# *Development of Graphical Interface in R Shiny for PBPK Model-based Prediction and Simulation of Drug Delivery in the Female Reproductive Tract*


PRESENTER:

**Xinnong Li**

**Authors:** Thomas Straubinger[1], Xinnong Li[1], Guru R. Valicherla[2,3], Zhongfang Zhang[2,3], Sharon L. Achilles[3,4], Mark Donnelly[5], Liang Zhao[5], Eleftheria Tsakalozou[5], Beatrice A. Chen[3,4], Lisa C. Rohan[2,3], Robert Bies[1]

1. Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo,New York, USA.
2. Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA, USA.
3. Magee-Womens Research Institute, Pittsburgh, PA, USA.
4. Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA.
5. Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Silver Spring, Maryland, USA.


## BACKGROUND

- Physiologically based pharmacokinetic (PBPK) models for the female reproductive tract may facilitate generic drug development of complex drugs which are delivered to the vagina, cervix and uterus. [1]
- As a graphical user interface (GUI), the Shiny app is convenient for simulating and visualizing data. It can be further applied in formulation optimization and dosing regimen adjustments.

## METHODS

- The female reproductive tract PBPK model was implemented in the R programming language (version 4.0.4) [2] using the open-source simulation package mrgSolve (version 1.0.3). [3]
- The GUI Shiny application was created using the R Shiny package (version 1.71). [4]

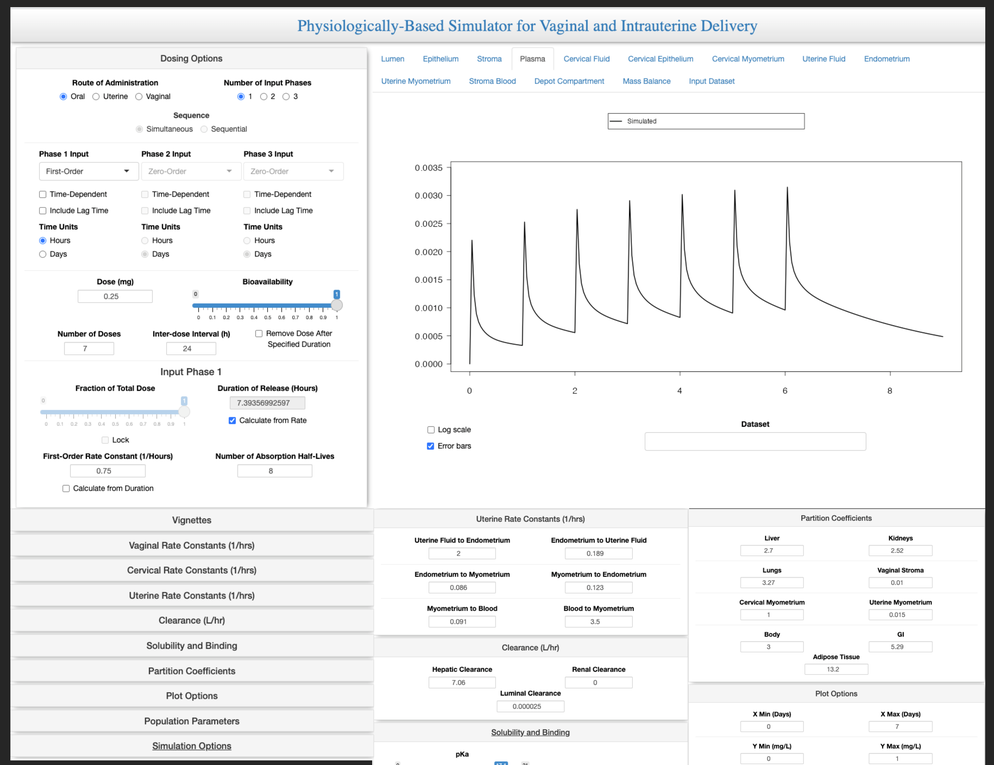
## RESULTS

- Users can specify up to three simultaneous or sequential dosing processes using first-order, zero-order, or Higuchi functions as shown on the figure panel.
- Drug physicochemical parameters, tissue permeation rates, and partition coefficients can each be independently specified.
- Simulation conditions including dose, dosing frequency, route of administration, and relevant bioavailability are provided as inputs.

