Position **Paper**

PBPK **Modelling** \

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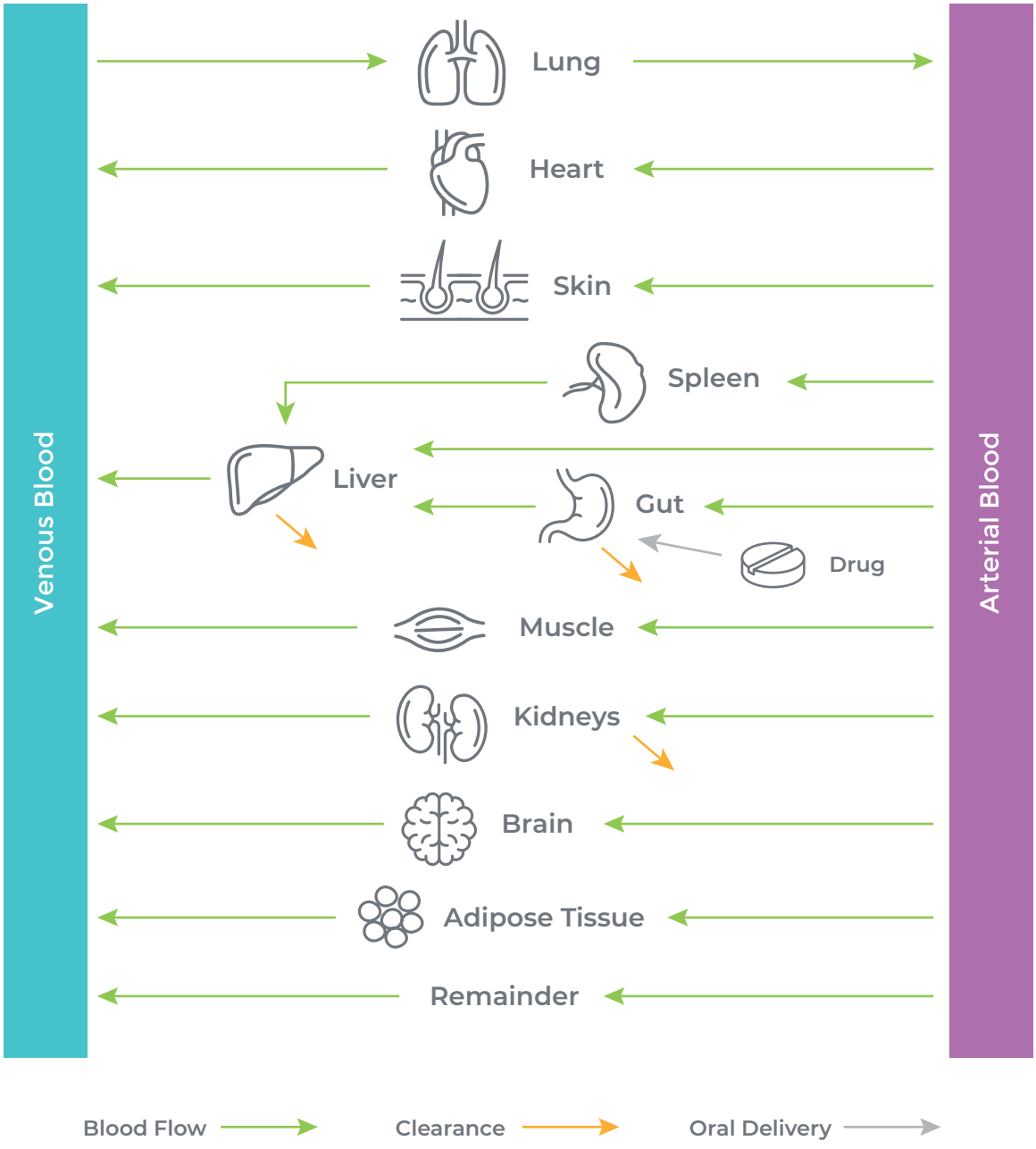
What is **PBPK Modelling?** \

