User Friendly Tools for Population PKand PBPK modeling

Robert R Bies

University at Buffalo

Population PKTools PyDarwin for Automated Model Selection

Examples in Pharmacometrics - pyDarwin

- FDA HHS grant announcement
  - Development of a model selection method for population pharmacokinetics analysis by deep-learning based reinforcement learning (RFA-FD-21-027)
- GA is a “brute force” global optimization algorithm
- Opportunity to explore other ML algorithms for model identification
- https://github.com/certara/pyDarwin
- “Development of a model selection method for population pharmacokinetics analysis by deep-learning based reinforcement learning” (1U01FD007355)

Examples in Pharmacometrics - pyDarwin - Model Selection

	Model Selection	Parameter Estimation
Search Space	Discrete	Continuous
Start	Trivial Model	Initial Estimate

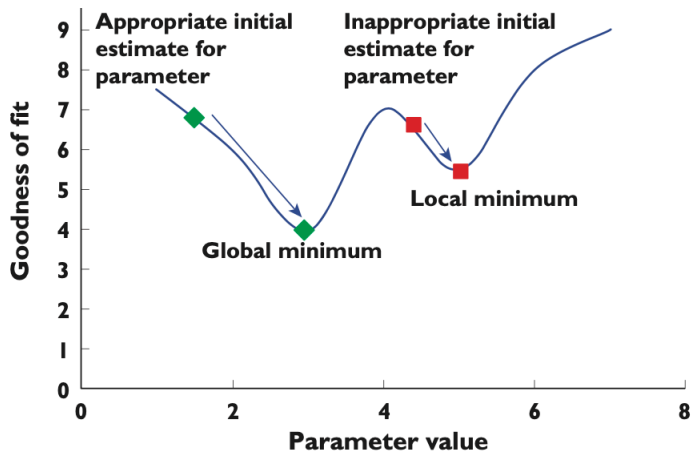
Traditional PK/PD Model Selection (Downhill Method):

- Start from the base model, then add features (COM#, covariate, etc.)
- Doesn't consider the complex interaction between the structural, covariate, and random effects
- Assumes the optimal solution is continuously downhill from every other point in the search space

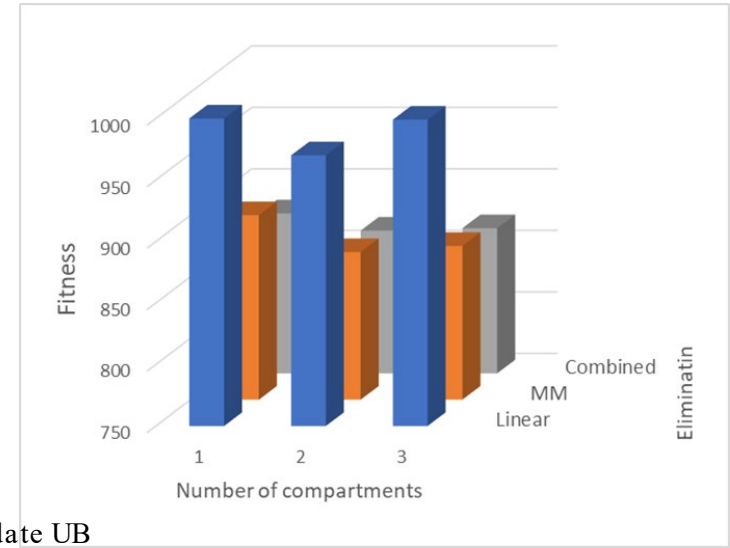
Machine Learning Model Selection:

- Start from multiple random models, test the models, have better idea about the model structure, update the information to the next generation and repeat this procedure

a. Local and global minima in a continuous simple search space



b. Discrete search space



Sale M, Sherer EA.. Br J Clin Pharmacol. 2015 Jan;79(1):28-39
Wade JR, Beal SL, Sambol NC. *J Pharmacokinet Biopharm*. 1994;22(2):165-177.
Chen X, Hamdan A, Wang S, et al. 2022. PAGE 30 (2022) Abstrt 10091
pyDarwin Handout by Certara

Slide courtesy of Xinnong Li, Ph.D. candidate UB

Examples in Pharmacometrics - pyDarwin - Algorithms

- Genetic Algorithm[1]
- Gaussian Process[2]
- Random Forest[2]
- Exhaustive Search
- Random Tree with Gradient Boosting[2]
- Particle Swarm Optimization[3]

1. Implementation with DEAP, 2. Implementation with scikit-optimize, 3. Implementation with pySwarms

Li X et al. pyDarwin: A Machine Learning Enhanced Automated Nonlinear Mixed-Effect Model Selection Toolbox. Clin Pharmacol Ther. 2024 Apr;115(4):758-773.

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

https://certara.github.io/pyDarwin/html/Overview.html

Slide courtesy of Xinnong Li, Ph.D. candidate UB

Examples in Pharmacometrics - pyDarwin -

- Data from a clinical study of dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) were available and previously reported
  - 951 observed concentrations were available from 66 subjects.
  - Multiple daily doses were administered, with sample collection for up to 102 hours.
  - Ages ranged from 28 to 82 years.
  - Weight ranged from 48 to 137kg.
  - 39% (26 of 66) were male, 61% (40 of 66) were female.
  - Renal function was normal with the highest serum creatinine of 1.8 mg/dL.

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

- Search space included:
  - 1 or 2 or 3 compartments
  - With or without between subject variability on V2, V3, Q2, Q3
  - With or without between occasion variability on CL, V2, Q2
  - Covariates:
    - All Volumes (Central and all peripheral)~ WT
    - All Clearances (Central and intercompartmental)~ WT
    - Central Volume ~ Age, Sex
    - Central Clearance ~Age, Sex, Serum creatinine
  - Residual error model (proportional or combined additive and proportion)

Li Xet al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

- The model search was conducted using each algorithm
- “Gold Standard” for robustness (did the algorithm find the optimal model?) is exhaustive search – running all 1,572,864 candidate models
- Criteria for efficiency is time to first appearance of the optimal model

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

- -2LL + penalties:
  - Parsimony – 10 points for each estimated parameter
  - Convergence – 100 points for models failing to converge
  - Covariance – 100 points for models failing covariance step
  - Correlation – 100 points for models with absolute value of any off diagonal element of covariance matrix > 0.95
  - Condition number – 100 points for condition number > 1000

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

FDAsupport: 1U01FD007355

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

- Final Model:
  - 3 compartments
  - Power function of centered WT for volume
  - BSV on central volume, clearance, peripheral volume 1, inter-compartment clearance 2
  - Between occasion variability on central volume, clearance and intercompartment clearance 1
  - Combined additive and proportional residual error model

