error.”

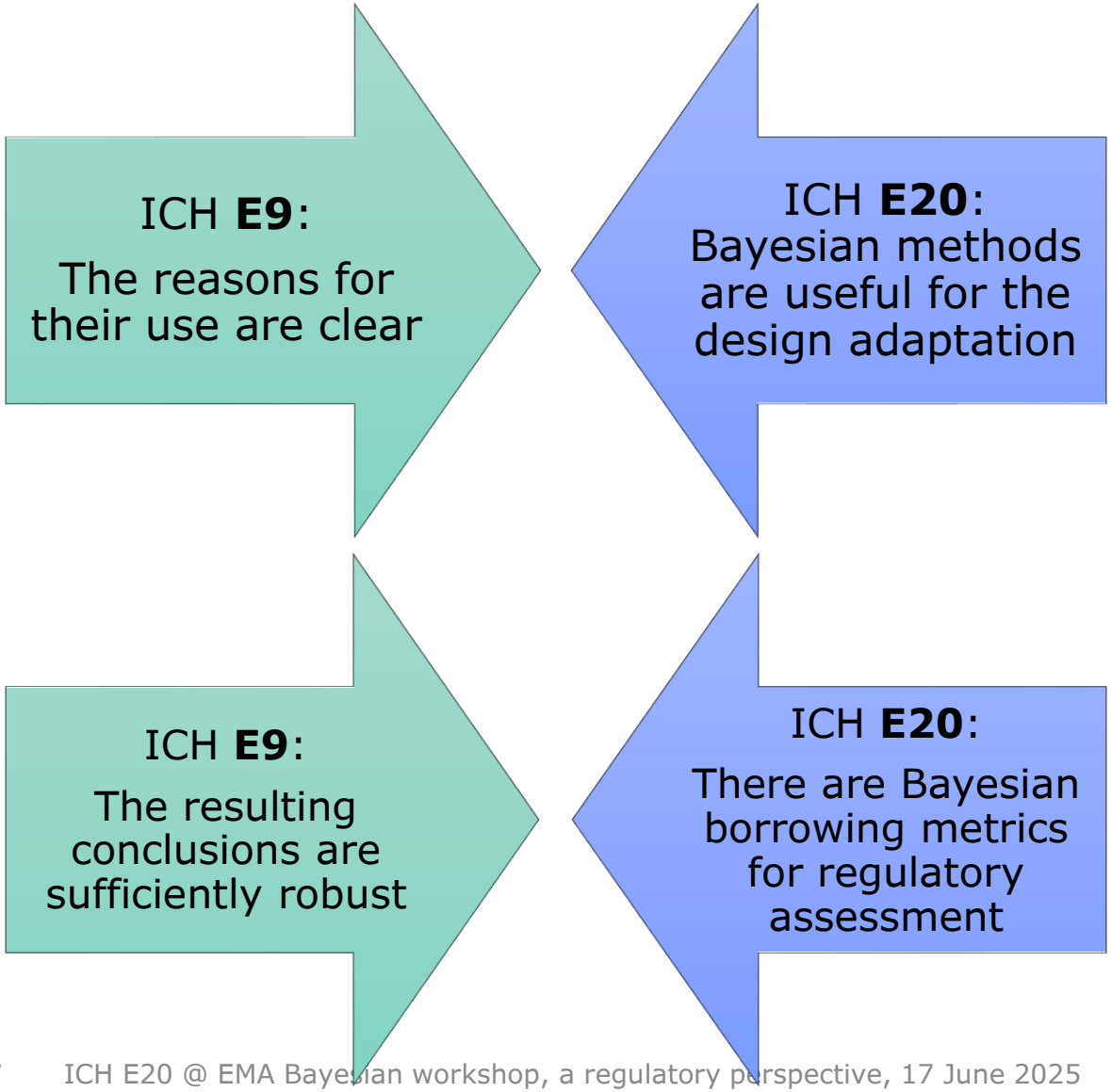


As a consequence, general statements regarding acceptability of Bayesian approaches will be read as **acceptability of Bayesian approaches for trials including a futility analysis**.

  - Trials including a futility analysis using Bayesian methods will also need to fulfil the two ICH E9 mandate criteria: “the reasons for their use are clear” and “the resulting conclusions are sufficiently robust”.

How to link ICH E9 to ICH E20?

We can learn from Bayesian adaptive designs to other Bayesian uses !



- For example, decisions on Bayesian borrowing can benefit from an interim analysis and potential adaptation.
  - Data from interim analysis can modify the level of Bayesian borrowing (e.g. by changing the randomisation ratio or increasing the sample size).
- Conditions about Bayesian borrowing for regulatory assessment mean (mainly) how to discuss with clinical assessors at the planning stage.
  - As is already happening for other design features like dropping treatment arms, selecting subgroups, sample size recalculation.

First use case: historical borrowing

- How can we guide the discussion with clinical assessors at the planning stage of the clinical trial?

Is a fully powered trial not possible? → What would be the size of a fully powered trial? → How many patients can be recruited within a reasonable time frame? → How many patients would be sufficient for benefit/risk assessment?

- Now that we're convinced that there is a reason for use of Bayesian methods for an adaptive design, what else do we need to plan?

Is there patient data to borrow from?
- Similar patients
- Similar risk structure
- Similar concomitant medication
- Similar outcome assessment

→ **Is patient-level data available?**
- Clinical assessors can check at the planning stage that old data will likely fit current medical context beyond PEP

→ **What is a prior-data conflict?**
- What factors define it?
- How much difference is acceptable or too much?
- How high is the overall risk of 'conflict'?

→ **Are there strategies for risk mitigation?**
- What can be done at the interim analysis?
- What can be at analysis stage? (pat-level data must be available)

→ **What is the consequence for decision-making?**
- What would lack of statistical significance mean?
- What role would prior-data conflict play?

First use case: example for historical borrowing of control patients at planning stage

Historical trial shows 20% response for the control treatment

- New trial shows 30% response for control
- Experimental response in the new trial is 40%

Is 30% substantially different from the historical 20%?

- From a medical perspective: is it an indicator that the **setting** has changed?
- From a statistical perspective: is it **conservative** to lump the historical control and new control together?
- Is it clinically acceptable to leave the down-weighting decision to an **algorithm**?

What is the impact of dynamic borrowing on decision-making?

- Is it acceptable that data which only fits 20% is allowed to help for 20%?
- If I can't borrow 'enough' because of down-weighting, where can this **missing** information be found?
- Can we **understand** the clinical differences between old and new control patients? And is it possible for **adjust** for that?

Still to be discussed…

- What is the meaning of a credibility interval?
- How much impact does any prior-data conflict have on the concept of statistically significance?

- Further considerations
  - Of course, assumptions need to be re-assessed at the end of the trial.
  - Need to pre-plan the assessment discussion at the start of the trial + in a way can medical expetrs can contirnute to it

Key messages

- EU guidelines should provide concrete recommendations and deviation is possible when justified.
- Regulatory recommendations for adaptive designs should be method-agnostic but also framework-agnostic.
- E20 discusses specific types of design adaptation (sample size re-estimation, dropping treatment arms), some types of adaptation (e.g. historical borrowing) may benefit from a Bayesian approach.
- Any potential adaptation should be discussed with the relevant pre-requisites from an experimental design perspective.
- Use of Bayesian methods to decide on trial success and other aspects needed for regulatory decision-making requires more work beyond adaptive designs.

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Thank you

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