

Introduction

Annually, 500,000 children are born with sickle cell disease (SCD) and 60,000 people are diagnosed with transfusion-dependent β Thalassemia (TDT).[1] Despite their recognized value, Important barriers still exist for modeling and simulation (M&S) methods to be fully embraced in the therapeutic area of haemoglobinopathies, including a lack of standardized methodology for integrating evidence from modeling studies into treatment guidelines.[2] The ICH M15 and the ERAMET project (Horizon Europe grant 101137141) aim to define the framework for the assessment of Model Informed Drug Development (MIDD) evidence to inform decision-making.[3] Moreover, the Question centric approach was recently proposed to combine and benchmark the methods and data used to answer regulatory questions, and to eventually inform the benefit/risk balance assessment.

As part of our work, a repository of key regulatory questions is proposed to characterize the extent and context of uses for M&S methods in drug development for SCD and Thalassaemia from January 2014 to December 2024 based on the review of EMA SAs.

Methods

The scientific advice (SA) requests submitted to the European Medicines Agency (EMA)’s Committee for Medicinal Products for Human Use (CHMP) for SCD and Thalassaemia between January 2014 and December 2024 by manufacturers were manually screened. The initial questions from the SAs were reformulated into key regulatory questions and classified as questions that inform the Benefit/Risk balance by characterizing Efficacy, Safety, or Pharmacokinetics (PK) or allowing bridging across conditions of use (Modalities)). The Hierarchical level (Population, Individual, Cellular, Molecular) was reflected in the repository. The data type and quality, and methods used for data generation and analysis were also reflected in the repository. The questions for which M&S was used as analytical method were identified, as well as the outcome of the related regulatory interaction.

Results

A total of 45 and 31 SAs were identified, 45 for SCD and 31 for Thalassaemia respectively, of which 288 and 215 questions were extracted and reformulated into regulatory questions. For both diseases, 15 of the 46 SCD SAs and 6 of the 31 Thalassaemia SAs contained questions related to M&S. The use of M&S was benchmarked against traditional methods by applying the credibility framework of the ICH M15 guidelines. An example of the credibility table filled is shown in table 1.

