



Model informed drug development and CAR-T cells : A review of their use and credibility assessment in the context of EMA centralized procedures

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Introduction

Six **CAR-T therapies** (*genetically modified T-cells*) are **approved in the EU**, mostly as 3rd/4th-line options, and hold **orphan status** for hematologic cancers.

The **limited number of patients** and the **technological requirements** make the standard drug development not feasible.

Modelling & Simulation (M&S) can support drug development

⚠ There is currently not streamline recommendation for the use of M&S in the context of **CAR-T therapies development and regulatory approval**.

🎯 To address this gap, we built a repository of EU procedures (2014–2024) in order to:

- Benchmark **M&S vs traditional and established methods**,
- Assess model credibility using the **ICH M15 framework**.

Results

A repository of **121 regulatory questions** were extracted from CAR-T submissions to EMA. See Figure 2 for general structure.

They were classified by domain:

- *Efficacy* (35), *Safety* (36), *Pharmacokinetics* (11), and *conditions of use* (39).

Most questions targeted the **population level**, especially in efficacy and safety.

As shown in Figure 3, only **22 questions (18,2%)** involved **M&S as methodology for data analysis**.

The main approaches used were:

- **popPK** models for PK characterisation and covariates,
 - **Dose-Exposure-Response** (DER) models for efficacy, survival and safety description.
- These models were used to support dose optimisation and inform benefit-risk assessments. **Bayesian models** supported stability criteria; **regression models** compared survival outcomes.

Credibility assessments using the **ICH M15 framework**, see Table 1, was implemented and showed:

- **Model influence**, and model **risk were of variable levels for the proposed applications**, but most of the time the model **impact was rather low** given the availability of clinical trial data.

Question of Interest	What is the optimal dose to be used in phase 3 ?
Context of Use	ER models developed for efficacy and safety endpoints using data from phase ½ in ~200 patients In addition to 2 clinical efficacy and safety studies were conducted in relapse/refractory patients
Model Influence	Medium influence because the models were used in addition to support of clinical data
Consequence of Wrong Decision	High consequence for phase 3 patients because wrong decision could lead to lack of response if underdosed or increased adverse events if overdosed.
Model Risk	Medium risk because the models were used as support of clinical data
Model Impact	Low impact because there are 2 clinical trials data to support the dose selection

Table 1 : Example of key assessment elements for defining the therapeutic window after phase 2 study using ER models

Materials & methods

A **systematic review** of regulatory documents, including Public assessment report and marketing authorization applications, was conducted for all approved CAR-T therapies.

A **screening** of relevant data and methods was performed, and each element was linked to regulatory questions (Figure 1).

A structured **repository** was built around :

→ *Efficacy, safety, PK, and modality of use*.

M&S as methods were identified using keyword screening.

The extracted models were mapped to the corresponding regulatory questions.

Their **credibility** was assessed using the **ICH M15 framework**.