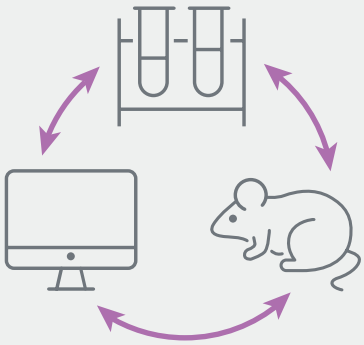
In contrast to empirical compartmental approaches, physiologically based pharmacokinetic (PBPK) modelling considers the organs and tissues of the body that are responsible for the adsorption, distribution, metabolism, and elimination (ADME) properties of drugs as a set of different compartments. Knowledge of the species-specific physiological parameters, for example blood flows, pH, volumes, and tissue composition, is combined with measured or predicted drug parameters to create a dynamic model that simulates the pharmacokinetics (PK) of the drug.



What is **PBPK Modelling** used for? \

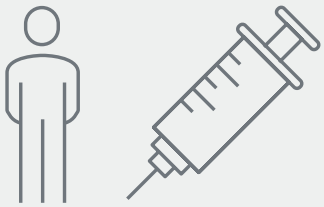
PBPK models can be used to simulate / describe PK profiles in preclinical species and once key parameters have been fitted, they can be translated to human settings to predict human PK and therefore aid compound selection and human dose predictions. Once the model is established, it is possible to investigate how physiological effects can alter PK. Furthermore, different scenarios can be modelled including predicting formulation and food effects, the impact of drug-drug interactions (DDIs) on pharmacokinetics and the effect on pharmacokinetics of moving into different clinical populations, for example moving from adults to a paediatric population. A validated model can improve understanding of product performance and help bridge the gap between in vitro and in vivo observations and can be used across drug discovery and development phases.

Discovery



- Human dose prediction
- Cross species exposure prediction
- Formulation strategy
- Absorption risk assessment

Early Development



- Single / multiple ascending dose exposure prediction
- DDI assessment
- Food effect simulations
- Dissolution targets
- Particle size targets

Late Development

- Special population modelling, e.g. Ethnic variations or Paediatrics
- Drug and Drug Product Quality Attributes
- Clinical study waivers, e.g. DDI
- Dissolution specifications
- Particle size specifications

Increasing cost and complexity of data inputs
Increasing model sophistication, robustness and applicability