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

Algorithms	Best fitness (OFV+ penalties) with one- and two-bit local downhill search	Number of unique models to the best model with one- and two-bit local downhill search	Best fitness with only one-bit local downhill search
Exhaustive Search	8201.271	n/a	n/a
Genetic Algorithm	8201.271	1307	8201.271
Random Forest	8201.271	880	8201.271
Gaussian Process	8201.271	495	8201.271
Particle Swarm Optimization	8201.271	1710	8220.745
Gradient Boosted Random Tree	8201.271	1328	8201.271

Li Xet al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

Examples in Pharmacometrics - pyDarwin -

Algorithms	Time to best model with one- and two-bit local downhill search	Total time with one- and two-bit local downhill search	Time (min)/unique model number before reaching the optimal
Exhaustive Search	34.2 min	60384.1 min	0.0035
Genetic Algorithm	169.3 min	321.8 min	0.130
Random Forest	126.7 min	461.6 min	0.144
Gaussian Process rerunning	114.6 min	2975.6 min	0.232
Particle Swarm Optimization	255.5 min	404.2 min	0.150
Gradient Boosted Random Tree	223.8 min	410.2 min	0.169

Li X et al. pyDarwin machine learning algorithms application and comparison in nonlinear mixed-effect model selection and optimization. J Pharmacokinet Pharmacodyn. 2024 Jun 28.

PBPKTools - Reprosim

GDUFA Research Contract

- In 2018, OGD funded a research contract titled: "Physiologically-based model of the female reproductive tract: vaginal and intrauterine delivery components" (HHSF223201810188C) with University at Buffalo[1]

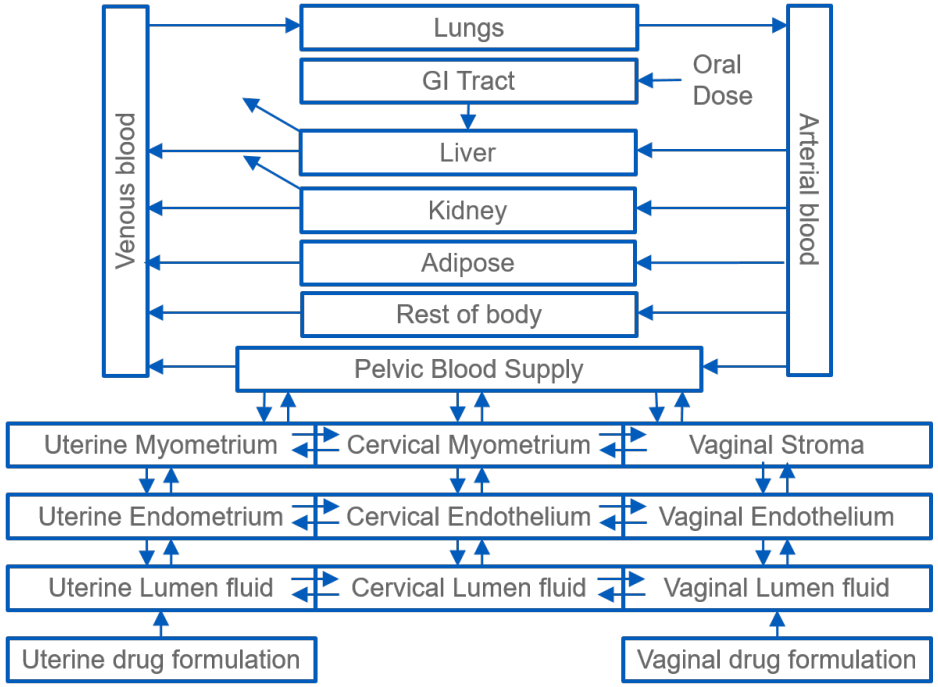
- Objective: Develop an open-source, user-friendly, generalized PBPK modeling and simulation platform for complex products delivered in the female reproductive tract
  - Collect available information from literature and previous modeling efforts
  - Conduct several in vitro, in vivo, and ex vivo studies to fill gaps in knowledge
  - Develop and validate PBPK model

- Supports one of the key scientific initiatives to accelerate access to generic drug products: "Improve PBPK models of drug absorption via complex routes of delivery"

1. FY2018 Awarded GDUFA Regulatory Research Contracts and Grants. U.S. Food & Drug Administration. Available at: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects. Accessed September 21, 2020.

PBPK Model for Drugs Delivered via Female Reproductive Tract

Once validated, this PBPK modeling platform may be used to assess the impact of differences in formulation and in vitro product performance on the rate and extent to which the active ingredient becomes available at the site of drug action and/or systemic circulation



This research may help facilitate development of generics for these complex drug products

- Assisting product development
- Supporting alternative approaches to establish BE
- Reducing the burden of comparative clinical endpoint BE studies

PBPKmodel – App to facilitate usage REPROSIM

- Created using R-Shiny linked to the MRG-Solve PBPKmodel.

- Options
  - 3 absorption processes
  - simulations with variability
  - individual parameters for any element of the model:
    - drug specific
    - system specific

What is Shiny?

- Shiny is a free, open-source package that allows you to create interactive web apps in R.
- Can be run locally, hosted on a webpage, or embedded in R Markdown documents.
- No knowledge of typical web design languages required.
  - Apps can be extended using CSS, HTML, JavaScript.
- Can provide a convenient user interface for exploring PK/PD models.

mrgSolve

- Free, open-source R package for simulating ordinary differential equation (ODE) based PK/PD and QSP models
- Incorporates a freely available ODE solver, LSODA, which is a variant of the Livermore Solver for Ordinary Differential Equations (LSODE)
- Allows for rapid and flexible simulations of PK/PD models

REPROSIM App Panel

Physiologically-Based Simulator for Vaginal and Intrauterine Delivery

Dosing Options

Route of Administration
○ Oral ◉ Uterine ○ Vaginal

Number of Input Phases
◉ 1 ○ 2 ○ 3

Sequence
◉ Sequential

Phase 1 Input	Phase 2 Input	Phase 3 Input
Zero-Order	Zero-Order	Zero-Order
☐ Include Lag Time	☐ Include Lag Time	☐ Include Lag Time
Time Units	**Time Units**	**Time Units**
○ Hours	○ Hours	○ Hours
◉ Days	◉ Days	◉ Days

Dose (mg): 63

Dose Fraction Released: 0 — 1 (0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1)

Number of Doses: 1

Inter-dose Interval (h): 24

☑ Remove Dose After Specified Duration

Input Phase 1

Fraction of Total Dose: 0 — 1 (0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1)

