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Using a Physiologically-based Pharmacokinetic Absorption Model to Establish Clinically Relevant Dissolution Safe Space for Oseltamivir in Adult and Pediatrics

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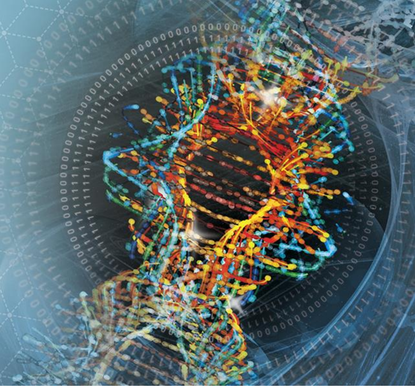

PURPOSE

- Influenza (flu) is a contagious respiratory disease caused by influenza viruses which affects all age groups, resulting in an average of 20,000 death per year in the United States.
- Oseltamivir (OP, Tamiflu®, Biopharmaceutics Classification System (BCS) Class I), an ester prodrug of the antiviral molecule oseltamivir carboxylate (OC), is the first FDA approved oral neuraminidase inhibitor to treat influenza A, B.
- Given the strategic importance of deploying OP in flu seasons for adults and pediatric populations, a timely assessment of drug product quality and bioequivalence (BE) through evaluation of clinically relevant critical quality attributes (CQAs) is highly desired.

OBJECTIVE(S)

- To establish a physiologically-based pharmacokinetic (PBPK) absorption model for biopharmaceutics for both OP and its active metabolite oseltamivir carboxylate acid (OC) in adults and extrapolated models to pediatric groups with different ages.
- To identify key parameters and set clinically relevant specifications/safe range of dissolution profiles for OP in adults and pediatric populations.

METHOD(S)

PBPK platform: GastroPlus® 9.6

a. Human Adult PBPK Absorption Model for Biopharmaceutics Development & Validation

- Absorption (OP): described by ACAT™ model
- Distribution and PK (OP and OC): PBPK-Plus™ module
- Dissolution model: use in vitro dissolution data as input
- Physiologies: generated by PEAR™ Physiology module
- Metabolism of OP to OC: liver carboxylesterase 1 (CES1)
- Renal clearance (OC) : filtration & active secretion
- Permeability/Perfusion-limited disposition model for liver and other organs.

b. Human Pediatric PBPK Absorption Model for Biopharmaceutics Extrapolation & Validation

- Physiology change: predicted using Age-related PEAR™ and ACAT™ module
- Drug-dependent parameters: obtained from adult model
- CES1 concentration & renal clearance of OC were changed

c. Pediatric & Adult Model Application

- Virtual BE performed to evaluate generic products and set clinically relevant specifications

RESULT(S)

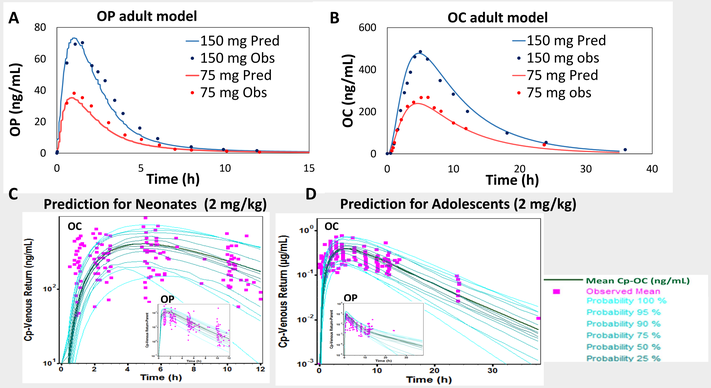

Figure 1: Simulated and observed concentration time profiles for OP and OC in adults and pediatrics based on PBPK absorption model for biopharmaceutics

Table 1: Validation of PBPK absorption model for biopharmaceutics in adult and pediatric population

