EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Current use of physiologically based pharmacokinetic modelling in new medicinal product approvals at EMA

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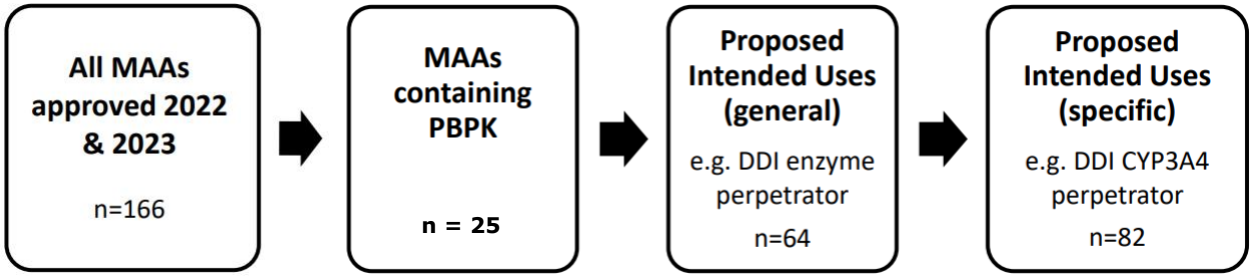
Methods

- Screened all EPARs from approved MAAs from 2022 – 2023 for reference to PBPK
- In-depth review of assessment reports (D80, D150, D210) and related LoQ/LoOI (D120, D180) to extract:

  (i) intended use of submitted PBPK model and
  (ii) the outcome of the assessment: *qualified* yes/no; used to inform SmPC

- The D120 LoQ were analysed to gain insight into concerns raised during the assessment of the a model

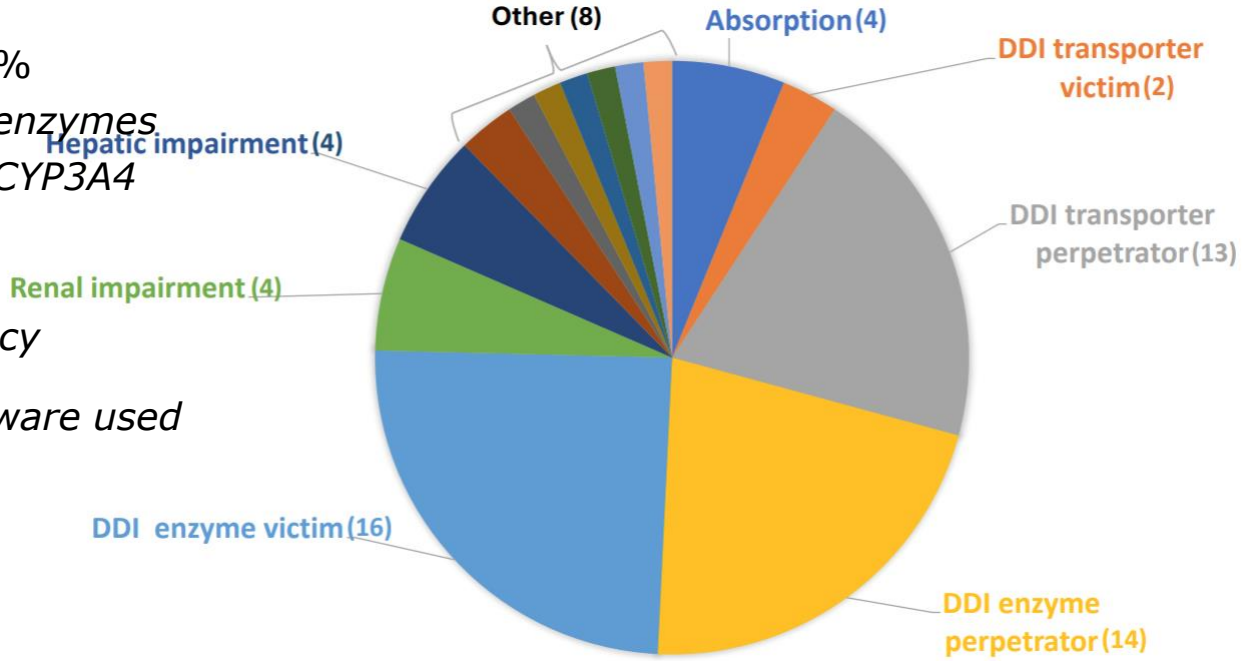
Results



- PBPK models identified in 25 out of 95 (26 %) Article 8(3) applications
- Use increased from 23 % in 2022 to 30 % in 2023.
- 22 small molecule applications, 2 mAbs, 1 peptide drug
- Suggestion of more frequent use of PBPK in oncology (36 %) compared to other TAs