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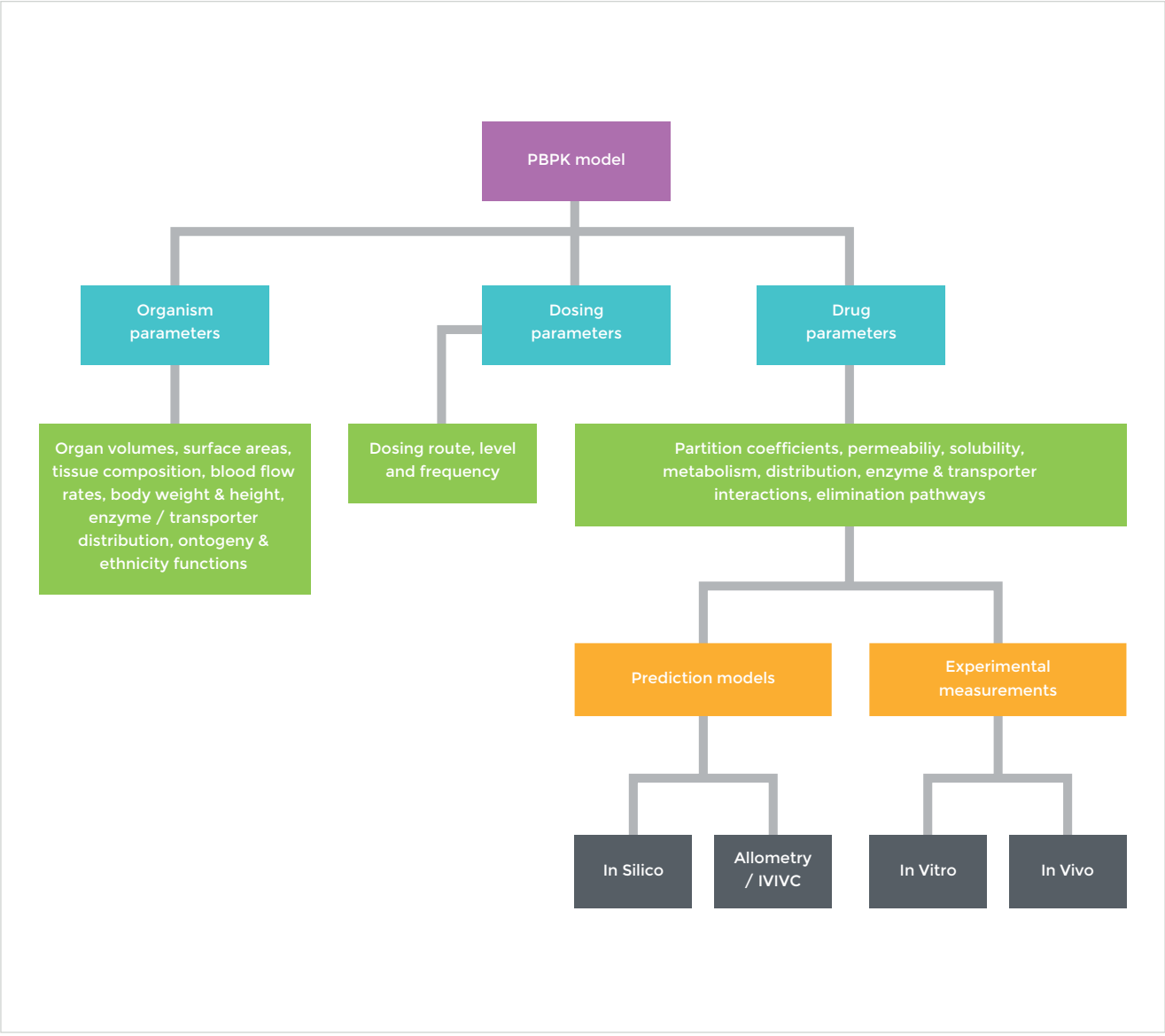
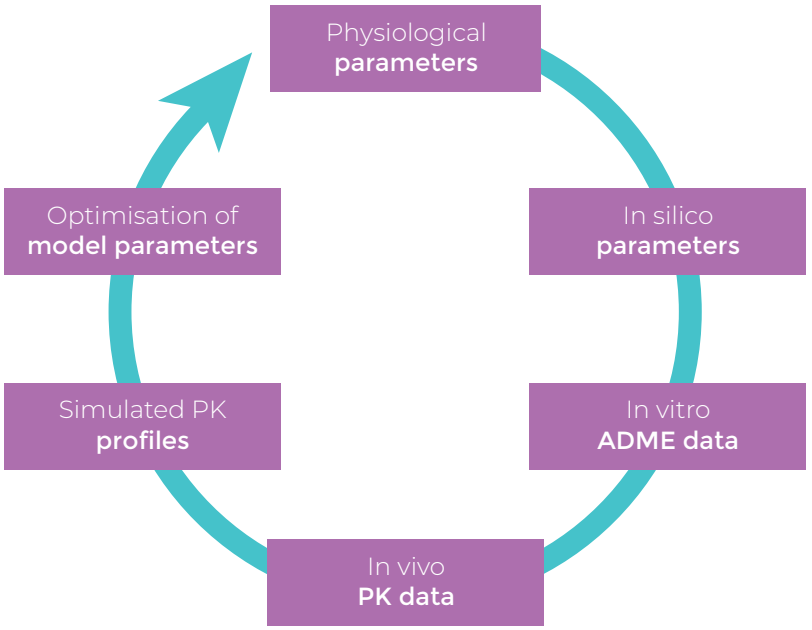
What is required to build a **PBPK model?** \

