**TEMPLATE for creating an MID drug report**

This document serves as a guidance

and can be tailored to the specific use case.

(Jan 2024)

|  |  |
| --- | --- |
| **Drug** | *<Please include generic drug name>* |
| **Population** | *<Please include population>* |
| **Version** | *<Please include version number>* |
| **Date** | *<Please include date (month/year)>* |

TABLE OF CONTENTS

[1. Rationale for model-informed dose 4](#_Toc161151937)

[2. Model credibility 4](#_Toc161151938)

[3. Dose-finding strategy 6](#_Toc161151939)

[4. Model-informed dose 8](#_Toc161151940)

[5. Considerations for implementation 9](#_Toc161151941)

[6. Comprehensive evidence & feasibility review 10](#_Toc161151942)

[7. Relevant literature 10](#_Toc161151943)

[8. Abbreviations and references 10](#_Toc161151944)

Disclaimer

*<Please include the disclaimer below.>*

This website provides model simulations of dosing regimen for drugs used by pediatric and pregnant patients. These are NOT dosing recommendations for clinical use. Drug dosing recommendations for clinical use in pediatric patients and pregnant patients and/or their fetuses, which may have been supported by modeling and simulation, are provided by the Dutch Pediatric Formulary (www.kinderformularium.nl, or any of its international affiliates) and the Teratology Information Service, Netherlands Pharmacovigilance Centre Lareb (www.lareb.nl), respectively. Final dosing recommendations on these websites are the result of a careful benefit-risk assessment of the model-informed dose in the context of all available clinical evidence and experience. Clinical boards endeavor to implement modeling and simulation information in their recommendations promptly, but a lag time is inevitable. Hence, dosing recommendations on these website may not (yet) take into account results from modeling and simulation.

Important links

*<In the case of a pediatric dosing recommendation add the links of the following formularies (add specific links for the drug of interest.>*

**Pediatric *<drug name here>* dosing recommendations for clinical practice can be found in one of the European Pediatric Formularies.**

The Netherlands: https://www.kinderformularium.nl/

Germany: https://kinderformularium.de/

Austria: https://kindermedika.at/

Norway: https://www.koble.info/

*<In the case of a pregnancy-specific dosing recommendation add the link below.>*

**Pregnancy-specific *<drug name here>* dosing recommendations for clinical practice can be found at the website of the Teratology Information Service, Netherlands Pharmacovigilance Centre Lareb:** Link

**The scientific publication of this study by *<Author>* et al. (PMID: …)**

“Title”

Journal, date of publication, doi: …

**Template for creating a model-informed dosing report**: download here.

# Rationale for model-informed dose

*<Please describe the rationale (i.e., motive that dictates the study). Examples: an adjusted dose is anticipated because of the expected effect of development, maturation or pregnancy on the drug’s pharmacokinetics or the clinical response with the current dose is suboptimal. Also, mention the aim of the study..>*

More information on physiologically-based pharmacokinetic (PBPK) modeling and the process of model verification can be found in the section Background information: Model-informed dosing of the MELINDA website.

# Model credibility

Credibility of the established PBPK model was evaluated by checking model parameterization and through verification simulations. This step is needed to ensure the model's trustworthiness for simulating drug pharmacokinetics (PK) with yet existing and alternative dosing regimen(s). The framework below was used to navigate through this process.

General information on PBPK model credibility can be found in the section Background information: Model-informed dosing of the MELINDA website.

*<Please complete the framework. Sufficient model quality is paramount for issuing credible model-informed dosing recommendations for use in clinical practice. Transparency regarding model credibility is essential for adequate interpretation and implementation of the results. The required level of model credibility depends on the context of use and clinical impact of the simulations. More details on this topic are discussed by Van der Heijden et al. 2023 (Clin Pharmacol Ther, PMID: 37553784).>*