Duration of Release (Days): 50

☐ Calculate from Rate

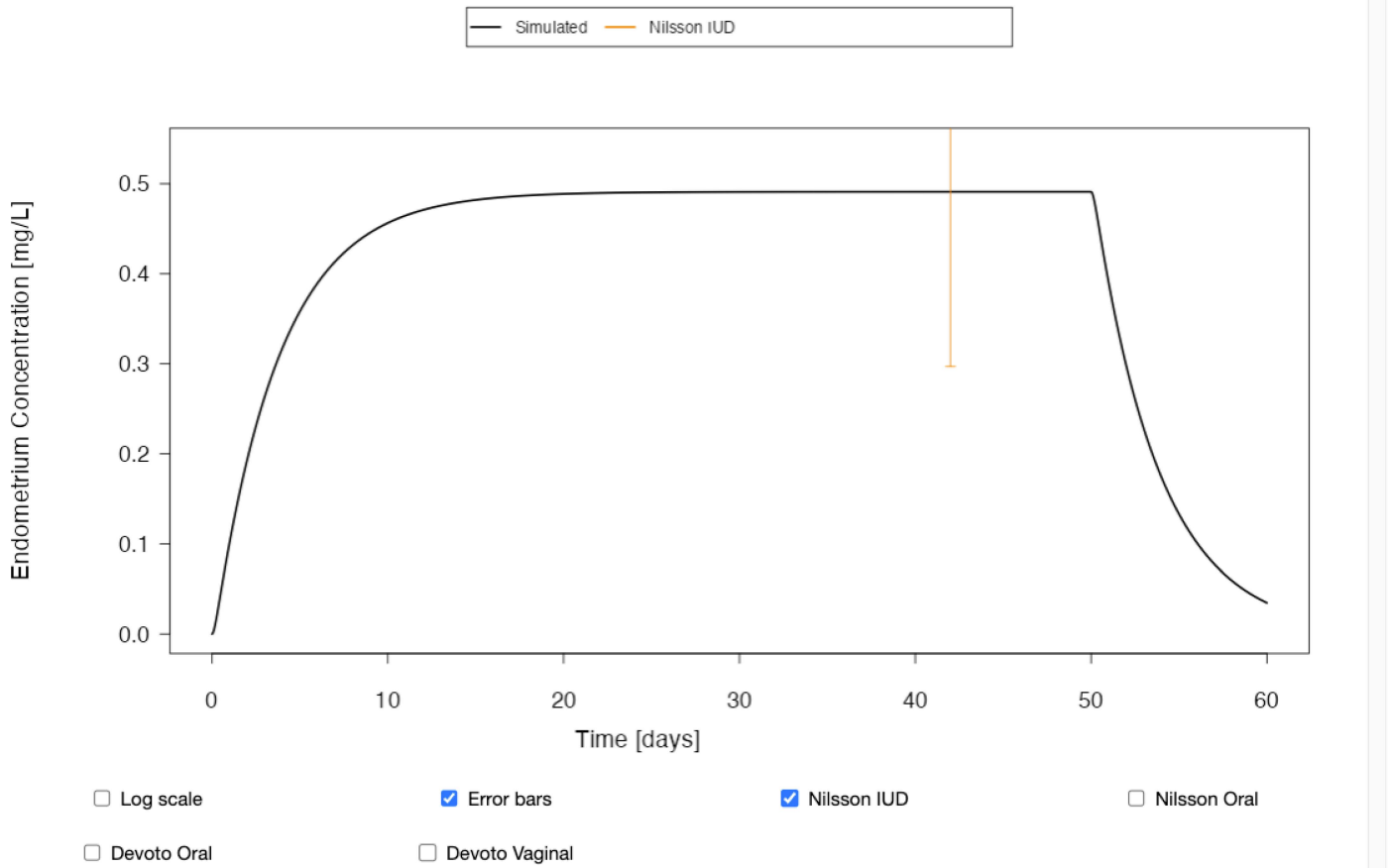
☐ Lock

Zero-Order Rate (µg/Day): 30

☐ Calculate from Duration

Lumen | Epithelium | Stroma | Plasma | Cervical Fluid | Cervical Epithelium | Cervical Myometrium | Uterine Fluid | Endometrium

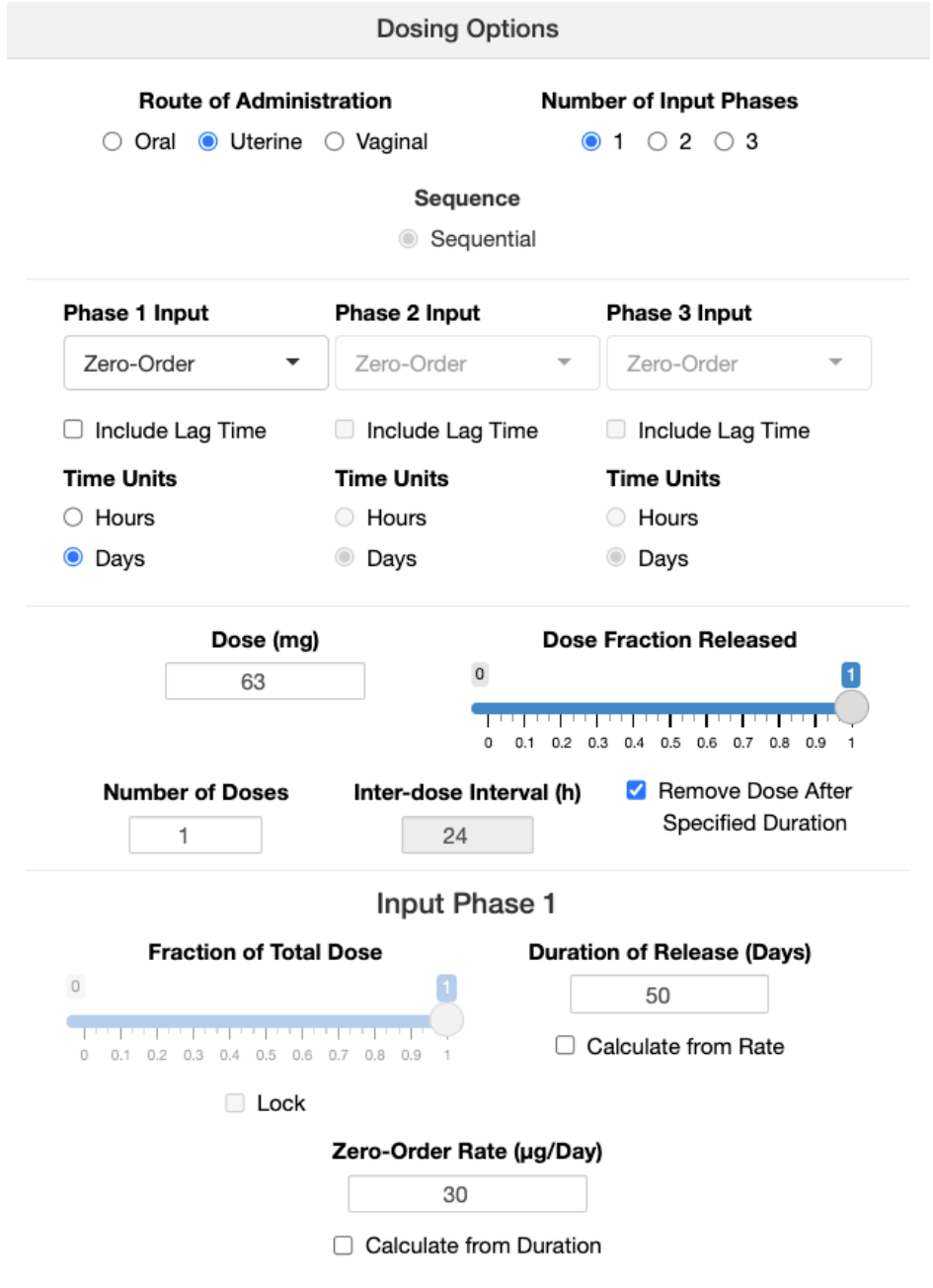
Uterine Myometrium | Stroma Blood | Depot Compartment | Input Dataset



