

# A best practice framework for applying physiologically based pharmacokinetic modelling to predict pH-dependent drug-drug interactions

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## Introduction

- ARAs, defined as antacids, histamine-2 receptor antagonists, and proton pump inhibitors, are widely used and can alter the absorption and systemic exposure of co-administered drugs with pH-dependent solubility. This interaction may lead to reduced drug efficacy for basic drugs or increased risk for adverse reactions for acidic drugs. Thus, it is essential to evaluate these risks during drug development.
- Physiologically based pharmacokinetic (PBPK) modelling has emerged as an effective tool for assessing pH-dependent DDIs [1,2,4]. Nowadays, such models are mainly used to guide formulation strategies.
- There are only a few examples where PBPK models have been used to inform clinical study designs, and regulatory decisions/labelling recommendations. Furthermore, a best-practice approach on how to develop, apply and interpret the results of such models at the different stages of drug development is currently lacking.

## Methods

- Case studies available inhouse and from the literature, of pH-dependent DDIs assessed with PBPK models, were reviewed. Current approaches and the respective regulatory feedback, when available, were used to inform the development of a best practice framework for applying PBPK to predict pH-dependent DDIs.
- The drug development process was divided into three major stages: Discovery/Preclinical, Early Clinical and Late Clinical Development.

## Results

- Model input (i.e., compound and formulation specific parameters used in PBPK models) and simulated physiology (i.e., simulated conditions of the gastrointestinal tract) were defined as the cornerstone of each simulation. Together with the model application, these guide the appropriate result interpretation and respective model use [Figure 1].