A PBPK model is developed using compound specific parameters which have either been measured in vitro or estimated in silico. These data sets are crucial in predicting the permeability, metabolism, transport, and binding of the drug. Key in vitro data sets would typically include fraction unbound in plasma, microsomal and / or hepatocyte metabolic stability, solubility, and permeability. Knowledge of the molecular weight, charge type and pK_a's, along with lipophilicity (LogD or LogP) is also required to build predictions of the ADME properties of the drug. Comparison of the predicted PK profile to the measured in vivo PK profile, ideally from an intravenous bolus administration of the drug, can then be used to refine the model. The model is continuously refined and evaluated as more experimental data becomes available, for example from other in vitro studies or PK studies following oral dosing and in additional species. Data that supports the involvement of specific drug metabolising or transporting enzymes can greatly improve the quality of the model, and solubility measurements in biorelevant media will also be key in predicting or understanding how poorly soluble compounds dissolve in the gastrointestinal tract. Based on the cross-species extrapolation of the model, the predicted human PK profile can be generated. Once the compound has entered the clinic, the model can be refined further, verified, and validated with incorporation of human PK data.



What is required to build a **PBPK model?** (continued)



Continuous PBPK model generation, evaluation, and refinement

How to **assess the quality** of a model? \

The predicted PK profiles are compared to the observed profiles and assessed visually, using visual predictive check (VPC), residuals vs time and confidence interval plots, and statistically, by assessing Akaike Information Criterion (AIC). The predicted PK parameters such as clearance, volume of distribution, $C_{max,}$ $t_{max,}$ $t_{1/2}$ and AUC and can be compared to the measured parameters and ensuring that fitted parameters appear feasible. Depending on the context of use, the question being asked, the model influence on the overall decision being made, and at what stage of development the model is being employed, the acceptance criteria for model validation should be appropriate for the specified application. For example, a 2-fold difference between the predicted and measured values may be acceptable. Alternatively, the predicted values may have to lie between 80 and 125% of the measured values for a model to be deemed suitable. Parameter sensitivity analyses can also be conducted to identify the inputs that have the most influence on the predicted PK profile. Once a model has been verified, it should be validated using an independent dataset. In addition to the verification and validation steps, activities to establish model credibility also include verification of the software code and calculations.