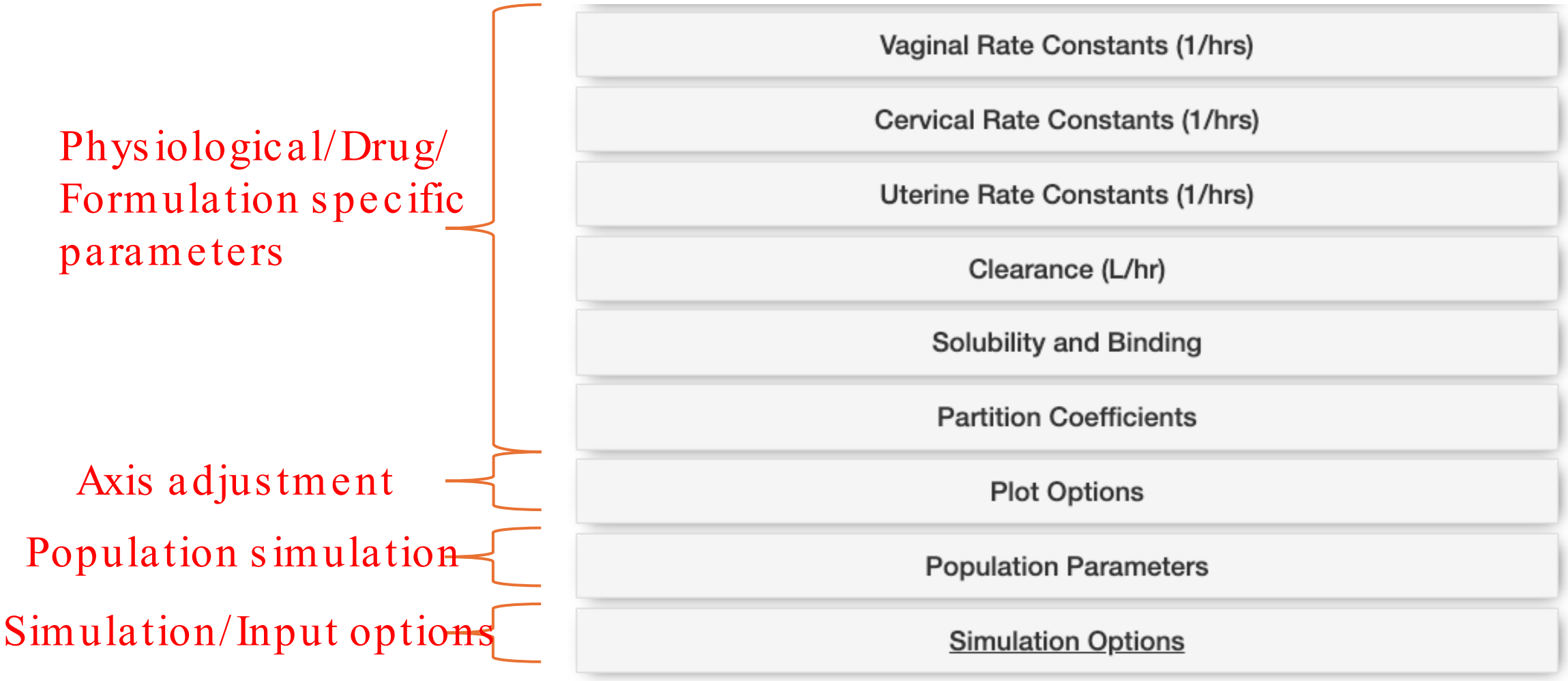
https://fda.zoomgov.com/rec/play/QKn3yvb8_y-NZiczfwPMnOdHHQKhn_4hcF25DmiapwawBikbdofBZNYRdmMM87zDNwx6wgGeX3yIS26Z.GI4DKMvpFNYzbU3a?canPlayFromShare=true&from=my_recording&continueMode=true&componentName=rec-play&originRequestUrl=https%3A%2F%2Ffda.zoomgov.com%2Frec%2Fshare%2F4UlXiz0JUisD1Thow_V_rcJafc7H9deFZBzYG9ZguqrKO4BIIcaoXjPFGuJcoeVl.iebHA_QiitQ4ImWW
Passcode: SF=5E&+f