*<Please specify which modeling software is used: general-purpose modeling tools (such as R) or a dedicated contemporary user-friendly PBPK software platform such as Simcyp® (include software version). If pre-parameterized population and/or drug models are used, report the source of these models and report any adjustments. If applicable,, include applied ontogeny profiles of relevant metabolizing enzymes (i.e., presented as a graph or equation).>*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Framework for assessment of PBPK model credibility** | | | | | |
| **Model parameterization** | | | | | |
| 1 | Is the drug model of the PBPK model adequately parameterized  (e.g. contributing eliminating pathways, placental drug transfer)? | No | Doubtful | | Yes |
| *<comment>* | | | | |
| 2 | Is the population model of the PBPK model adequately parameterized  (e.g. incorporation of biological variability, relevant ontogeny profiles, abundance of relevant placental transporters)? | No | Doubtful | | Yes |
| *<comment>* | | | | |
| 3 | Are there any assumptions made regarding model input parameters?  If yes, comment on the influence of a change in model input parameters on modeling output (‘sensitivity analysis’). | Yes | Doubtful | | No |
| *<comment>* | | | | |
| **Model verification** | | | | | |
| 4 | Is model performance verified using clinical PK data\* from a similar population (i.e., comparable pediatric age group), using the drug of interest for a similar indication?  If no, comment on the data used for model verification (which age, drug, and/or indication) and whether PK may differ between the population from which PK data are derived and the virtual healthy individuals. If that is the case, it must be carefully examined whether the model-informed dose is appropriate for the real-life patient population or if dose adjustment is needed. | No | | Yes | |
| *<comment>* | | | | |
| 5 | Is PBPK model performance considered adequate? To answer this question, the predicted and observed\* plasma concentration-time curves should be compared and agreement of predicted and observed PK parameter values (e.g., volume of distribution and clearance) should be evaluated.  If no, comment on whether this discrepancy can be explained by differences between the populations (e.g., clinically observed PK data are collected from patients that suffer from a severe infection that may have impacted PK, see 4). | No | Doubtful | | Yes |
| *<comment>* | | | | |
| **OVERALL MODEL CREDIBILITY** | | | | | |
| How credible are the outcomes of the PBPK model considering model parameterization, robustness and verification? | | Inadequate | Adequate | | Satisfactory |
| *<comment>* | | | | | |

\* Clinical observed PK data generally includes plasma concentration-time data and PK parameters such as the volume of distribution and clearance). Abbreviations: PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic, etc.

*<If applicable, include/delete descriptions of abbreviations below the framework.>*

*<If applicable, assess model performance for each population subgroup separately and include descriptions of relevant age or gestational age-related physiological changes (e.g., ontogeny profiles or mathematical equations describing drug metabolizing enzyme activity). This may be relevant as model credibility may vary between different pediatric age groups and pregnancy trimesters. If the model could not be verified for the population of interest (limited or no PK data available), it should be investigated whether data from another population (e.g., infants instead of neonates) or disease state are available for model verification. More information on this topic can be found at the MELINDA website: Background information, Model-informed dosing.>*

**Model verification**

*<Please present the results of verification simulations: visual predictive checks and predicted-to-observed PK parameter ratios. Only a representative set of verification plots can be displayed providing that all plots can be retrieved from the publication or upon written request from the researchers.>*

More information on model verification can be found in the section Background information: Model-informed dosing of the MELINDA website.

**Based on the verification simulations and assessment of model credibility**

**using the framework above, PBPK model credibility is considered *<result>* .**

# Dose-finding strategy

The framework below is completed to address pivotal aspects concerning the process of dose-finding with the established PBPK model.

More information on dose-finding methods can be found in the section Background information: Model-informed dosing of the MELINDA website.