## CONCLUSIONS AND FUTURE DIRECTIONS

The Shiny app of PBPK model enables users to easily adjust parameters and visualize the results. More adjustment options (e.g., between subject variability) and confidence bands will be included in the future.

This GUI R-Shiny App enables the users to **quickly and easily** utilize the **PBPK model** to simulate delivery of complex drug products via **oral, vaginal, or uterine** routes of administration.





References

1. Donnelly M et al. J Clin Pharmacol. 2020 Dec;60 Suppl 2:S26-S33.
2. R Core Team. 2020. Available from: https://www.R-project.org/
3. Baron KT. 2020. Available from: https://CRAN.R-project.org/package=mrgsolve
4. Chang W et al. 2020. Available from: https://CRAN.R-project.org/package=shiny
5. Nilsson CG et al. Clinical Endocrinology. 1982;17:529–36.
6. SKYLA (levonorgestrel intrauterine device), NDA 203159, Clinical Pharmacology and Biopharmaceutics Review (203159Orig1s000), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf (Figure 3)


**Fig 1**. Shiny app panel screenshot


**ACKOWLEDGMENTS/DISCLAIMER:** This work was supported by the U.S. Food and Drug Administration (FDA) under Contract HHSF223201810188C. The authors thank FDA for this funding. This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.


Example 1: Impact of Changing Clearance on Plasma Concentration Predictions [5]

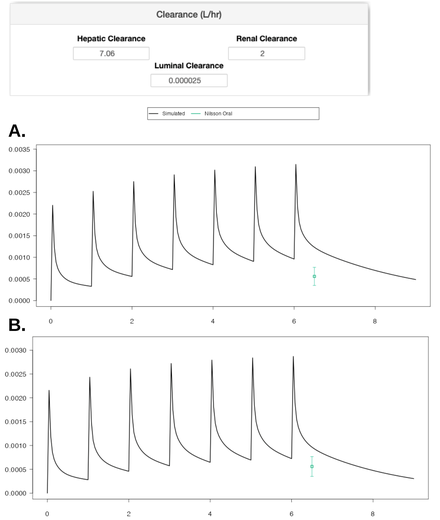



**Fig 2.** Simulation results (black line) without renal CL (A) and with renal CL (B) and observed data with confidence interval (blue square)

Example 2: Illustration of First Order and Zero Order Input on Predicted Concentration [6]

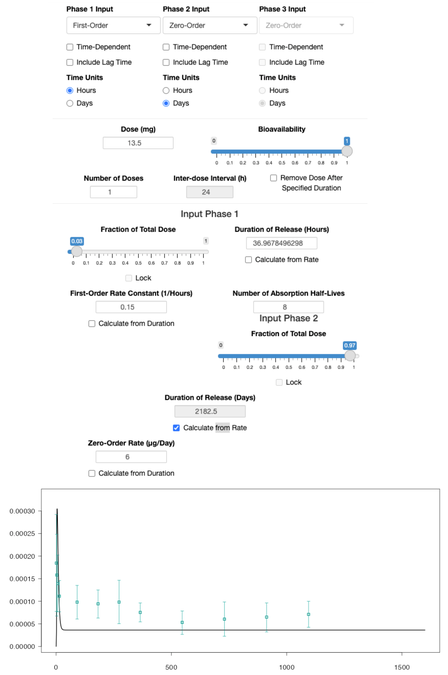



**Fig 3.** Simulation results of combination inputs (black line) vs Observed data (blue squares with 95% confidence intervals