



Use of modeling and simulation to inform the development of monoclonal antibodies to treat moderate-to-severe asthma: a review of EMA centralized procedures from 2014 to 2024.



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Introduction

- Biologics have treated moderate-to-severe asthma since 2003. Unlike small molecules, modeling and simulation (M&S) methods remain underused due to persistent barriers, such as the lack of standardized ways to incorporate their findings into treatment guidelines.[2]
- Assessment of evidence generated by alternative or more innovative methods by regulatory authorities can be challenging due to a lack of systematic and integrated approach to assess and establish the acceptability of these methods.
- The ICH M15 and the **ERAMET** project (Horizon Europe grant 101137141) aim to define the framework for assessment of model informed drug development (MIDD) evidence to inform decision-making.[1]

Objectives

- Building **a repository of key regulatory questions** answered in centralized procedures and evaluate the place of M&S methods in marketing authorization process for biologics approved for the treatment of moderate-to-severe asthma from 2014 to 2024.
- **Benchmarking M&S versus traditional methods** by assessing their quality using the table for assessment of MIDD evidence, a communication tool between applicant and regulatory authorities that has been set up in the ICH M15 guideline.[1]

Methods

- **Systematic review of** marketing authorization applications and related EPARs for the 5 biologics approved for asthma from 2014 to 2024.
- **Screening** of the relevant information (quality, primary pharmacodynamic, toxicology, clinical efficacy, clinical safety and clinical pharmacology).
- Translation into essential **regulatory questions** and classification of the questions based on their nature (Pharmacokinetics, efficacy, safety, Benefit/risk) and hierarchical levels (i.e. cellular, molecular, tissular, individual or population) and identification of data and methods used to address them.
- Identification of Questions for which **M&S are proposed as methods**.
- **Benchmarking of M&S methods** with traditional methods by applying the credibility framework of the ICH M15 guidelines.

Results

Repository of key regulatory questions, data and methods

- 247 questions were formulated from initial and variations of MAAs (**Figure 1**).