REPROSIM App Panel

Dosing Options

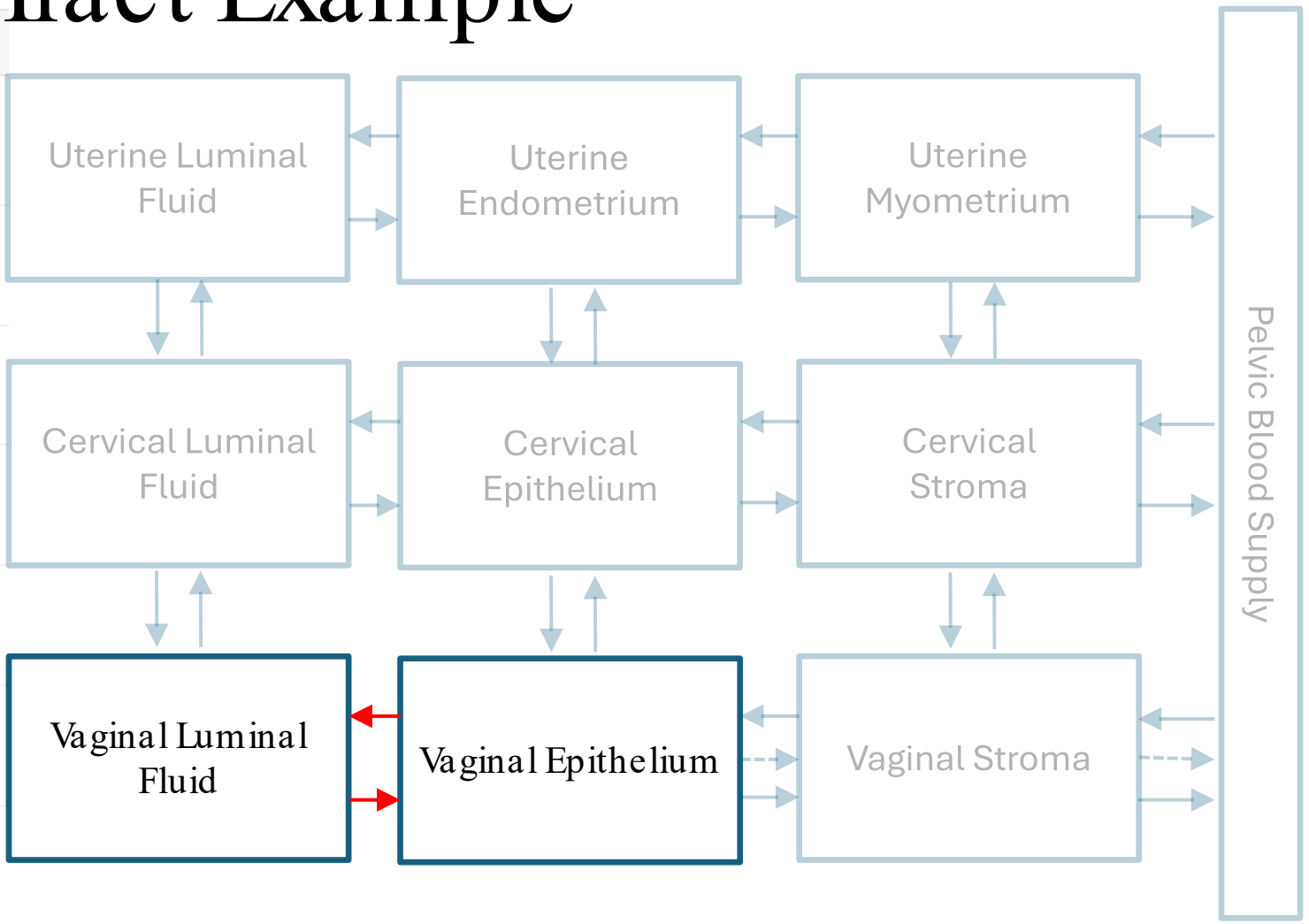


REPROSIM App Panel



REPROSIM App Panel – Female Reproductive Tract Example

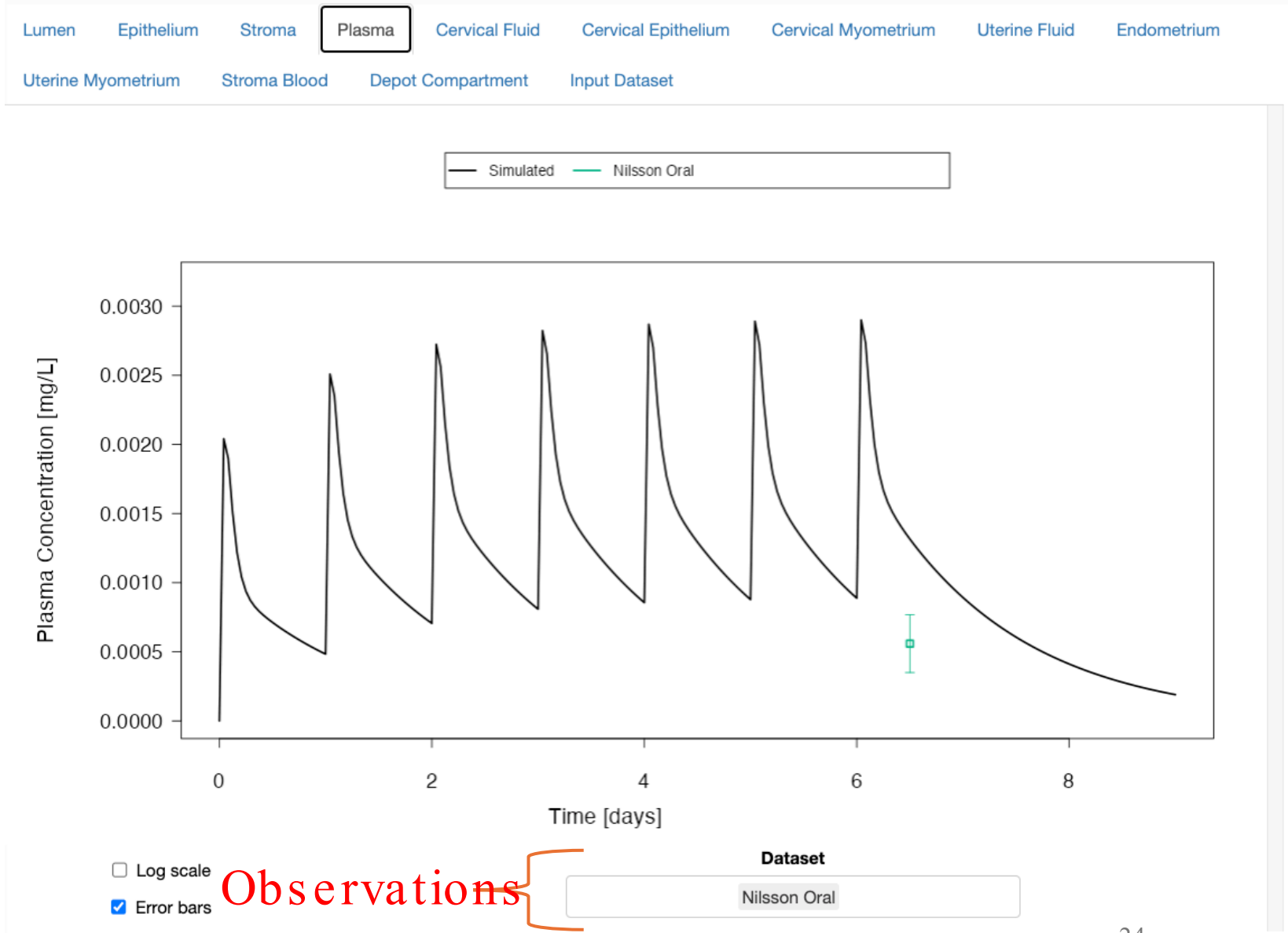
Vaginal Rate Constants (1/hrs)	
Lumen to Epith	**Epith to Lumen**
5	0.01
Epith to Stroma	**Stroma to Epith**
0.43	0.01
Stroma Tissue to Blood	**Stroma Blood to Tissue**
0.15	0.2
active Epith to Stroma	**active Stroma Tissue to Blood**
0.01	0.01
Lumen to CF	**CF to Lumen**
0.0001	0.0001
Vag to Cerv Epi	**Cerv to Vag Epi**
0.01	0.0001
V Stroma to Cerv Myometrium	**Cerv Myometrium to V Stroma**
0.0001	0.0001



