Physiological-based absorption modeling and simulation of bioequivalence between pelleted, modified-release products differing in the mechanism of release from the rate-controlling polymer

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Introduction

Product X, containing drug substance Y, is a multi-component innovator product composed of a specific ratio of immediate-release (IR) and modified-release (MR) pellets. Substance Y is a BCS Class I active ingredient with moderate half-life and is a non-racemic mixture of enantiomers. The MR portion of Product X is achieved by the use of an enteric, delayed-release (DR) polymer coating which allows drug release only at pHs above 5.5, which therefore delays drug release until the pellets exist the stomach into the small intestine (i.e., pH-dependent release). Product Z, a generic to Product X, has a similar formulation design as Product X except that MR is achieved with the use of sustained-release (SR) polymers that allows drug release in the acidic pH environment of the stomach as well as the more basic environment of the intestines (i.e., pH-independent release). In order to investigate potential risks associated the generic due to different formulation design, chemistry, manufacturing, and control, ORS staff conducted extensive formulation analysis and developed a physiological-based absorption and pharmacokinetic (PK) model to identify potential risk factors that may contribute to bioinequivalence. Specifically, ORS staff examined any potential physiological factors/subpopulations that would be impacted by the different rate-controlling mechanisms of Product X and Product Z (IR/DR vs. IR/SR) and assessed the validity of Product Z's dissolution test and acceptance criteria.

Materials and Methods

Physiologically-based absorption modeling and PK modeling in GastoPlus™:
Drug absorption models based on human physiology have been developed and applied to orally administered drug products . These models incorporate the physiochemical properties of the drug substance (such as molecular weight, pKa, LogP, solubility, permeability, …), the properties of the formulation/drug product (dose, dosage form, particle density, …), and physiological parameters (transit time, volume, pH, ... of GI compartments) to predict oral absorption. Commercial software, such as GastroPlus™ combine the absorption models with compartmental PK models or physiologically-based PK (PBPK) models to predict plasma concentration levels over time. In GastroPlus™, the physiologically-based absorption model component is called the Advanced Compartmental Absorption and Transit (ACAT) model.

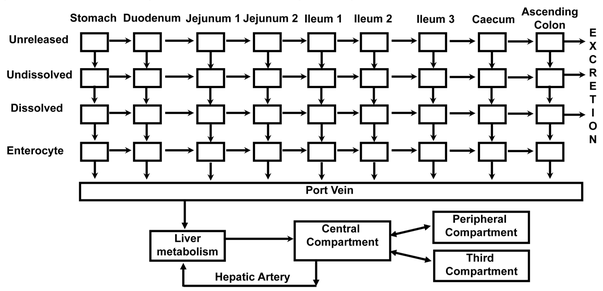


Figure 1: GastroPlus™ ACAT model

Separate models were created for the two enantiomers of Product Z. The absorption and PK models developed for Product X and Substance Y was validated on PK data from intravenous (IV), immediate-release (IR) and extended-release (ER) formulations. Product X is modeled as a mixture of IR and DR pellets, where dissolution from the individual pellets is optimized with a Z-factor (Takano) model. In GastroPlus™, it is not possible to specify a trigger pH for enteric disintegration; instead enteric formulations automatically begin to release once they enter the small intestine. For Product Z, the *in vivo* dissolution was modeled directly from the approved *in vitro* dissolution test (i.e., *in vitro* dissolution test is *in-vivo*-indicating).

Results

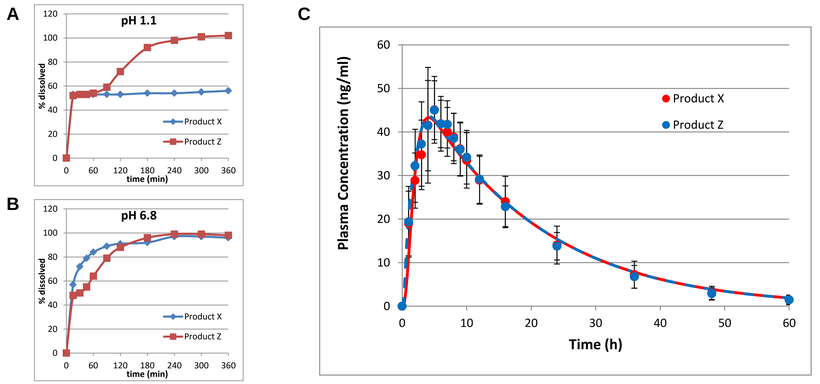


Figure 2: (A) *in vitro* dissolution of Product X and Z at pH of 1.1. (B) *in vitro* dissolution of Product X and Z at pH of 6.8. (C) PK simulation of Product X (red line) and Product Z (blue line) against observed plasma concentrations (points of same color). Note that the Product Z PK simulation is dashed in order to make the Product X PK simulation visible.