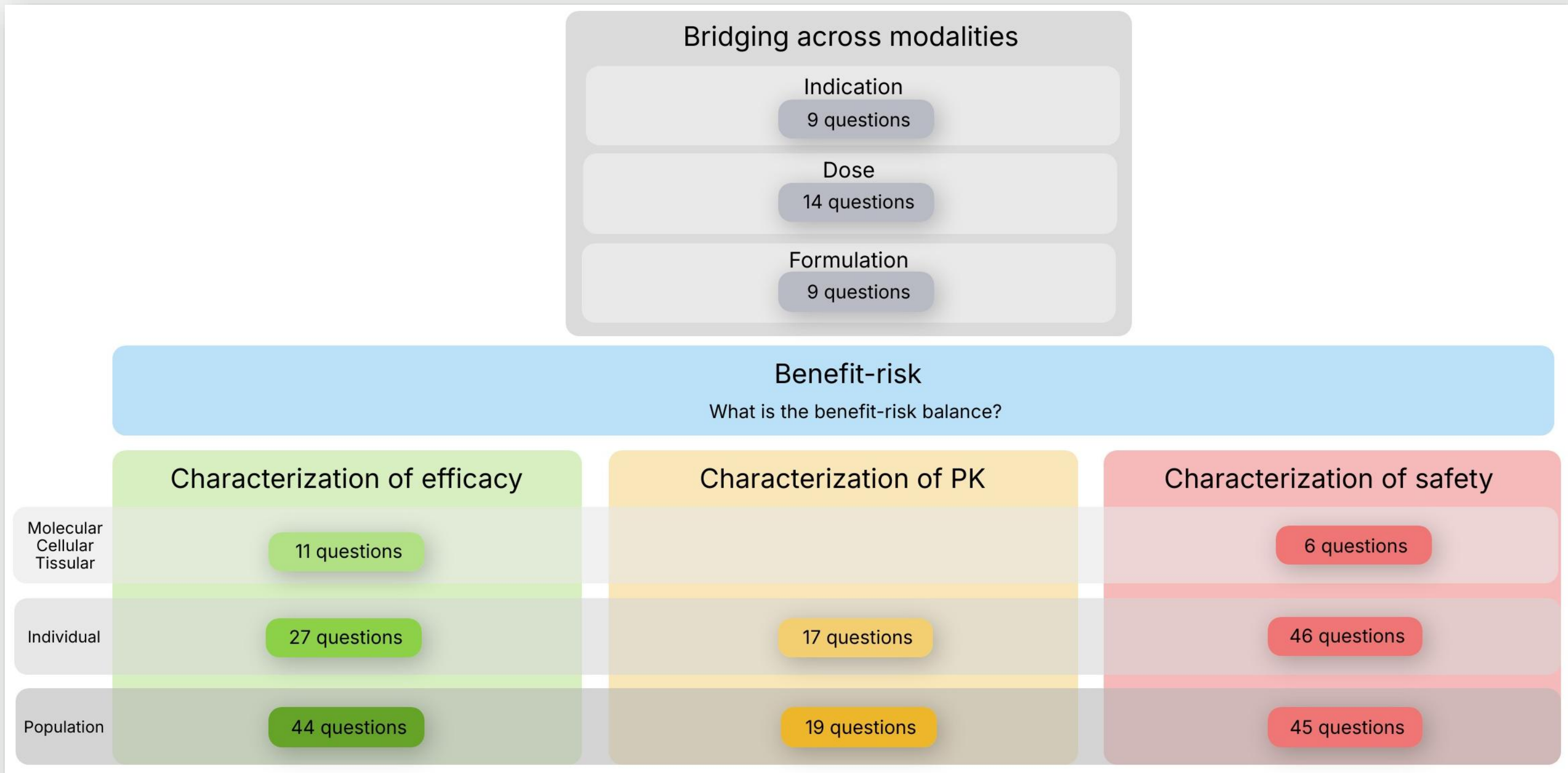


Figure 1. Overview of the repository of key regulatory questions

Results

Positioning of the use of M&S in marketing authorization applications

- M&S methods were overall used to address 17% of questions, ranging from 11% to 29% across drugs. The place of M&S by level and types of question is described in **Figure 2**.

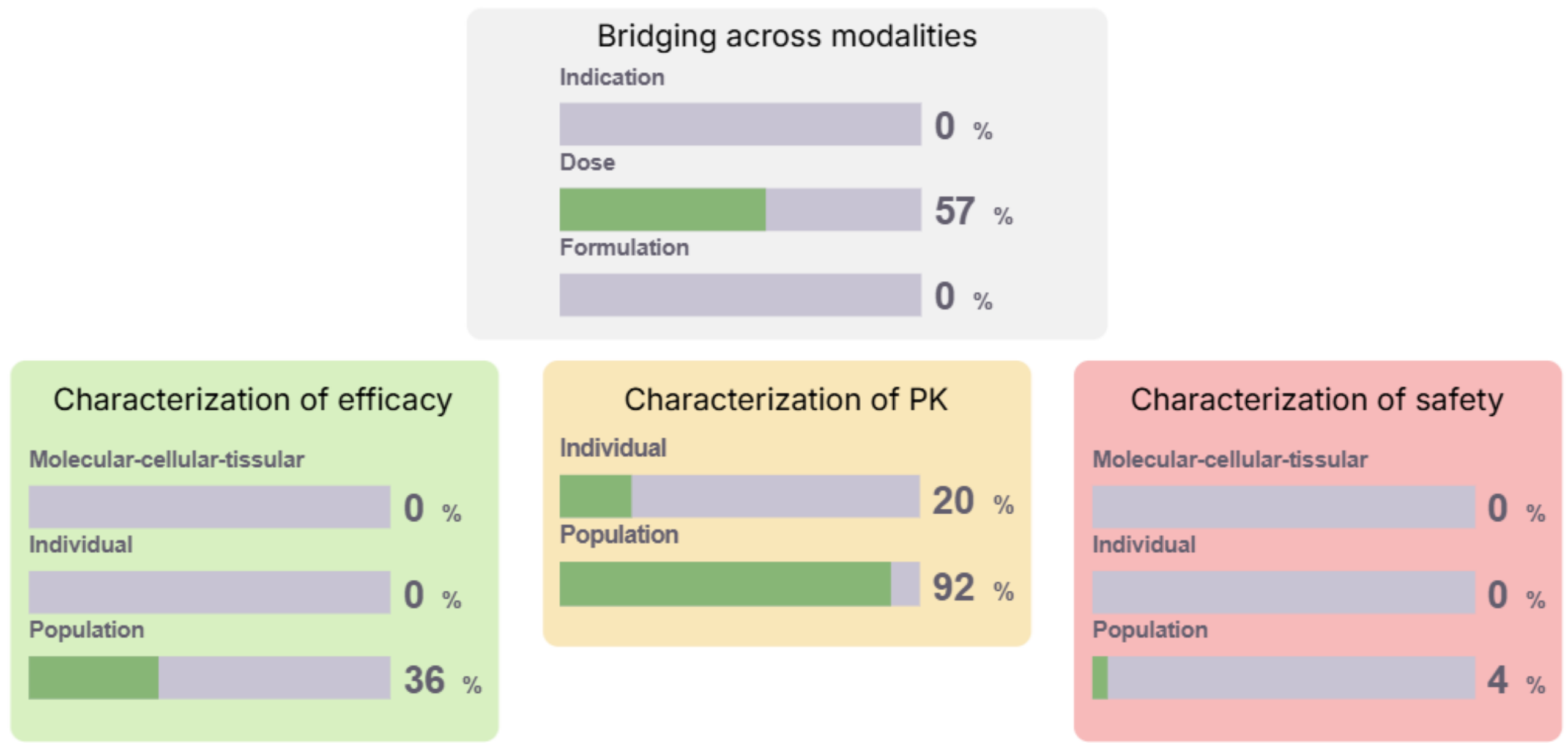


Figure 2. Incidence of M&S methods by questions in marketing authorization applications of biologics approved for asthma treatment

- M&S approaches used are mostly pop PK/PD models to predict PK in human from nonclinical data, popPK and ER models (**Table 1**).