REPROSIM App Panel

Tissue compartments simulation results

Simulation profile



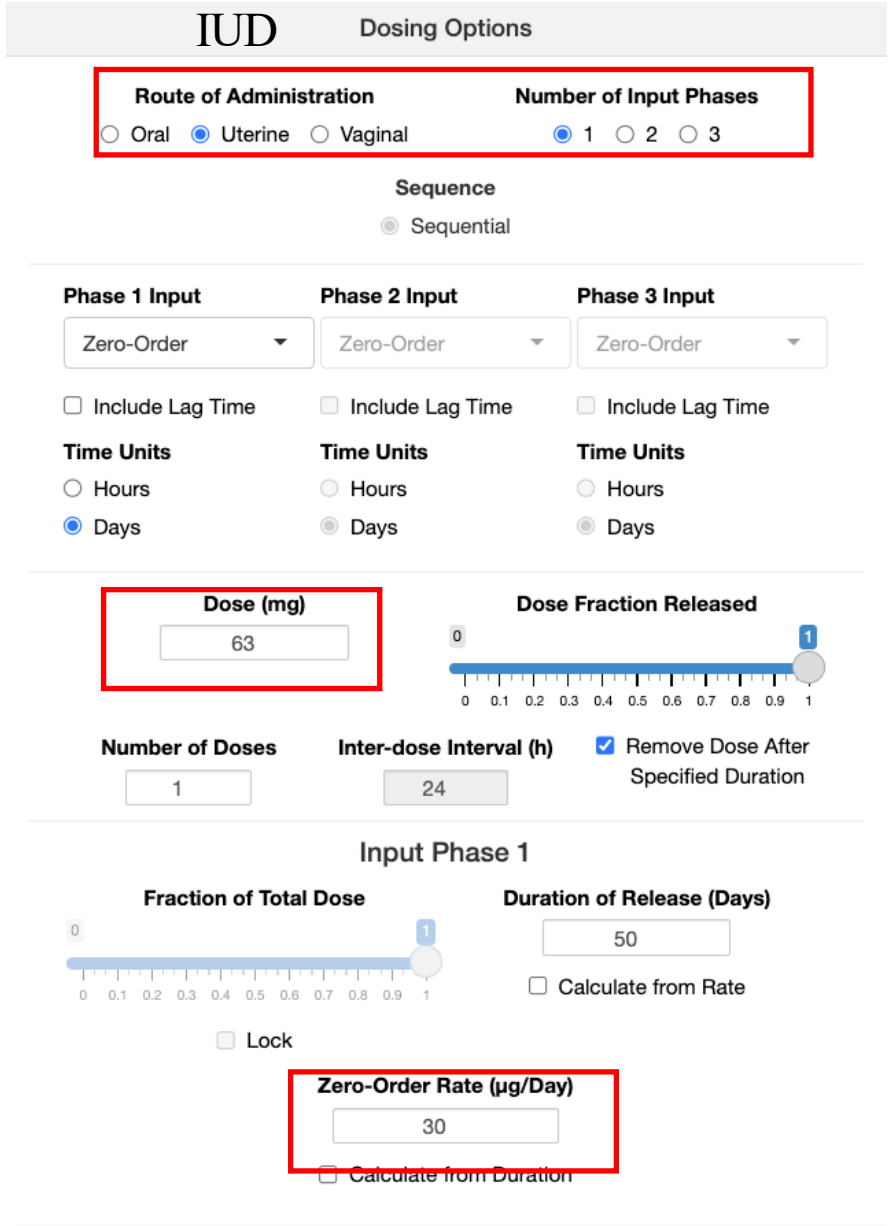
Observations

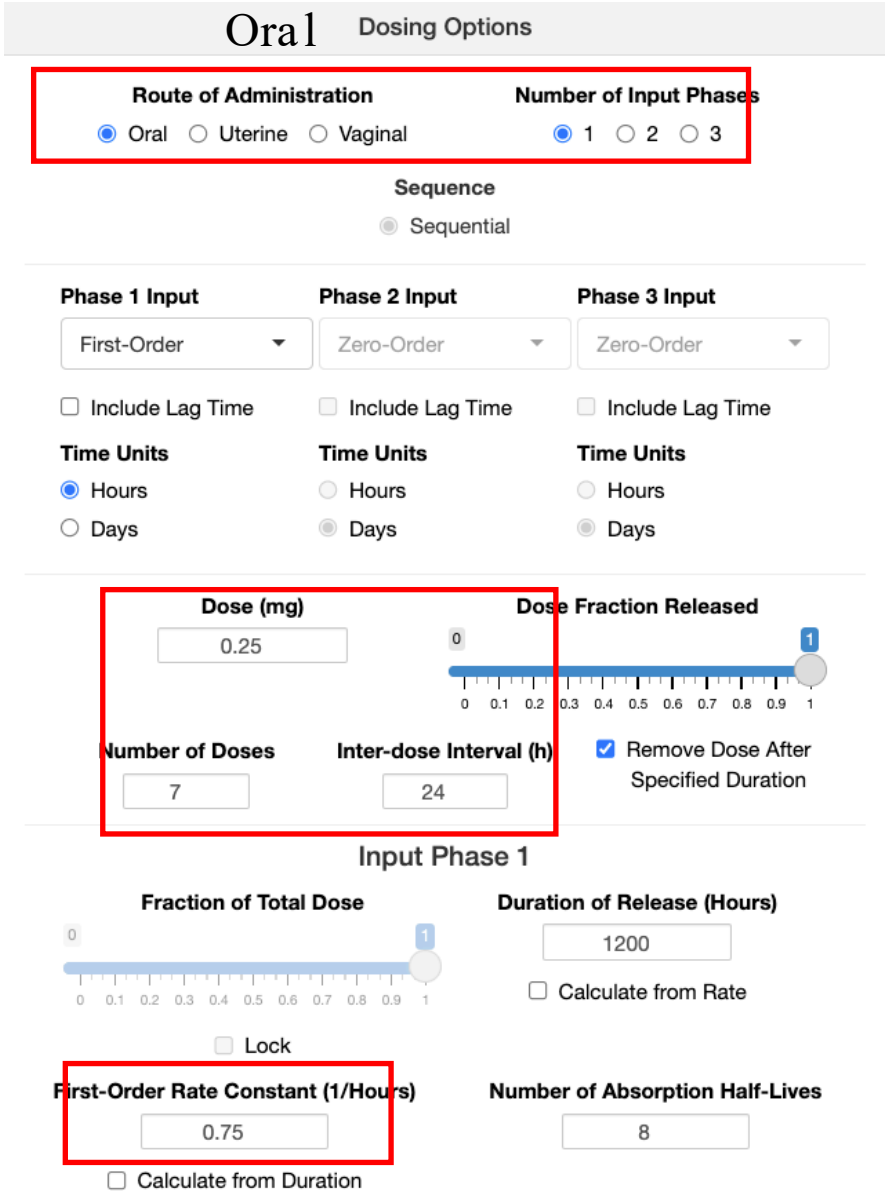
Case Example 1 - Vignette: Nilsson et al.

