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FDA's guidance and recent workshop on food effect supports use of PBPK.

In June 2022, the US FDA issued new guidance for Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations, and held a webinar on the topic in June 2023. Both can be found here: https://www.fda.gov/drugs/news-events-humandrugs/ overview-clinical-pharmacology-considerations-food-effect-studies-06152023.

Food is one of the major factors that affect oral drug absorption by influencing drug/formulation properties (e.g., solubility and dissolution rate) and physiological factors (e.g., metabolism and transport across the gastrointestinal tract). These food effects (FE) can impact drug safety and/or efficacy by either increasing the systemic exposure of the drug, potentially leading to a higher pharmacologic effect, or lowering the systemic absorption of a drug, thus reducing efficacy. About 40% of all orally administered drugs are subject to FE[1].

FE studies aid in understanding whether food affects the systemic exposure of a drug, assessing if variances in meal types lead to differences in drug exposures, and offering dosing instructions in connection with food intake.

PBPK modeling has been recognized by regulators as a valuable tool for assessing food effect and can be used to support and/or replace clinical studies where appropriate.

Model-Informed Drug Development Approaches

- In conjunction with FE data in subjects, physiologically based pharmacokinetic (PBPK) analyses can sometimes be used to further assess FE
- PBPK modeling is still evolving, and new applications of PBPK simulation are continously being evaluated by the FDA
- Sponsors are encouraged to consult the appropriate review division regarding the suitability of the PBPK approach

www.fda.gov June 15, 2023 FDA workshop[2]

The FDA guidance states:

In conjunction with FE data in subjects, PBPK analyses can sometimes be used to further assess the effects of food on a drug. For example, PBPK models can guide in vitro experimental designs to generate data that can be used to further support PBPK model development, and to identify and optimize parameters that are important to understanding and predicting food-drug interactions in conjunction with FE data. PBPK approaches can also be useful to guide clinical study designs.

"PBPK models present critical tools to assess the food effect for bioequivalence (BE) extrapolation from fasting BE studies to fed BE studies and potential space expansion for BCS waivers, especially on the BE risk assessment for excipient effect of drug absorption permeability and drug transporters[3]"

Raj Madabushi,
Associate Director of Guidance and Scientific Policy, US FDA.

PBPK and FE: case studies and applications

In September 2020, the IQ Food Effect working group published a paper that evaluated the use of PBPK for predicting FE in 30 compounds. The compounds represented an equal distribution of compound, BCS, and food effect type (positive, negative, none). Among these cases was the evaluation of aprepitant.

Case study: Aprepitant (Emend®) – Simcyp for predicting FE in BCS Class II drug.

Aprepitant is used for chemotherapy-induced and post-operative nausea and vomiting and is in the neurokinin-1 antagonist class of medications. It is a poorly soluble compound with moderate to high permeability (BCS Class II) and is non-ionized at intestinal pH values. Micronized aprepitant showed significant positive food effect. As part of the PEARRL European research consortium, a program using biorelevant in vitro tools and in silico PBPK modeling (the Simcyp Simulator) was used to simulate and better understand the in vivo performance of the marketed formulation of aprepitant in the fasted and fed states. This study demonstrated the importance of evaluating the effect of gastric residence time as well as the permeability-solubility interplay when predicting the absorption of a poorly soluble API under various dosing and prandial conditions. Using these in vitro and in silico biopharmaceutical tools, the performance of poorly soluble compounds can be characterized using a mechanistically based framework. This approach can support new and generic drug development by promoting rational formulation design and fewer and smaller, but equally robust clinical trials[4].

Case study: Tegoprazan – Simcyp for predicting intragastric pH changes from drug:

Approved in Korea in 2018, Tegoprazan is an alternative to conventional protein pump inhibitor (PPI) drugs, as it provides much faster action and full effect from the first dose. Since this class of drugs (potassium-competitive acid blocker) does not require activation in the presence of gastric acid, it can be administered independently of food intake. The Simcyp Simulator was leveraged for the development of tegoprazan and its major metabolite in a PBPK/PD modeling approach. The PBPK model was applied to predict PK profiles following repeated administrations of tegoprazan, postprandial PK profiles, and alteration of gastric acid pH profiles after tegoprazan administration. When the clinical study and predicted results were compared, predictive nature of the model was evident under studied conditions. This PBPK/PD model may be used to predict PK profiles after repeated tegoprazan administrations and to predict differences in physiological factors in the gastrointestinal tract or changes in gastric acid pH after tegoprazan administration[5].

Case study – Simcyp for predicting FE in BCS Class IV drug.

GSK3640254 (GSK254) is a maturation inhibitor demonstrated to inhibit all HIV-1 subtypes with efficacy against a broad range of polymorphisms. It is a BCS Class IV zwitterionic drug with complex interactions with mixed micelles (an aggregate of different molecules in a colloidal solution). A zwitterion is a molecule with separate positively and negatively charged functional groups. Per the US NIH, more than 70% of BCS Class IV drugs exhibit a positive food effect. In the case of zwitterionic drugs, their solubility in biorelevant media is an interplay between the ionization of the drug within the physiological pH range of the gastrointestinal tract (GI tract), and the charge (zeta potential) of the micelles.

A successful predictive modeling approach was formulated and applied using Simcyp to predict the food effect of this BCS class IV zwitterionic drug with complex interactions with mixed micelles. In vitro data alongside the modelling suggested that the positive food effect observed in the clinical studies was attributed to micelle-mediated enhanced solubility and permeability. This study demonstrated that the predictive capacity of PBPK modeling is enhanced when the comprehension of food effects extends beyond the usual approach and when high-quality in vitro data is incorporated[6].

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