Question	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Use of M&S
How inter-individual factors contribute to variations in PK?	popPK MA	popPK	popPK	popPK + non-M&S	popPK	1
What is the impact of comedication on PK exposure?	popPK	popPK	popPK + non-M&S	popPK	popPK	1
What is the impact of demographics on PK exposure?	dose-reponse popPK MA + non-M&S	popPK + non-M&S	popPK + non-M&S	popPK + non-M&S	Non-M&S	4/5
Which disease characteristics influence the efficacy?	Non-M&S	Non-M&S	E-R + non-M&S	E-R + non-M&S	Non-M&S	2/5
What is the PK profile in adolescent (12-18 years)?	popPK	Non-M&S	NA	Non-M&S	popPK	2/5
What is the dose-exposure response?	NA	NA	E-R	NA	PK/PD	2/5
Should the dose be flat or adjusted based on individual factors?	NA	popPK + non-M&S	NA	Non-M&S	popPK	2/5
Is the PK exposure influenced by the condition of injection?	Non-M&S	Non-M&S	Non-M&S	popPK	NA	1/5
What is the clinical efficacy of the product in adolescent (12-18 years)?	Non-M&S	Non-M&S	NA	E-R + non-M&S	NA	1/5
What is the relationship between biomarkers and clinical outcome?	Non-M&S	Non-M&S	Non-M&S	NA	PK/PD	1/5

Table 1. Examples of questions answered by M&S methods in marketing authorization application for the biologics approved for asthma treatment. NA means not answer by the applicant.

Benchmarking of M&S methods versus traditional methods

- Tables of assessment of MIDD evidence (per ICH M15) were filled for questions answered by M&S methods. We selected an exposure-response model as an example (**Figure 3**).

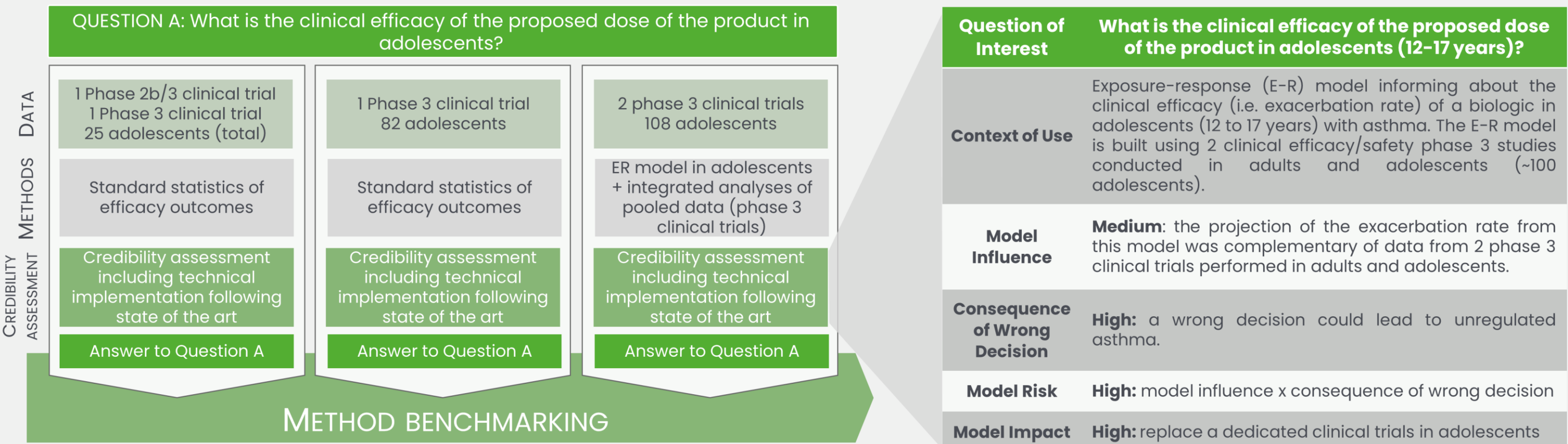


Figure 3. Example of method benchmarking including credibility assessment through the ICH M15 table for assessment of MIDD evidence.

- Credibility assessment reveals various levels of maturity.

Conclusions

We characterized the extent and context of uses of M&S in regulatory submissions related to marketing authorization access and proposed an approach for their benchmark vs more established approaches for biologic used to treat moderate-to-severe asthma and approved from 2014 to 2024.

Credibility assessment reveals various levels of maturity and therefore the regulatory acceptance was also found variable. This repository will be completed by review of pediatric investigation plans to assess the place of M&S in the context of pediatric drug development.

References

- [1] International Council for Harmonisation. (2024). ICH M15 Guideline on general principles for model-informed drug development.
- [2] Sriprasart, T. et al. (2023) 'The role of modeling studies in asthma management and clinical decision-making: a Delphi survey of physician knowledge and perceptions', Journal of Asthma, 60(9), pp. 1687–1701. doi: 10.1080/02770903.2023.2180748.

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ERAMET



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