# Implementation of Oral Drug Absorption in Older Adults in the Physiologically Based Pharmacokinetic (PBPK) Modelling Platforms



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### BACKGROUND

The older adult population, consisting of persons aged 65 years or older, is the fastest-growing population group and also the major consumer of pharmaceutical products. Due to the heterogenous aging process, this age group shows high interindividual variability in the dose-exposure-response relationship and, thus, a prediction of drug safety and efficacy is challenging. Although PBPK modelling is a well-established tool to inform and confirm drug dosing strategies during drug development for special population groups, age-related changes in absorption are poorly accounted for in current PBPK software.

## **OBJECTIVES & METHODS**

This research aims to characterise the incorporation of physiological changes caused by increasing age that can influence the oral absorption of dosage forms in the PBPK software. The representatives of PBPK modelling platforms Open Systems Pharmacology - OSP (PK-Sim), SimCyp, and GastroPlus filled in a questionnaire concerning multiple absorption-related parameters and their implementation in the software. Besides, if the different software incorporate physiological changes in their respective older adult population databases.

#### RESULTS

Parameters Software Current incorporation in the software

Incorporated change

In the table, the absorption-related parameters are given with their incorporation in the different software. All parameters can be manually adapted but most of them do not incorporate standard changes in the older population database of all three platforms. Also, no age-dependent variability is incorporated in the different platforms for these parameters. Simcyp and OSP additionally did not inform the stomach pH, duodenum pH, gastric emptying time, small and large intestinal transit time, micelle-mediated solubility, and bile salts concentrations. Since conflicting results were observed in literature for these parameters, GastroPlus retains the parametrization for the young adults. Furthermore, none of the software providers incorporated the effect of the gut microbiome for different age groups. On the other hand, food effects are handled differently in every software. Simcyp considers a different rate of return for their older adult model. The rate of return to fasted gastric pH for subjects above the age of 65 years is described with a linear formula instead of an exponential one. For GastroPlus, age has, an indirect effect on the gastric emptying rate in fed state. The software has an inbuilt correlation between the calories in the meal and the gastric emptying time. As the calories are defined as a percentage of the total daily calorie intake which differs for gender and age, it allows scaling to all ages and gender. OSP did not report or include an age-informed rate of return to fasted pH or a difference in gastric emptying in the absorption model.

| and<br>Svallowing<br>CapacityPK-SimStomach acid output, and the pH of the stomach,<br>dudenum, jejunum, leum, cecum, ascending, and<br>descending colon are incorporated and can be manually<br>altered.No change.GastroPius<br>Intestinal pHStomach, duodenum, jejunum, leum, cecum ascending,<br>and descending colon are incorporated and can be manually<br>altered.No change.GastroPius<br>Intestinal pHStomach, duodenum, jejunum, leum, cecum ascending,<br>and descending colon are incorporated and can be<br>manually altered.No change.GI Transit<br>TimesBF.SimGET, SITT, and LITT are incorporated and can be altered<br>manually. When taking a meal the gastric emptying time<br>is altered based on a Welbull equation.No change.GI Transit<br>TimesGET, SITT, and LITT are incorporated and can be altered<br>manually. When taking a meal the gastric emptying time<br>is altered based on a Welbull equation.No change.GI Fluid<br>VolumesFK-SimStomach, small and large intestinal luminal fluid are<br>incorporated and can be manually altered.No change.GI Fluid<br>VolumesStomach, small and large intestinal luminal fluid are<br>incorporated and can be manually altered.No change.GI Fluid<br>VolumesStomach, small and large intestinal luminal fluid are<br>incorporated and can be manually altered.No change.GI Fluid<br>VolumesStomach, small and large intestinal luminal fluid are<br>incorporated and can be manually altered.No change.GI Fluid<br>VolumesStomach, small and large intestinal luminal fluid are<br>incorporated and can be manually altered.No change.GI Fluid<br>VolumesStomach, small and large intestinal lumi  |               |            |   |                        |
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#### CONCLUSION

The results of the questionnaire led to the conclusion that the impact of age on several gastrointestinal physiological parameters is marginally informed and considered in the various modelling software tools. Considering the complex aged-related changes and additional extrinsic factors reported in literature, more joint efforts should be made to integrate data obtained from various *in vitro* permeability, solubility, and dissolution experiments that mimic the older population, as well as clinical studies into PBPK models. This strategy allows to better predict *in vivo* clinical response. Ultimately, the outcomes from these studies may be used to support dosing recommendations and drug development and pharmacotherapy in this population.

Publication

LinkedIn

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