- 13 women ages 41 – 49, scheduled for hysterectomies because of uterine fibroids or menorrhagic bleeding
- 9 women had an LNG-releasing IUD inserted 36 – 49 days prior to surgery
  - Average Release rate of 30 µg/day of levonorgestrel
  - Each IUD contained a total dose of 63 mg
  - Uterus removed with IUD in situ
- 4 women were on oral LNG for 7 days prior to surgery
  - 2 mg estradiol and 250 µg levonorgestrel daily
  - Final dose was administered 12 h before the surgery
- Plasma concentrations were measured, as well as endometrial, myometrial, and fat tissue concentrations

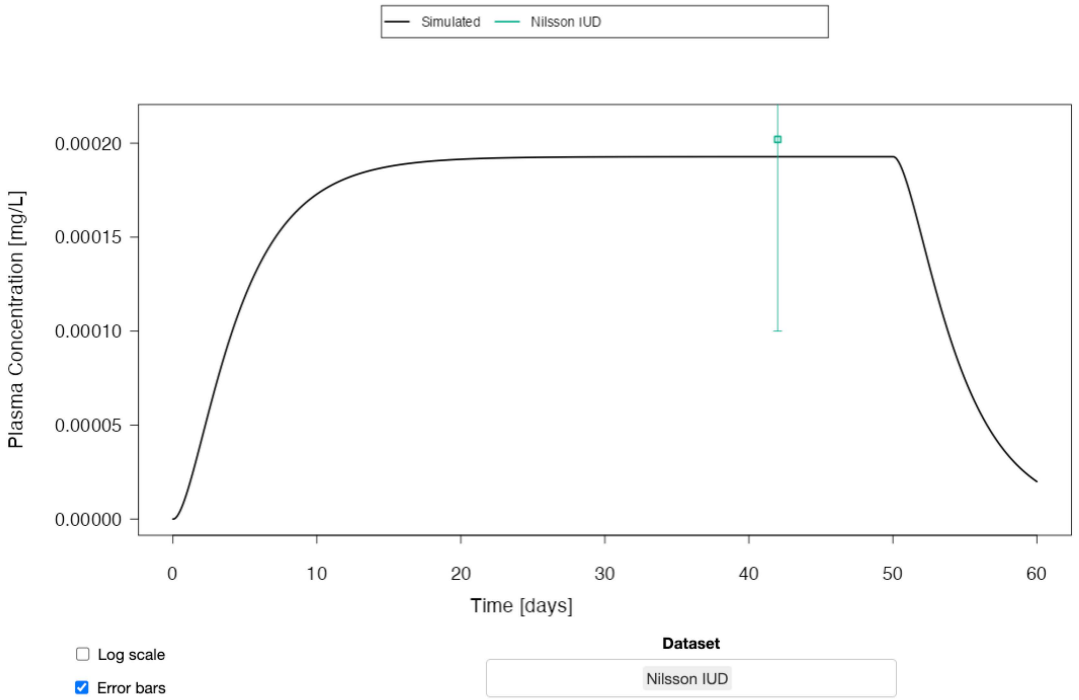
Nilsson, C. G. et al. *Clinical Endocrinology* **17**, 529–536 (1982).