*<Please present modeling results: predictions of the plasma concentration-time curve and PK parameters with yet existing clinical dosing regimen (if available) as well as with exploratory new MID regimens.>*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Framework for establishing a model-informed dose** | | | | |
| 1 | Is exposure adequate with the current < *year/month* > dosing regimen? | | | |
| *<comment>* | | | |
| 2 | Which dose-finding method is applied?  See general section ‘Background information, Model-informed dosing’ (MELINDA website).  Note: If the MID is based on exposure matching, comment on the population for which the plasma exposure target (AUC or Cmax) is established. Also, comment on whether the plasma level serves as a surrogate measurement of an organ concentration] (e.g., lungs) and hence a similar plasma:organ concentration is assumed between the populations. | | | |
| *<comment>* | | | |
| 3 | How wide is the therapeutic window of the drug? | Narrow | Intermediate | Wide |
| 4 | How wide is the interindividual variability in PK?  If narrow, comment on whether you expect that some individuals will reach the efficacy or safety limit of the therapeutic window. | Wide | Intermediate | Narrow |
| *<comment>* | | | |
| 5 | Do alternative dosing regimens result in more adequate exposure? | | | |
| *<comment>* | | | |

Abbreviations: AUC, area under the curve; Cmax, maximum plasma concentration; Ctrough, trough plasma concentration; PK, pharmacokinetic.

*<If applicable, include/delete descriptions of abbreviations below the framework.>*

Prediction of most relevant PK parameters are displayed in Table 2.

**Table 2. Predicted population-specific pharmacokinetic parameter values**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Population** | **Pharmacokinetic parameter** | | | | |
| **Cmax** | **tmax** | **Vd** | **CL** | **t1/2** |
| *a* | *..* | *..* | *..* | *..* | *..* |
| *b* | *..* | *..* | *..* | *..* | *..* |

Abbreviations: CL, clearance; Cmax, maximum plasma concentration; tmax, time to maximum plasma concentration; Vd, volume of distribution. AUC, area under the curve; Cmax, maximum plasma concentration; DPF, Dutch Pediatric Formulary; MELINDA, model-informed dosing for all; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics; t1/2, elimination half-life.

*<If applicable, include/delete descriptions of abbreviations below the table.>*

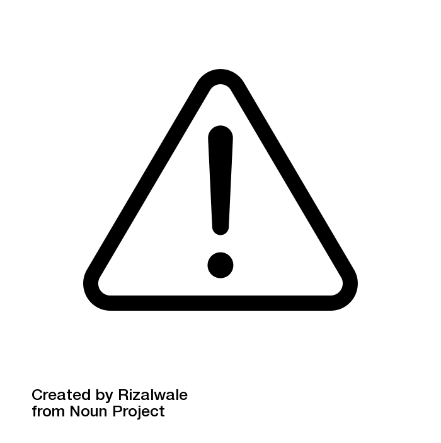
# Model-informed dose

*<Please describe the dosing regimen(s) as suggested by modeling and simulation. Multiple model-informed dose regimens, for instance for different age groups, weight bands or various trimesters in pregnancy can be presented (example format: Table 1). The modeling results that form the basis of the model-informed dose can be included in the section Dose-finding strategy.* *If available, a reference to the dosing recommendation for clinical practice (with month/year) should be given. This could be a link to a website such as the Dutch Pediatric Formulary (DPF) or one of its international affiliates or any other (inter)national guideline for pediatric drug dosing. For dosing recommendations in pregnancy, this can be a link to an (inter)national guideline providing the standard dose for non-pregnant adults or, if available, specific dose recommendations for pregnant women (e.g., the Teratology Information Service, Netherlands Pharmacovigilance Centre Lareb, www.lareb.nl.)>*

**Table 1. *<Drug>* dosing regimen(s) as suggested by PBPK modeling**

|  |  |  |
| --- | --- | --- |
| **Population subgroup** | **Dosing regimen as suggested**  **by *<formulary/guideline>* in *<date>*** | **Dosing regimen based on *<type of modeling>* to maintain optimal gentamicin plasma levels** |
| *a* | *..* | *..* |
| *b* | *..* | *..* |

Abbreviations: PBPK, physiologically-based pharmacokinetic.

**Note that dosing regimens as suggested by modeling do not necessarily represent final dosing recommendations for clinical practice**. Final dosing guidelines are the result of a careful assessment of the benefits and risks of the model-informed dose in the context of all available clinical evidence and experience of healthcare providers. Consult the *<website of the Dutch Pediatric Formulary/Lareb>* for *<drug>* dosing recommendations for clinical practice.