Advantages of **PBPK models** \

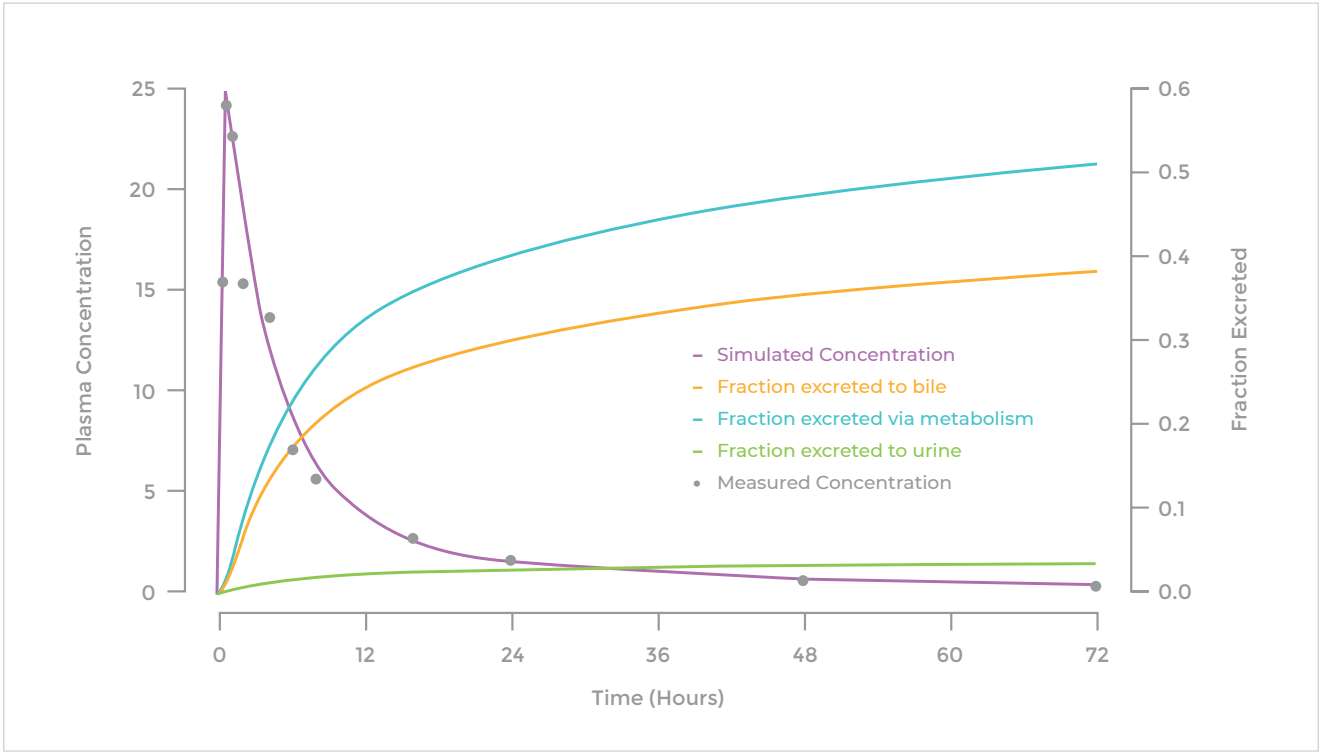
PBPK modelling can be applied across drug discovery and development and can even be included as part of regulatory submissions. Once a model has been specified it can be used to simulate the PK in various species following different administration protocols. This can be useful for supporting the design of preclinical studies in terms of assessing drug exposure in relation to safety and efficacy and can also be used to optimise the dosing interval. Human PK predictions can be used to propose safe starting doses as well as potentially efficacious doses. As PBPK modelling is a mechanistic approach to understanding and simulating pre-clinical and clinical PK profiles, it is inherently more flexible and potentially more informative than static compartmental models. PBPK can be used to identify what may be the mechanistic cause of differences in prediction between species. Preclinical experiments can then be performed to confirm which species is mechanistically most like humans thus providing confidence that prediction of human dose should be weighted to these species. Other advantages include:

- Active processes and non-metabolic elimination pathways can be included in the model to better understand and simulate PK profiles. For example, hepatic clearance in human can be predicted from the use of in vitro microsomal or hepatocyte incubations. If the model is found to under predict in vivo clearance in the pre-clinical species using this approach, this may be indicative of additional routes of elimination for which additional evidence may be obtained experimentally. If identified, biliary and renal clearance and active transport processes can be included in the model.

- Specific enzyme metabolism, inhibition and induction processes can be included in the model. Therefore, the results of pre-clinical studies aimed at informing DDI risk, for example CYP inhibition or induction, can be combined with PK data to simulate clinical DDI studies.

- Time dependent events such as meal intake with defined calorific content or gallbladder emptying at a specified time can be incorporated into the model.

- Prediction of the PK of the drug in different patient populations can be performed where the effects of physiological variability due to factors such as age, obesity, impaired hepatic or renal function, and pregnancy can be simulated.