Study	Form	Dose	OP Prediction Error (%)			OC Prediction Error (%)		
		mg * mg/kg	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
1 Adult	Caps	75	-0.1	7.8	-4.4	5.6	12.2	4.42
2 Adult	Caps	75	-14.7	10.2	8.1	2.15	12.8	3.73
3 Adult	Susp	75	-8.4	-9.1	-9.1	0.4	-1.5	-1.5
4 Adult	Susp	75	-14.8	-2.2	-8.7	-6.0	-2	-3.2
5 Adult	Susp	75	-6.4	-7.1	-8.6	-5.5	-1.7	-1.7
0-2 m	Susp	2*	-25.3	7	5	-3	11	-1
3-9 m	Susp	2*	-22.1	-15.3	-14.5	-16.6	-5.3	N/A
1-5 y	Susp	2*	-15.3	-11.2	-10.5	-13.5	15.5	N/A
9-18 y	Susp	2*	-20.3	-19.5	-18.3	-10.6	-6.5	N/A

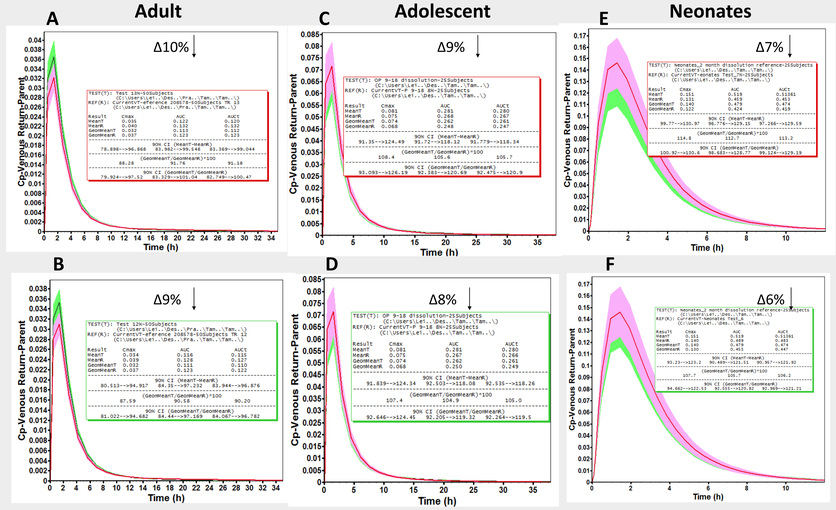

Figure 2: Population and virtual BE analysis between reference products using pivotal dissolution profile (pink curve) and theoretical slower dissolution profile (green curve) in adults (A, B) and pediatric populations (C-F) to determine the "safe space" for dissolution profiles. Dissolution profile of 75 mg Tamilfu® was used as reference listed drug (RLD).

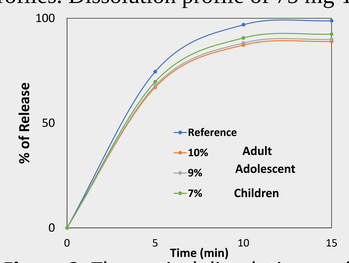

Figure 3. Theoretical dissolution profiles

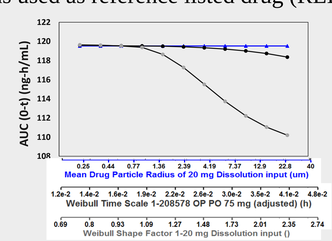

Figure 4. Parameter Sensitivity Analysis

RESULTS (CONTINUED)

- ✓ The models predicted in vivo PK of Immediate Release (IR) capsules and suspensions of OP with prediction error within ± 20% for both OP and OC in adults and ± 25% in pediatrics (Figure 1 and Table 1).
- ✓ The virtual BE analysis indicated that drug products with the dissolution boundary at 9% slower than dissolution profile of pivotal bio-batch could maintain BE to RLD in adults. In contrast, a stringent trend of dissolution boundary (safe space) was observed for pediatrics (8% slower for 8-18-year-old adolescents, 6% slower for children, infants and neonates).

CONCLUSION(S)

This study highlights the utility of PBPK absorption modeling and simulation for biopharmaceutics in prediction of BE and providing a quantitative basis for setting clinical relevant specifications for dissolution for OP in both adults and pediatric populations.

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