The CHMP’s advice on the use of M&S methods

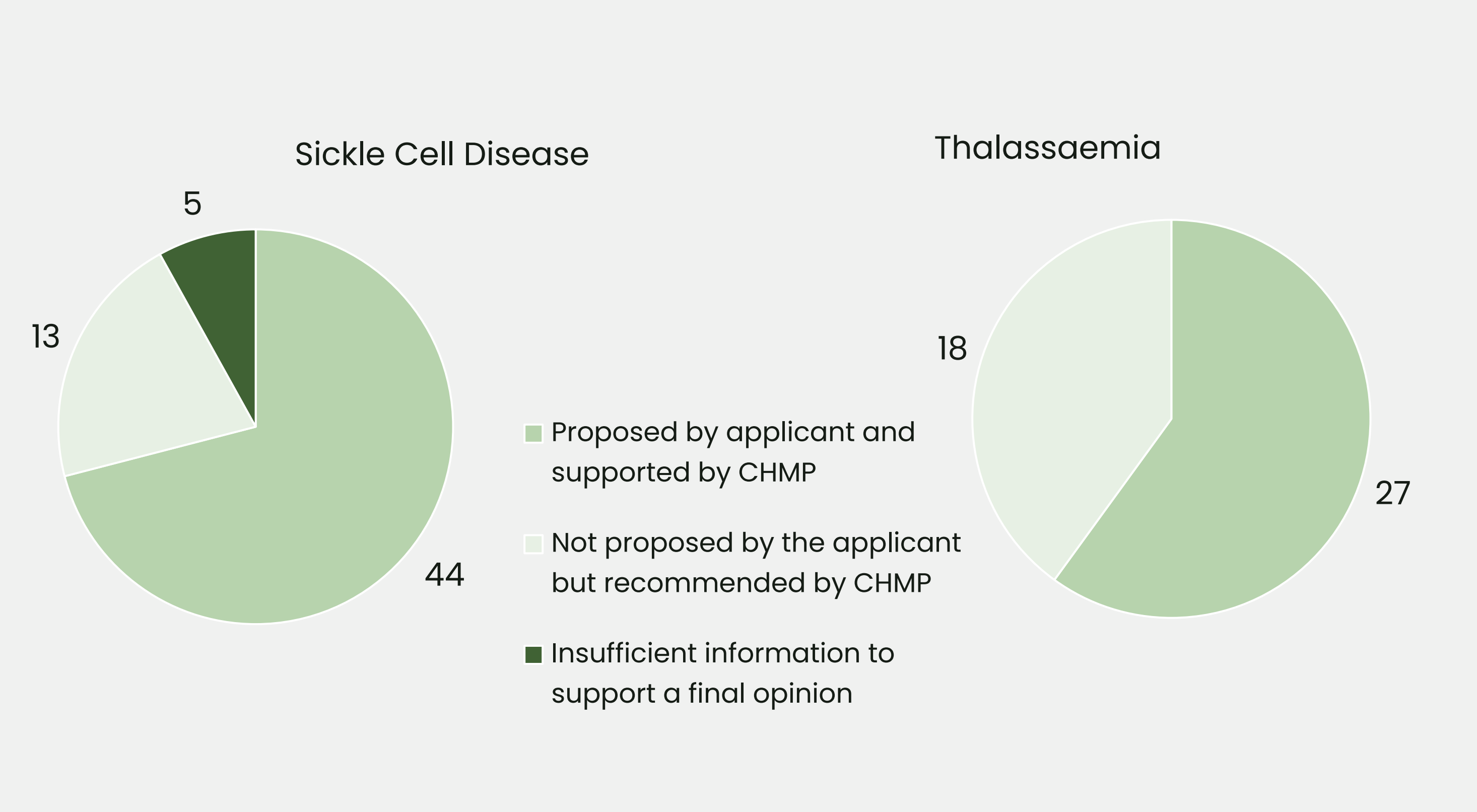


Figure 2: The feedback and recommendations of the CHMP on the use of M&S methods

M&S methods were used to inform nonclinical and clinical study design and data analysis. Their use included informing the extension of indication, dose selection, and the characterization of drug’s PK, efficacy or safety, as well as their determinants.

The feedback by the CHMP was overall positive when M&S was proposed by the applicants; with sometimes, some advices for amendment of their implementation, as shown in Figure 2 and table 2. Interestingly, the recommendation to use M&S originated from the CHMP in 13 and 18 cases, for SCD and thalassemia, respectively (see Figure 2 and table 2) .

Table 2: Responses from the CHMP – Examples

Clinical Study	M&S method	Intended Use	CHMP response	CHMP Comments
Phase 1 study	PKPD model	Dose selection	Recommended by the CHMP	Base dose selection for the young adults and adolescents on PK, PD and safety data from clinical studies performed in patients, preferably using a PKPD model
Phase 2 study	POPPK model	Establishing PK profile (ADME) in paediatrics (Down escalation of adult dose for paediatrics)	Supported by the CHMP	The approach could be acceptable but sufficient points should be collected for the validation of the model
Phase 3 study	POPPK model	Extension of the drug’s indication to paediatrics	Supported by the CHMP	The approach is supported but body weight and maturation must be included in the model to see their influence on PK in the paediatric population

Discussion and Conclusion

Most of the questions in the repository concerned the characterization of drugs’ efficacy and safety at population level, which is reflective of the fact that most questions in SAs concern clinical studies’ implementation or information needed to establish the positive benefit/risk balance for regulatory approval. M&S methods were mostly proposed for phase 3 and phase 2 study design optimization or data analysis. 33% (SCD) and 19% (Thalassaemia) of screened SAs included questions or recommendations related to M&S, which indicates that M&S methods have real potential and are increasingly used in drug development for Haemoglobinopathies. Intrestingly, For 92% (SCD) and 100% (Thalassaemia) of the questions, the use of M&S methods was either supported or recommended by the CHMP. The credibility framework (described in the ICH M15 guideline) which is centered around drug development questions is being implemented to assess the quality of these model-based approaches in relation to their context of use, the patient risk and the regulatory impact. Overall, the use of M&S methods to address drug development and regulatory questions for haemoglobinopathies is promising, if sufficient data can be provided to develop and qualify the M&S models.

References

[1] Locatelli F et al. 2024. Autologous gene therapy for hemoglobinopathies: From bench to patient’s bedside. Molecular Therapy, pp. 1202-1218.

[2] Tsakalozou E et al. 2025. Considering Opportunities and Challenges When Implementing the Model Master File Framework – a Meeting Report. Pharmaceutical Research.

[3] International Council for Harmonisation, 2024. General Principles for Model-Informed Drug Development M15, Amsterdam: European Medicines Agency.