Results

- DDI predictions: 69 %
  46 % DDI involving enzymes
  31 % DDI involving CYP3A4
- *No PBBM or pregnancy*
- *No open-source software used*

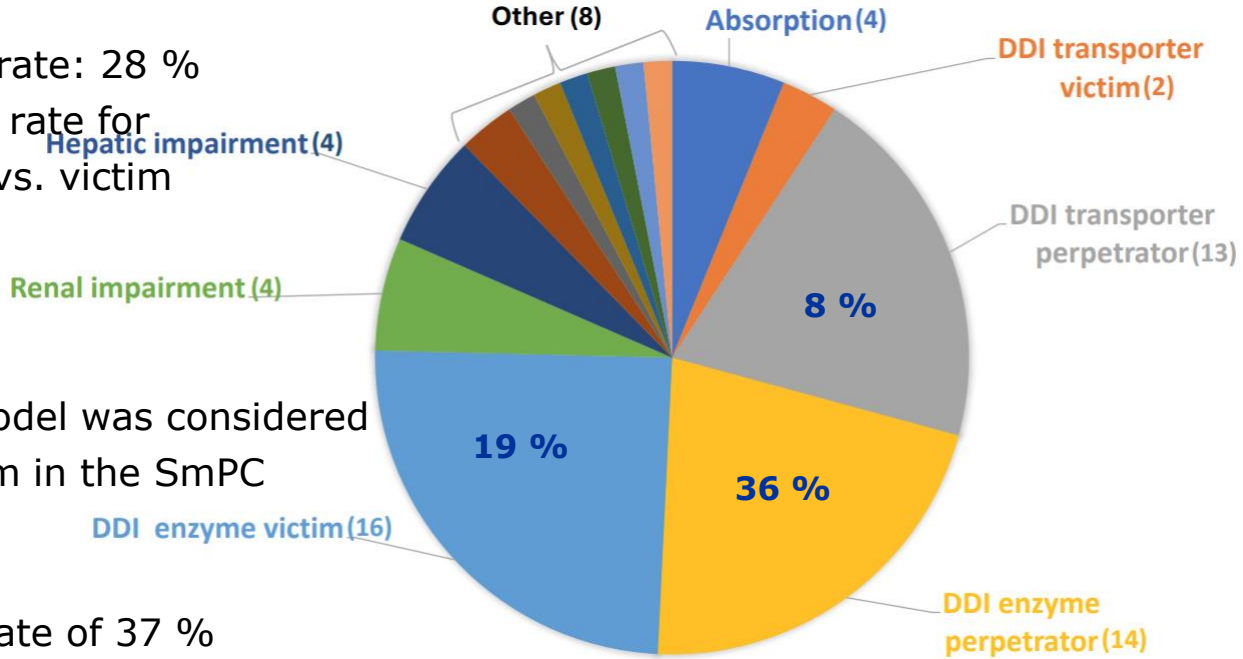


Results

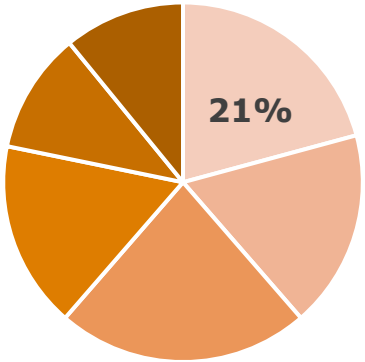
- Overall qualification rate: 28 %
  Different acceptance rate for drug as perpetrator vs. victim

- In 6/65 cases the model was considered *supportive* for a claim in the SmPC

- Overall acceptance rate of 37 %



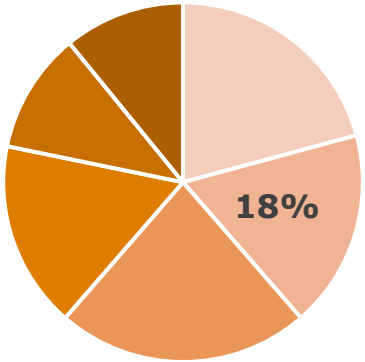
Results: reasons for non-qualification



1) Concerns around structure of the PBPK model:

   - omission of elimination pathways relevant to the PK (e.g. intestinal enzymes, transporters) or interaction mechanisms (e.g. auto-inhibition/-induction)

Results: reasons for non-qualification

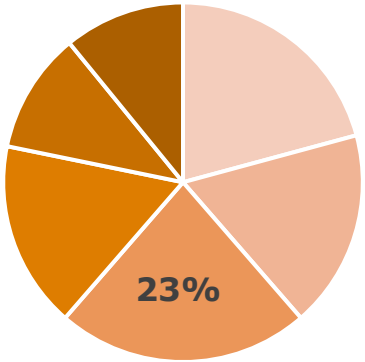


2) Insufficient justification of key assumptions:

- missing or questionable justification for value of input parameters used

- Often related to uncertainty around the source (literature vs. in-house) or methods used to derive the input values (e.g. f_m)

Results: reasons for non-qualification



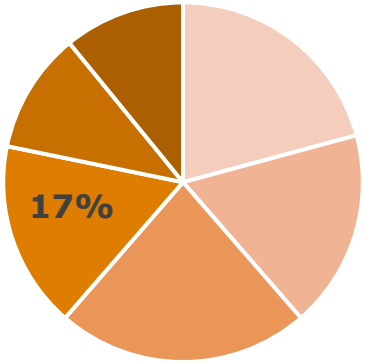
3) Lack of relevant data to assess model's predictive performance:

- Relevant data not submitted; incl. data to reproduce the PBPK results (input parameters, etc.)

- Clinical data not considered relevant: non-representative population, e.g. only data from HVs

- Poor quality clinical data: sparse PK samples, too low sample size, ...

Results: reasons for non-qualification

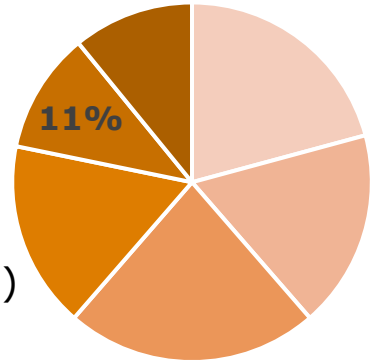


4) Poor predictive performance:

- Relevant over-/under-prediction of secondary PK parameters for victim/perpetrator or GMR for DDI

- Acceptance criteria depend on the regulatory impact, no single threshold (two-fold criterion, etc.)

Results: reasons for non-qualification

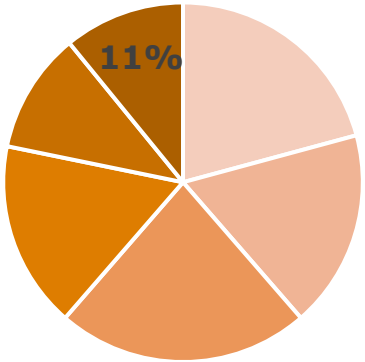


5) Insufficient number of compounds in qualification dataset:

- The # and variety of compounds (substrates, inhibitors & inducers) did not allow to assess the PBPK model's robustness

- Often referred to EMA PBPK guideline that '(…) It is considered that e.g. eight to ten compounds is indicative of a sufficient number.'

Results: reasons for non-qualification



6) Reasons unclear from assessment report:

- Likely implicit reason for non-qualification is the less established intended purpose: transporter mediated DDIs (5/7),
prediction of enzyme induction (1/7) and mechanism-based inhibition of an enzyme (1/7)

Conclusions

More (detailed) guidance:

- ✓ Distinguish better between “generic” qualification and qualification in the context of a MAA and impact on qualification requirements – new terminology
- ✓ High volume for certain intended uses could justify a Q&A with more specific guidance on qualification requirements
- ✓ More standardised approach to the assessment of PBPK models and the reporting thereof, e.g. via the credibility matrix approach.

Conclusions

PBPK community:

- ✓ High acceptance rate for some intended uses (e.g. drug as perpetrator of CYP enzymes) suggests the possibility to achieve CHMP qualification.
- ✓ EMA workshop planned for Q4 2025 on 'Reporting and qualification of mechanistic models for regulatory assessment' foresees opportunities for stakeholders to feedback experience with the assessment of PBPK models in regulatory submissions
- ✓ Planned efforts around PBPK (and M&S) are reflected in MWP workplan; stakeholders can interact during public consultation of draft (updated) workplans

Q&A?