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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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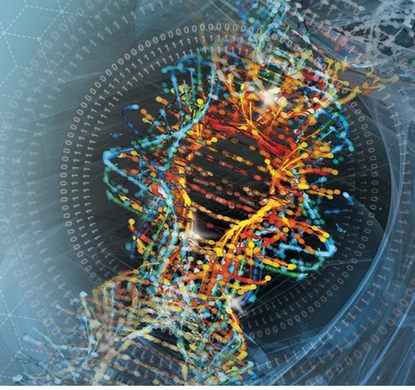

## PURPOSE

- 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)

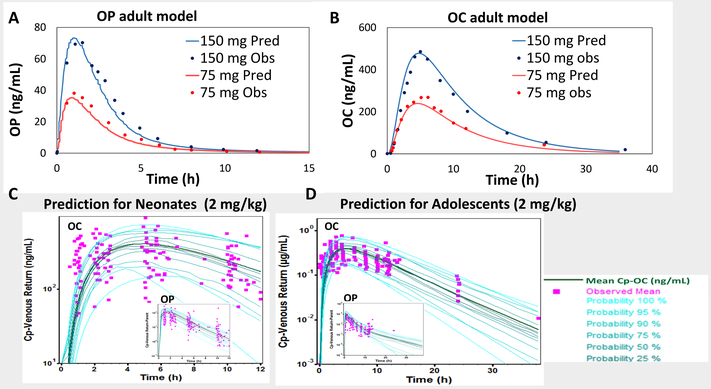


**Figure 1:** Simulated and observed concentration time profiles for OP and OC in adults and pediatrics based on PBPK absorption model for biopharmaceutics

**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 |

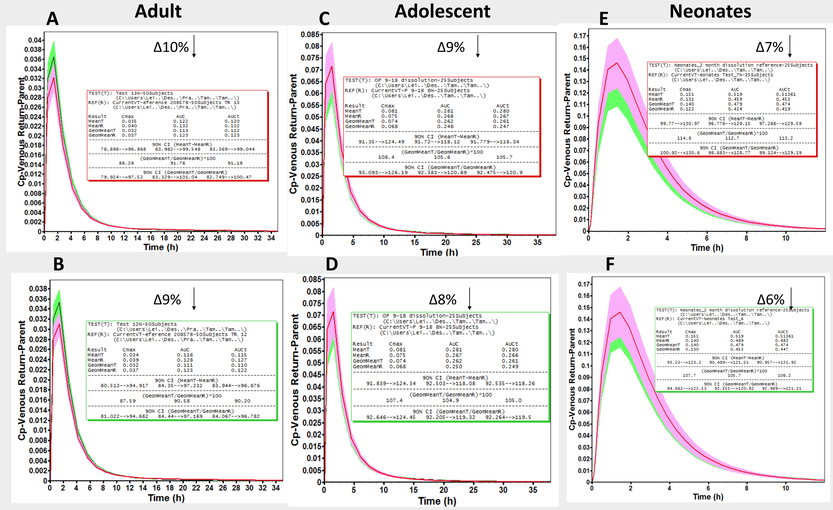


**Figure 2:** Population and virtual BE analysis between reference products using pivotal dissolution profile (pink curve) and theoretical slower dissolution profile (green curve) in adults (A, B) and pediatric populations (C-F) to determine the "safe space" for dissolution profiles. Dissolution profile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

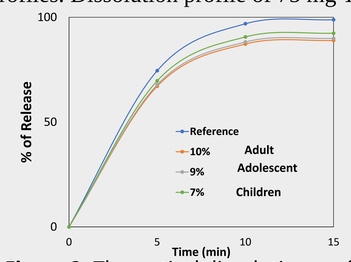


**Figure 3.** Theoretical dissolution profiles

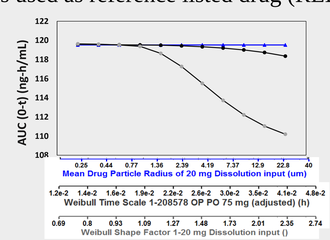


**Figure 4.** Parameter Sensitivity Analysis

## 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.

## ACKNOWLEDGEMENT


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