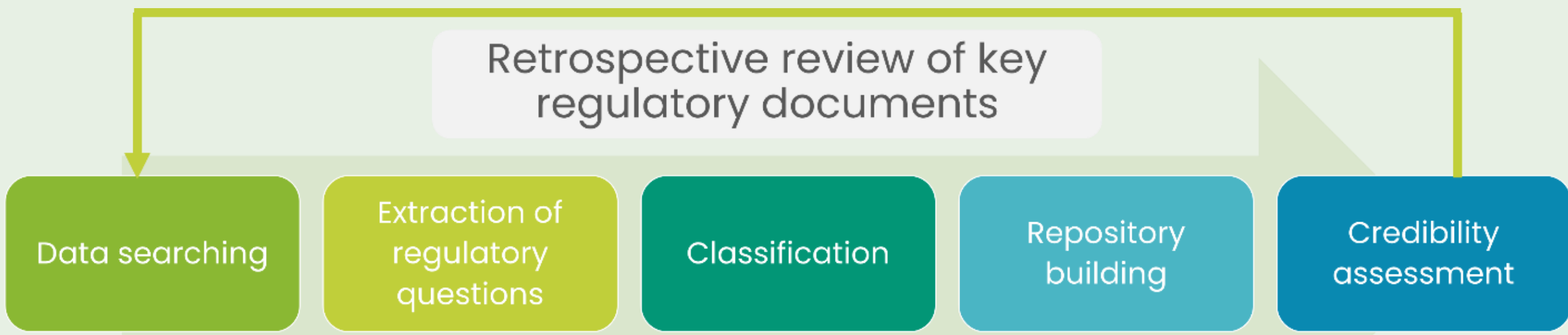


Figure 1 : Methodology framework

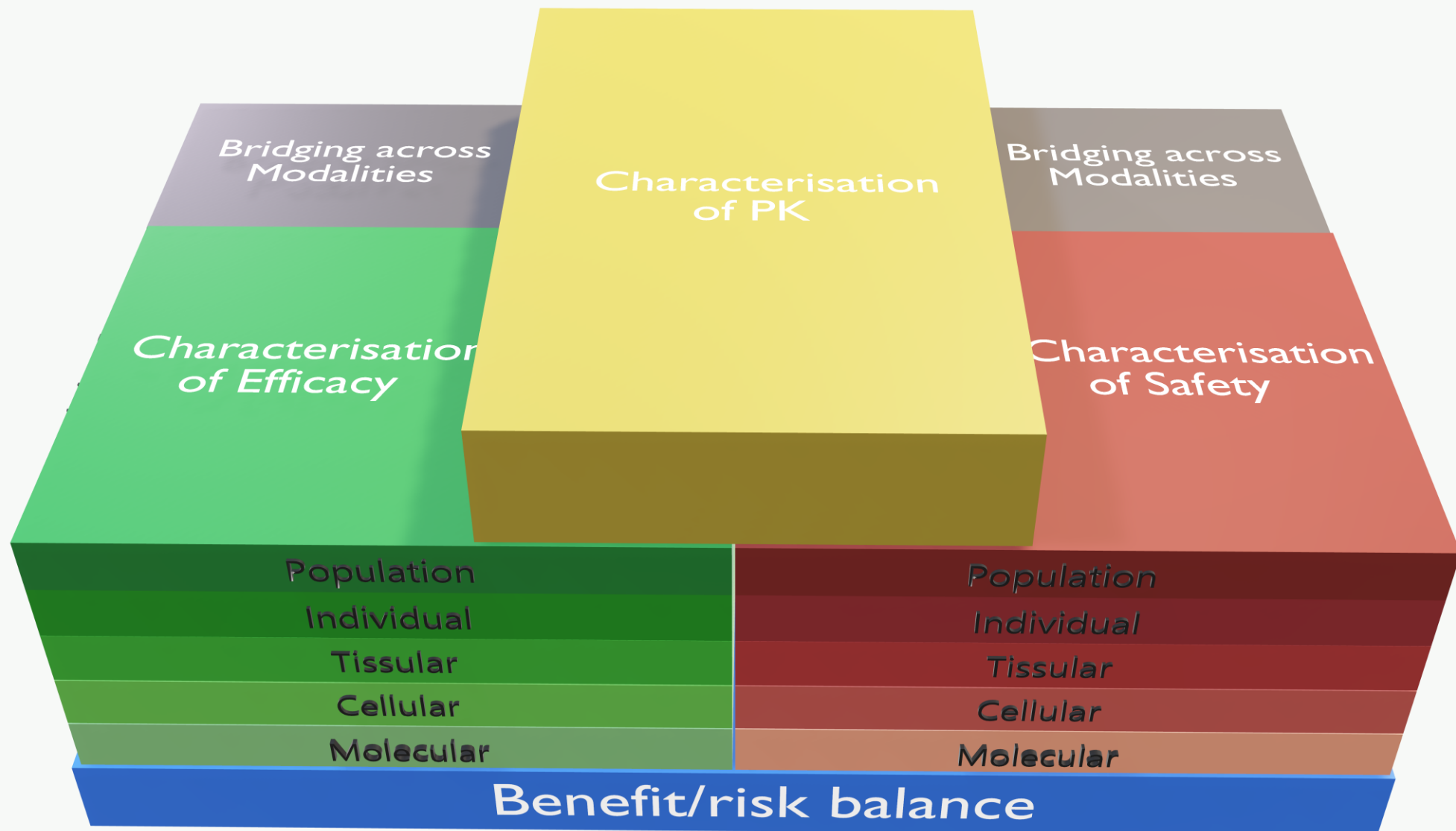


Figure 2 : 3D structure of the repository

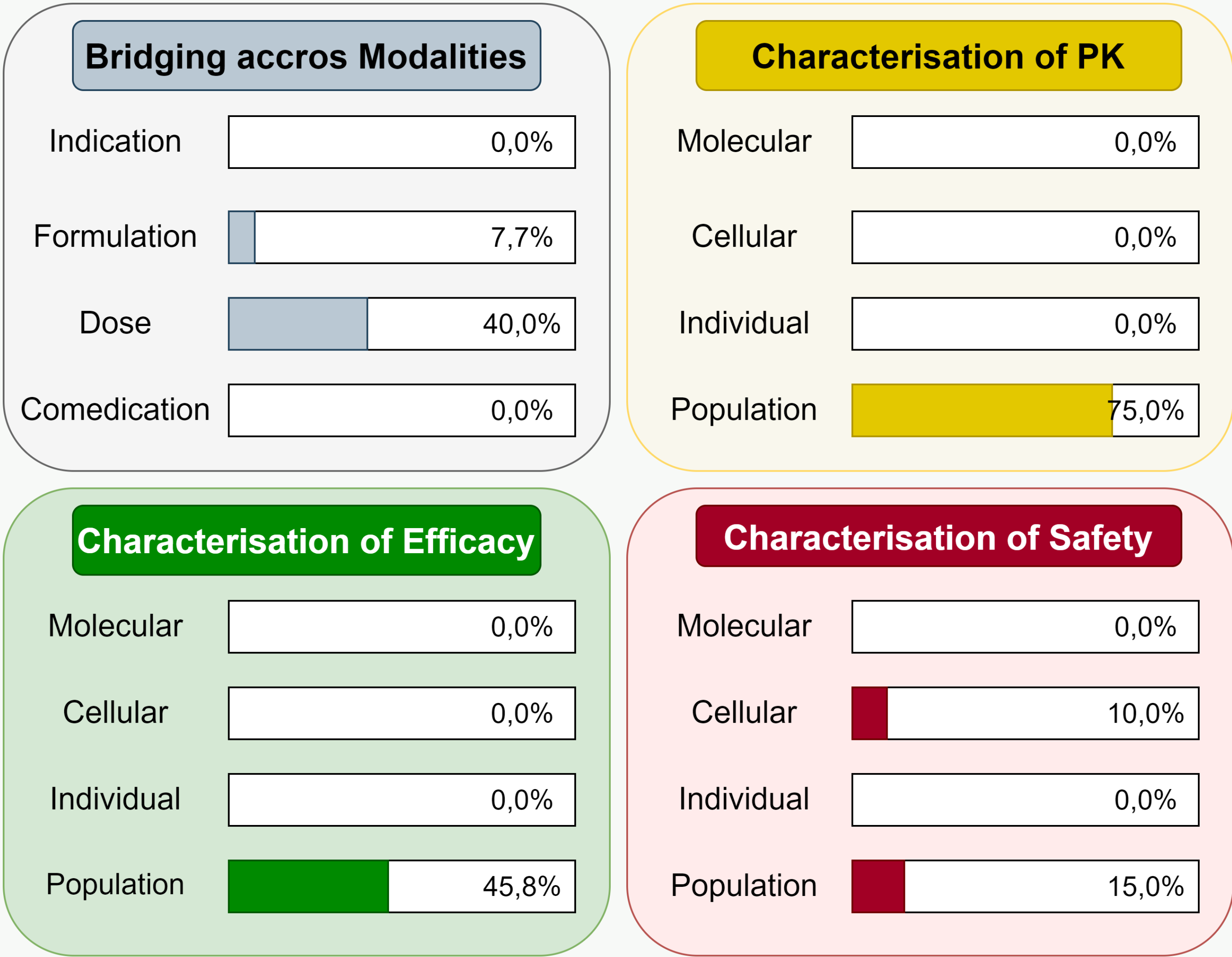


Figure 3 : Proportion of M&S in questions by category and level

Conclusion

🔍 M&S remain **underused** in regulatory submissions related to CART cell therapies.

The described models are mostly **supportive**, with **variable credibility** and **regulatory impact**.

👶 The repository will be extended to **paediatric investigation plans** to explore M&S use in paediatric drug development and assessment.