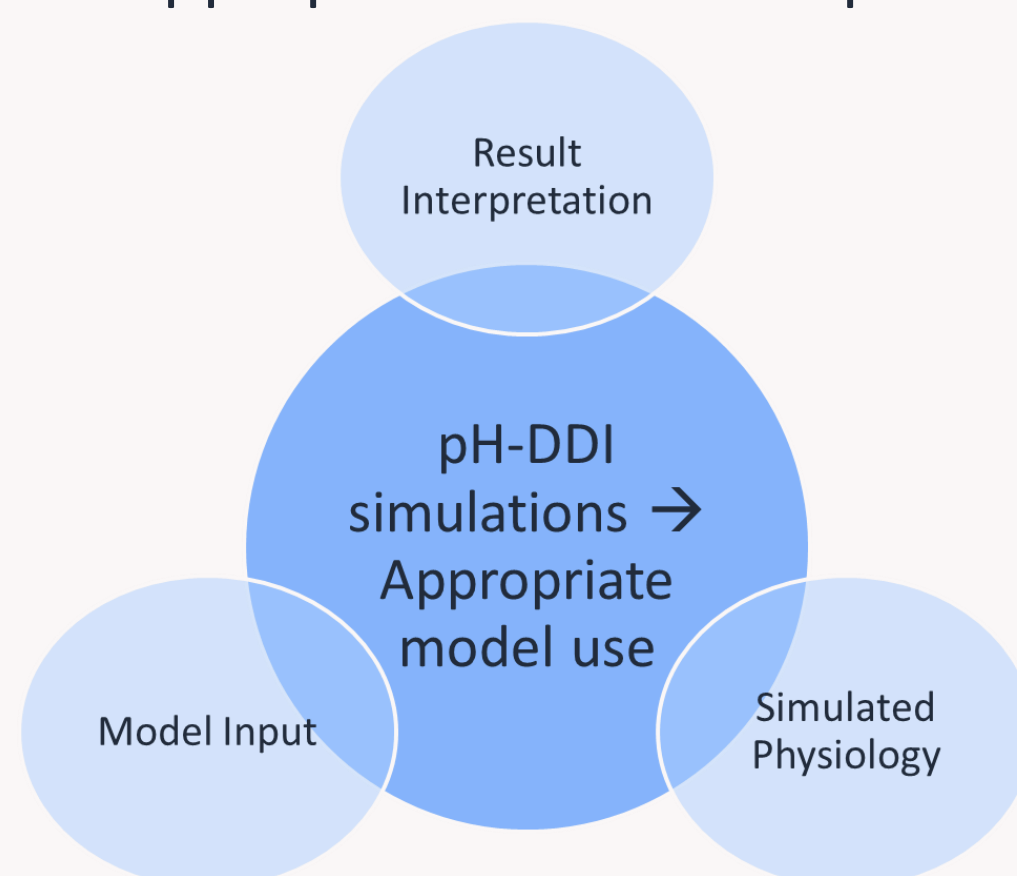


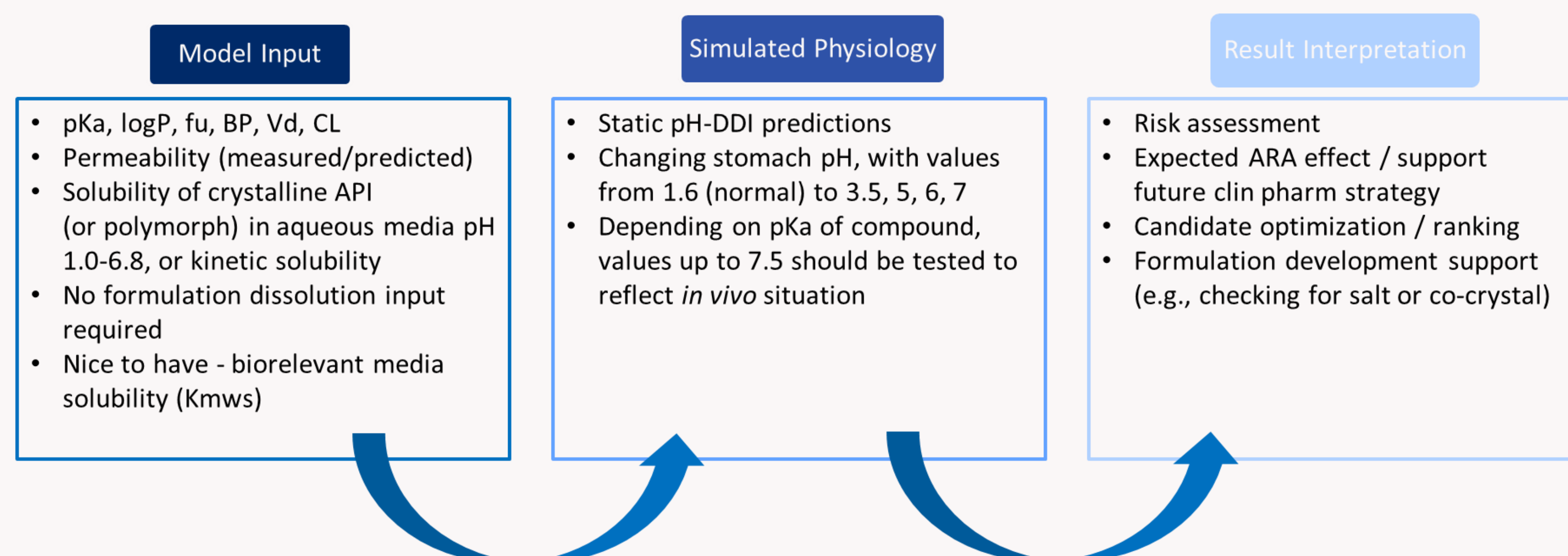
Figure 1: Schematic representation of key components for appropriate use of pH-Dependent Drug-Drug Interaction (pH-DDI) Simulations

- Physicochemical properties, solubility, dissolution, permeability and disposition of the compound are crucial at all stages. However, the amount of detail that is needed as well as the type of measurement required at each stage are different and can have a major impact on the predicted PK [Figure 2].
- Simulated pH physiology changes should reflect the actual pH changes observed *in vivo* in co-administration scenarios with ARAs [2,3,4].
- Most of the ARA-DDI clinical studies are performed in the fasted state.
- Limited knowledge is available for ARA-DDI clinical studies in fed state. It is challenging to separate effects resulting from the administration of food vs. from pharmacodynamics of the ARA.
- Static pH-DDI predictions are recommended in the first two development stages, where a DDI-risk assessment is required.
- Mechanistic-DDI predictions are recommended after Phase 1 and generation of mass balance data to inform clinical design and regulatory decisions.
- Fasted state simulations → gastric pH should be varied up to values of 7.0 or 7.5, [3]. Simulated effects are dependent on the pKa of the compound. For weak bases, if the pKa is around 4-5, the main impact is between pH values of 1.6 to 5, while smaller differences are expected between pH values of 5 to 7. For bases with a pKa of approximately 7.0, gastric pH values up to 7.5, along with possible changes in intestinal pH [3] should be assessed.
- Fed state simulations → gastric pH should be varied up to 7.0 or 7.5. Mean fed state conditions after co-administration of an ARA are usually represented with gastric pH values of 5.0.

