

Supplementary material 3

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Physiologically Based Pharmacokinetic (PBPK) Modeling of Antidepressants: A Scoping Review of existing models, applications, and software-tools

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Supplementary File 3: Model Development Stage Assessment

1. General Procedure

Data extraction was performed using an AI-assisted workflow. The large language model Claude was used as a structured extraction tool to support the identification of relevant information from the included publications and their supplementary materials. Prior to use, the model was guided through an iterative prompt development process, including predefined definitions, extraction rules, assessment criteria, and annotated examples. The training prompts were refined until consistent and acceptable extraction performance was achieved.

For each included study, the full-text article and, where available, supplementary materials were uploaded to the model. The model was instructed to extract predefined variables, including the origin of model parameters, the type and number of studies used for model development and validation, and the presence and type of sensitivity analyses. Wherever possible, extracted information was required to be supported by direct textual evidence from the source documents to ensure traceability and reproducibility.

To ensure data quality, all extracted information was subsequently reviewed by the authors. In addition, a random sample of 20% of all models was independently verified. Any discrepancies or uncertainties identified during the extraction process were resolved through re-examination of the original source documents.

2. PBPK model development stage assessment score

Category	Points
1. Development / Refinement/ Parameter origin	6
2. Robustness / Sensitivity	3
3. Validation	11
Total	20

1. Development / Refinement/ Parameter origin across all PBPK development stages (0–6)

Criterion	Points
Predominantly mechanistic / literature-based; very little or no fitting (bottom-up)	6
Both literature-based / experimental and fitted parameters (mixed bottom-up and middle-out)	4
Predominantly data-driven (top down) / unclear	0

2. Robustness / Sensitivity analysis across all PBPK development stages (0–3)

Analysis	Points
Global sensitivity analysis	3
Local sensitivity analysis	1
none	0

3. Validation (0–11)

a) Type of validation across all PBPK development stages (0–5)

Type	Points
External independent	5
Mixed internal and external	4
Internal only	2
None	0

b) Scope of validation across all PBPK development stages (0–4)

Scope	Points
≥ 10 or ≥5 to <10 studies	+2 or +1
≥ 2 dose levels	+1
≥ 2 routes of administration/ formulations	+1

c) Validation of the Final model / Final application (0–2)

Scope	Points
≥ 2 studies	2
1 study	1
none	0

Overall Rating

Score	Model development stage
17-20	very extensive
13-16	extensive
9-12	substantial
5-8	intermediate
0-4	initial

Assumptions:

- if multiple model development stages were present (e.g., base model, intermediate model, final model), all stages were considered during assessment
- modeling approach, model structure, and sensitivity analysis refer to the parent compound (not the metabolite)
- studies used for validation of an active metabolite are included (as they also contribute to validation of the parent compound)
- if the distinction between internal and external validation studies was unclear, the most likely classification was inferred from the manuscript description; in cases of uncertainty, studies were conservatively classified as internal validation
- if multiple model development stages were present the least mechanistically independent modeling approach was applied for the overall classification (e.g., if the base model was developed using a middle-out approach, while subsequent model extensions were bottom-up, the overall model was classified as middle-out)
- when counting studies, individual studies rather than datasets were considered. Accordingly, multiple datasets originating from the same study were counted as one study