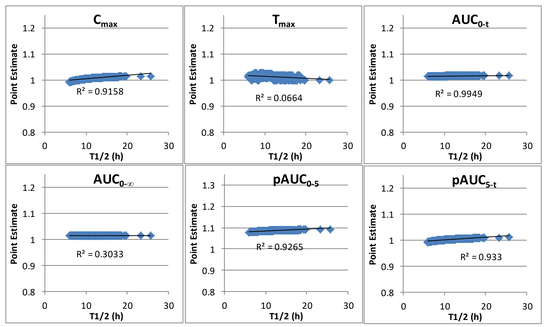


Figure 3: Sensitivity analysis (clearance, CL; volume of distribution, V_D; and subject weight) of the one-compartment PK model. Test-to-reference ratios (Product Z / Product X) for various BE metrics are plotted against the elimination half-life ($T_{1/2}$ = ln2*V_D/CL).

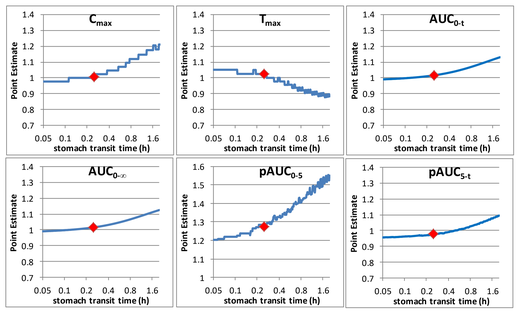
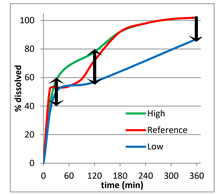


Figure 4: Sensitivity analysis of BE metrics to stomach transit times. Diamond points represent the values for the baseline simulation in Figure 2C.

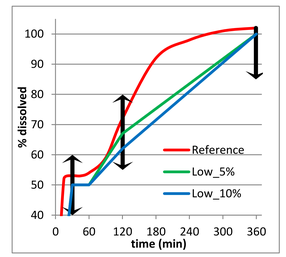
Results



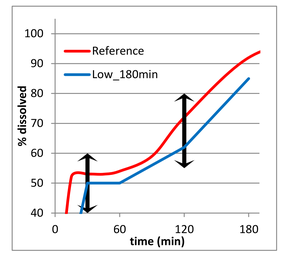
Condition	Number of subjects	Reference vs. Reference	Low vs. Low	High vs. High	Reference vs. Low	Reference vs. High
Fasting	12	88.9	79.9	89.0	0.6	83.5
	24	100	99.2	99.9	0.6	99.4
	36	100	100	100	0.2	100
	48	100	100	100	0.2	100
	72	100	100	100	0.1	100

Figure 5: Left panel: Dissolution profiles representing the extremes of the acceptance criteria (Low and High). Right panel: summary of passing ratios (%) for virtual BE trials comparing PK profiles derived from the alternative dissolution profiles.

A



B



C

Condition	Number of subjects	Reference vs. Low_10%	Reference vs. Low_5%	Reference vs. Low_180min
Fasting	12	10.6	29.6	40.9
	24	14.6	55.0	72.5
	36	16.3	72.7	89.8
	48	22.7	84.6	94.8
	72	31.8	95.7	99.2

Figure 6: (A & B) Dissolution profiles testing alternative acceptance criteria to ensure BE. (C) Summary of passing ratios (%) for virtual BE trials comparing PK profiles derived from the alternative dissolution profiles in Panel A & B.

Conclusions

- Variability in the PK model parameters represents intersubject variability in the healthy adult population and also extends to the different populations such as pediatrics. Negligible deviations in BE metrics are observed.
- Stomach transit time is a critical physiological parameter that intensifies the formulation difference between Product X and Product Z. A the highest transit times, each BE metric is observed to trend towards failing the 90% confidence interval BE criteria. However, the significance of this parameter is unclear since the transit times with issues are in the very upper range of reported values.
- Due to the *in-vivo*-indicating nature of the *in vitro* dissolution, it is possible to simulate the impact of BE from several acceptable dissolution profiles. A 'Low' virtual batch will pass the dissolution test, but is predicted to fail BE. Alternative virtual batches are simulated to identify the appropriate acceptance criteria to ensure BE in future commercial batches.

Disclaimer

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