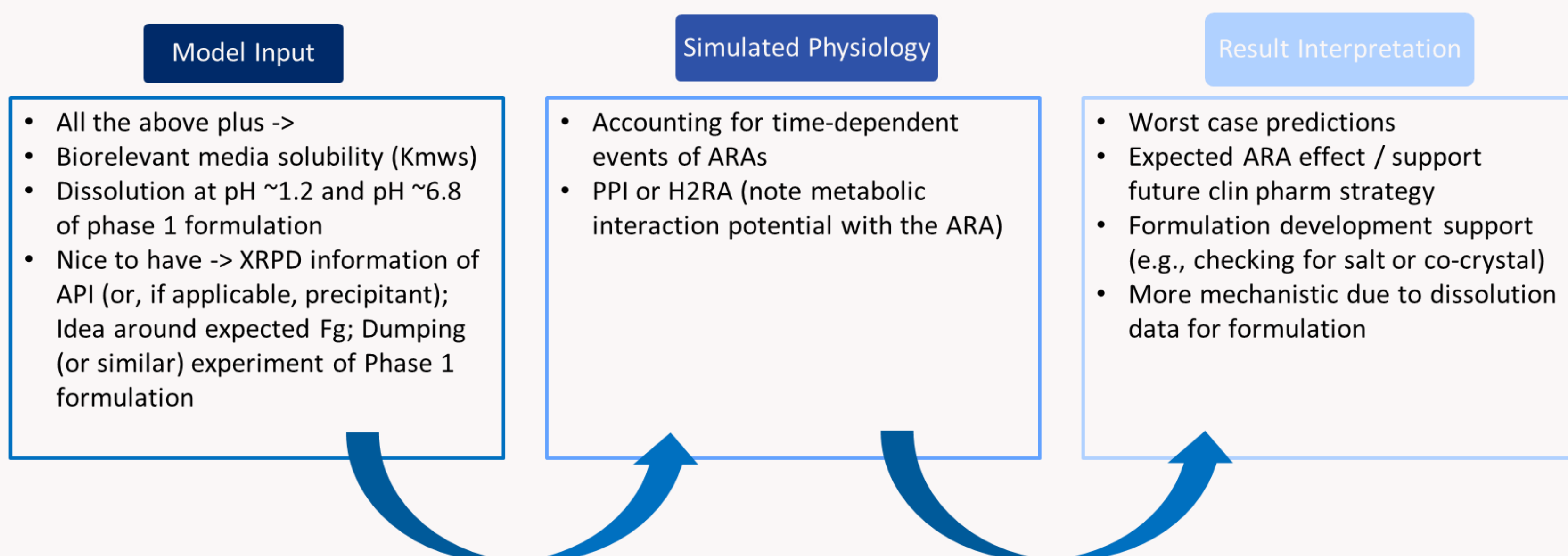
## References

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## Discovery/Preclinical



## Early Clinical



## Late Clinical

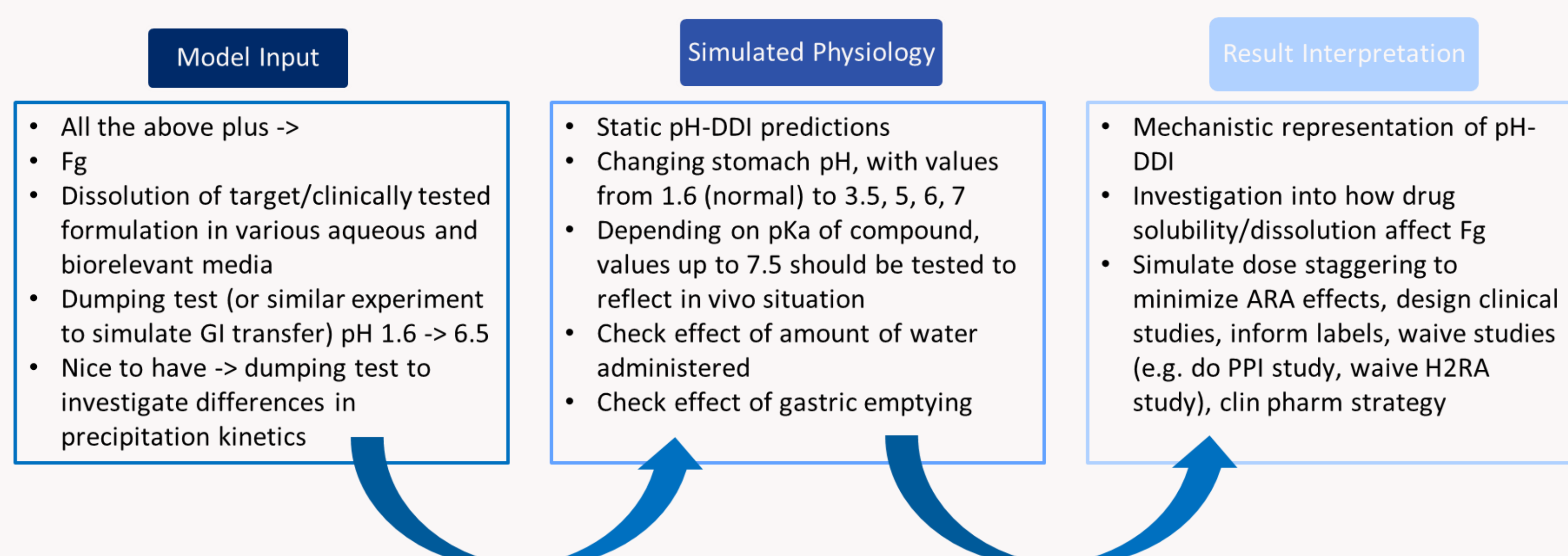


Figure 2: Best practices for pH-dependent drug-drug interaction (pH-DDI) simulations

## Conclusions

A best practice framework for developing, applying and interpreting results of PBPK models to predict pH-dependent DDIs was created. This framework can allow for harmonization and consistency around the pH-DDI PBPK predictions, thus paving the way for more routine use of such models in informing clinical and regulatory decisions.