Physiologically Based **Biopharmaceutics Modelling** (PBBM) \

PPBM is a specific subset of PBPK modelling focussed on understanding the absorption of drugs and the impact of formulation on drug absorption and thus systemic exposure, it combines the DMPK based models of traditional PBPK software with physical chemistry models of dissolution. Consequently, PPBM integrates data from Pharmaceutical Quality / CMC, DMPK and Clinical disciplines to address issues such as:

1. Likely fraction absorbed at clinical predicted dose and risk that absorption will limit exposure in first in human (FIH) studies
2. Formulation strategy required for FIH
3. Particle size specification of drug substance
4. Definitions of key quality attributes of the drug and drug product
5. At product registration: establishing the safe space for commercial drug product and achieving clinical study waivers
6. Model-informed risk assessment on the effects of acid reducing agents (DDI)
7. Bridging of dissolution methods and support of clinically relevant dissolution specifications (CRDS)

Constraints of **PBPK models** \

The quality of the model is dependent of the accuracy of the in silico parameter estimations as well as the quality of the in vitro data. As there are multiple methods available for the measurement of key parameters such as solubility and permeability, the choice of method will impact the quality of model developed. In the case of solubility, chemical impurities and lack of knowledge of the solid state of the drug can increase the uncertainty of the input values. PBPK models are also dependent on the prediction of in vivo tissue distribution parameters for which there are different methods available. In practise, various methods are evaluated and the one with the best fit is employed in the model following verification. Robust measured data for the key input parameters and those identified via parameter sensitivity analysis greatly improves the quality of the model, however, the in vitro to in vivo extrapolation for all active processes has not yet been demonstrated. Best- and worst-case scenarios can also be simulated to estimate changes in PK brought about by the variation of certain parameters. Ideally PK profiles after dosing via intravenous injection are required for model development although this is not always possible for human PK. In this case, the successful development of a model relies on the accurate prediction of human PK parameters from in vitro assays and PK studies in pre-clinical species.

PBPK modelling **Conclusion** \

PBPK modelling is the combination of a set of known physiological parameters, in vitro ADME and in vivo PK data, along with certain in silico values to create a dynamic model that describes the PK of a drug. This model can be used to understand and simulate PK in pre-clinical species and for first-in-human PK predictions. Due to the mechanistic nature of the model, experimental data that would enhance the understanding of the in vivo ADME properties of the drug can be identified and incorporated into the model. PBPK can be further utilised to explore factors that can impact the PK of a drug, such as formulation or food effects, patient population and the potential for DDIs. If PBPK models can be successfully be developed they have the potential to reduce the need for animal and human testing.

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Key **Reading** \

Physiologically based pharmacokinetic modelling in drug discovery and development: a pharmaceutical industry perspective: HM Jones et al, Clinical Pharmacology and Therapeutics, 2015, 97 (3), 247. https://pubmed.ncbi.nlm.nih.gov/25670209/

Physiologically based pharmacokinetic modelling for FIH predictions: An updated model building strategy illustrated with challenging industry case studies; NA Miller et al, Clinical Pharmacokinetics, 2019, 58, 727. https://link.springer.com/article/10.1007/s40262-019-00741-9

Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation; C Kuemmel et al, CPT Pharmacometrics Syst. Pharmacol., 2020, 9(1), 21–28. https://pubmed.ncbi.nlm.nih.gov/31652029/

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation; SF Marshall et al, CPT Pharmacometrics Syst Pharmacol., 2016, 5(3), 93-122. https://pubmed.ncbi.nlm.nih.gov/27069774/

FDA guidance for PBPK analyses: https://www.fda.gov/files/drugs/published/Physiologically-Based-Pharmacokinetic-Analyses-%E2%80%94-Format-and-Content-Guidance-for-Industry.pdf

FDA guidance for the use of PBPK models in biopharmaceutics applications: https://www.fda.gov/media/142500/download

For more information on our PBPK modelling capabilities, contact:
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