Repository of Questions

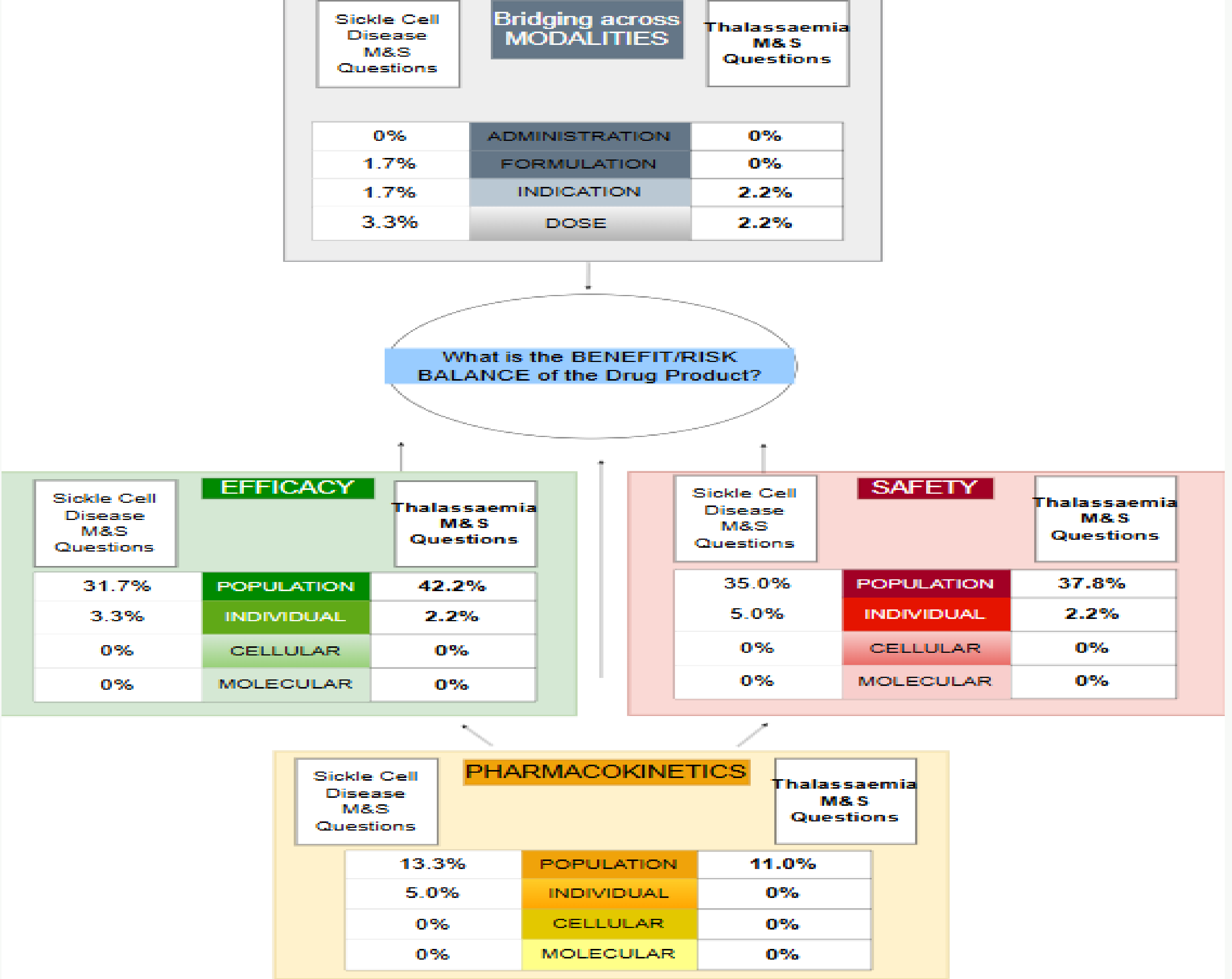


Figure 1: The outline of the repository showing the classification of questions that feed into the Benefit/Risk balance and classification by Hierarchical level

Table 1: The Assessment of a M&S method using the Credibility Framework (ICH M15)

Credibility Table – Thalassaemia example	
Question of Interest	What is the dose of the drug in children (12 to <18 years) with TD β -thalassaemia
Context of Use	The popPK model and the exposure response analysis (adults) is built based on phase 2 and 3 studies. The 2 models will be refined using data from the dose escalation study in adolescents determined from the extrapolated PK. Efficacy data will be derived from a phase 3 study in adults.
Model Influence	Medium – The evidence to inform efficacy is derived from the 2 models, the dose finding phase 2 study in adolescents and the efficacy study in adults
Consequence of Wrong Decision	High – Risk of toxicity and lack of efficacy
Model Risk	Medium/High – Model Influence x Consequence of wrong decision
Model Impact	High – The model replaces efficacy and safety studies in children
Appropriateness of M&S Approach	The modeling approach is deemed appropriate if the model displays acceptable predictive performance and if the data collected in children are informative.
Technical (Acceptance) Criteria	Technical assessment of the model using graphical and numerical tools. Both models need to display plausible parameters and estimation with acceptable precision
Model Evaluation	Not applicable – data still to be collected