1. Considerations for implementation

Implementing the model-informed dose in clinical practice is NOT STRAIGHTFORWARD. Several aspects should be taken into consideration. Using the framework below, the model-informed dose can be evaluated in the context of model extrapolation, model influence, decision consequence and practical considerations.

*<Please complete the framework. This information is critical for assessing the model-informed dose in the context of available clinical evidence and experience and subsequently clinical implementation. Further details on the most important considerations (e.g., specific assumptions or limitations of the model/study) can be provided in a separate paragraph below the framework.>*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Framework for implementation of the model-informed dose** | | | | | |
| **Model extrapolation** | | | | | |
| 1 | Are there any differences expected in drug pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) between the virtual population and the real-world population intended to receive the model-informed dose? \*  If yes, comment on the disease, co-morbidity, treatment, etc., that is likely to affect pharmacokinetics. | Yes | Minimal | | No |
| *<comment>* | | | | |
| 2 | Are there any differences expected in drug pharmacodynamics (i.e., pharmacological effect) between the virtual population and the real-world population intended to receive the model-informed dose? \*  If yes, comment on how pharmacodynamics may be different in the real-world population. | Yes | Minimal | | No |
| *<comment>* | | | | |
| **Model** **influence** (the weight of the model in the totality of all evidence) | | | | | |
| 3 | Does the model-informed dose deviate from the current dosing advice of <*year/month*> or from dosing strategies applied in clinical care (incl. expert opinion, scientific clinical studies and dosing handbooks)? | Yes | | No | |
| *<comment>* | | | | |
| **Decision consequence**  (the significance of an incorrect decision) | | | | | |
| 4 | What is the level of certainty of the accuracy of the pharmacokinetic therapy goal that is used to establish the model-informed dose? # | Low | Doubtful | | High |
| *<comment>* | | | | |
| 5 | Is the risk at and consequences of under- or overdosing deemed acceptable? In case a model-informed dose is established for pregnant women, both maternal and fetal risks should be taken into consideration. | No | Doubtful | | Yes |
| *<comment>* | | | | |
| 6 | Is it possible to monitor exposure (e.g., with TDM or a clinical measurable effect) to assess whether the dose is adequate? | No | | Yes | |
| *<comment>* | | | | |
| 7 | Is it practical and feasible to administer the model-informed dose? Take into account the drug formulation, difficulty of dose calculation, and excipient safety. | No | | Yes | |
| *<comment>* | | | | |

\* Real-world population: patients who are intended to receive the MID in clinical care.

Abbreviations: MID, model-informed dose; PK, pharmacokinetics; PD, pharmacodynamics; TDM, therapeutic drug monitoring.

*<If applicable, include/delete descriptions of abbreviations below the table.>*

1. Comprehensive evidence & feasibility review

*<This section is only applicable to model-informed dosing reports of drugs used in pregnancy. If available, include a link to the ‘comprehensive evidence & feasibility review’ of the proposed dose during pregnancy (Pdf provided by Project MADAM).>*

# Relevant literature

*<Please list relevant scientific literature, preferably with corresponding PubMed Identifier (PMID). Also, include a live hyperlink directing the online paper. This can include other PBPK modeling studies or population-PK studies on the drug of interest, noteworthy review papers or teratogenicity studies.>*

# Abbreviations and references

**Abbreviations**

*<Please list the abbreviations used in this full report. Please delete abbreviations/definitions that are not applicable and add any new ones that are used.>*

AUC area under the curve

CL clearance

Cmax maximum plasma concentration

Ctrough trough plasma concentration

DPF Dutch Pediatric Formulary

MID model-informed dose

MIC minimum inhibitory concentration

PBPK physiologically-based pharmacokinetic

PD pharmacodynamic(s)

PK pharmacokinetic(s)

PNA postnatal age

t1/2 elimination half-life

TDM therapeutic drug monitoring

Vd volume of distribution

**References**

*<Please include references supporting statements.>*

1. …

2. …