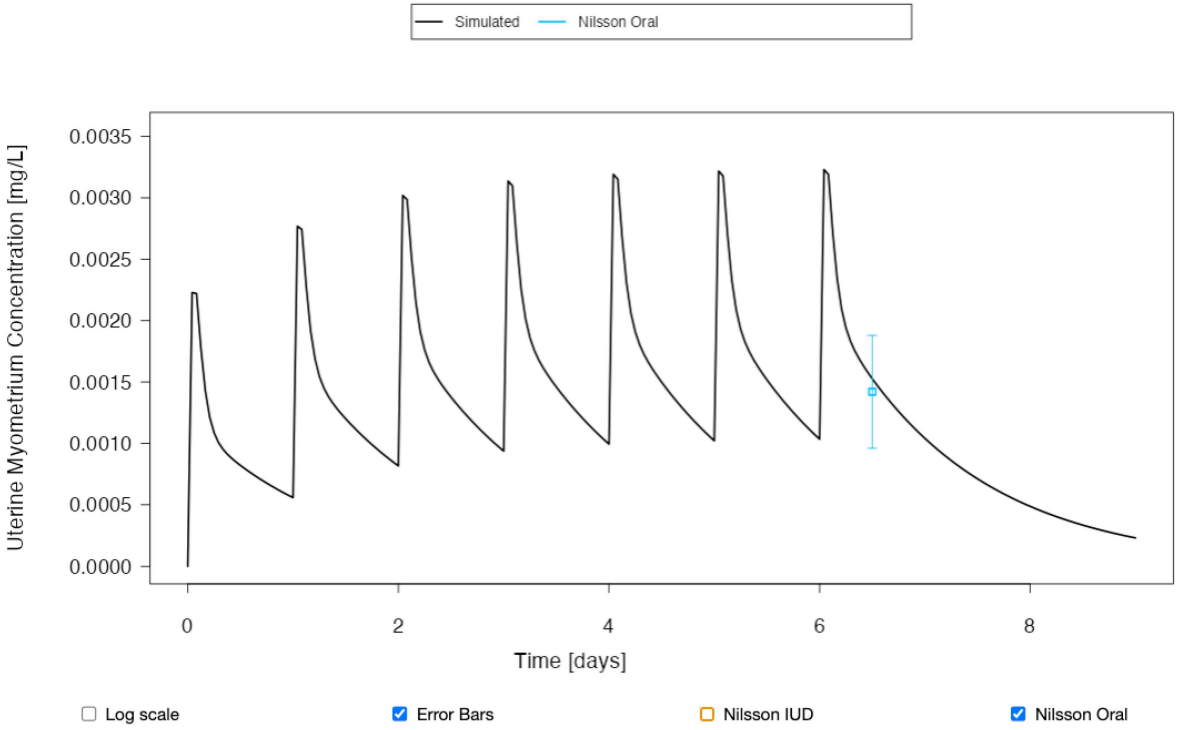
Example 1 Options





Example 1 Results

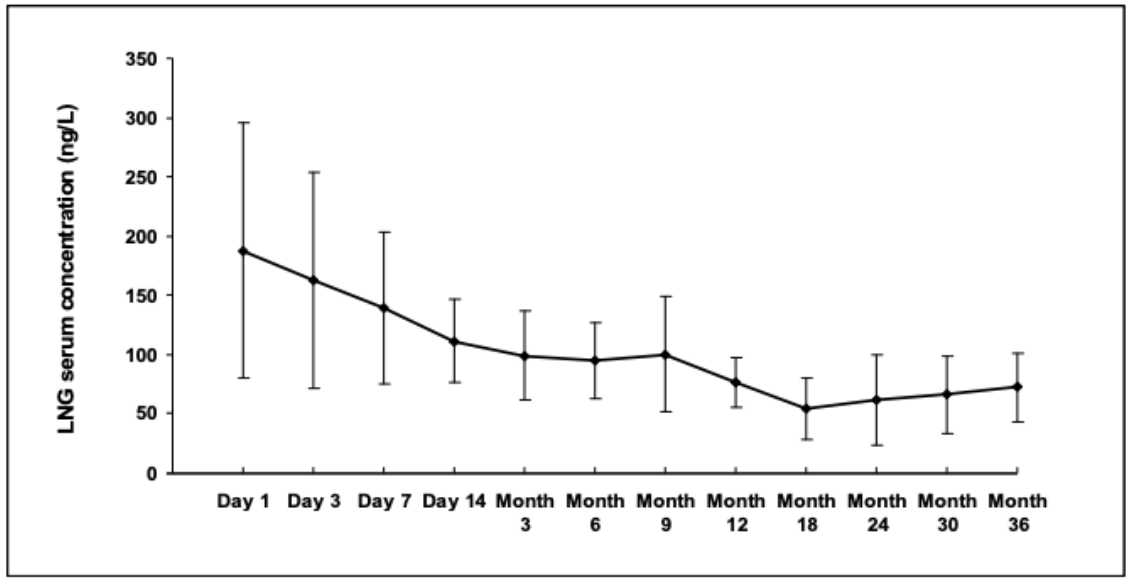




Nilsson, C. G. et al. *Clinical Endocrinology* **17**, 529–536 (1982).

Case Example 2 – Skyla IUD Multiphase Input

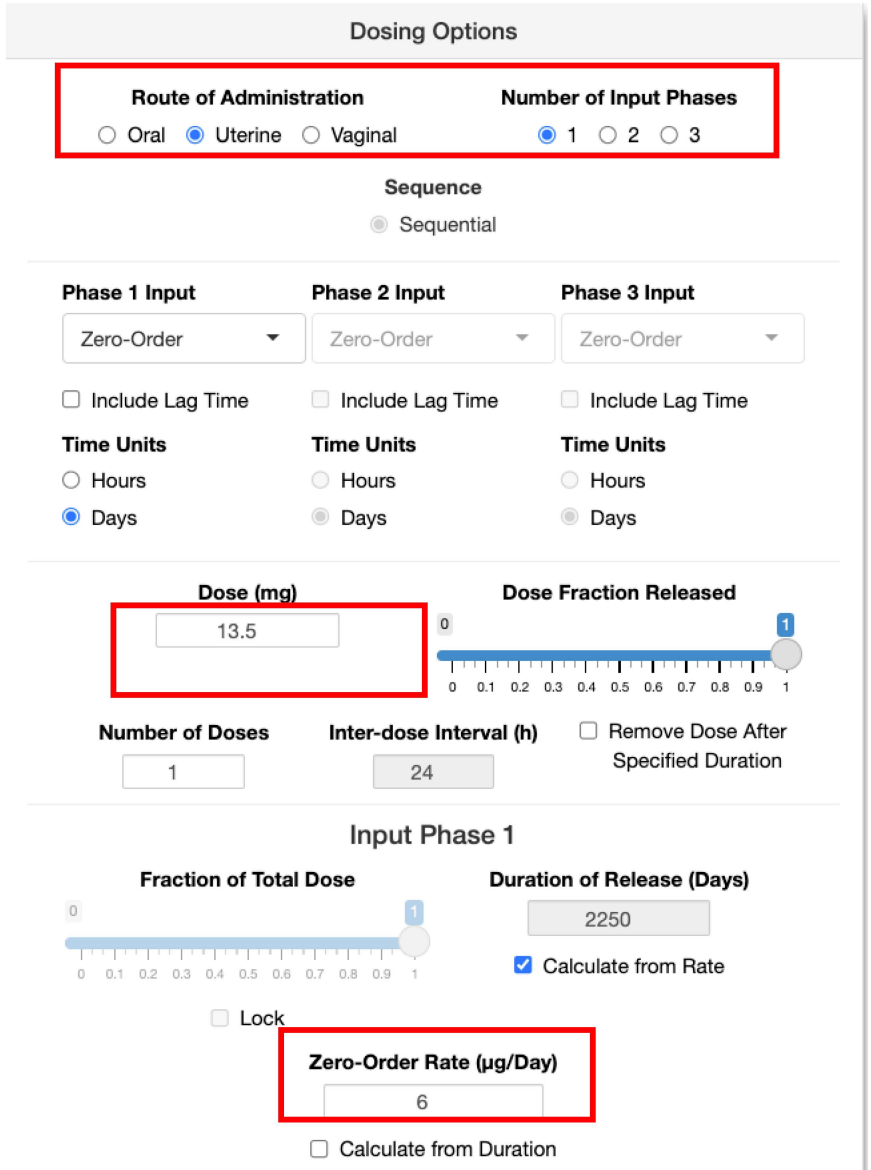
Figure 3 Arithmetic mean (±SD) LNG concentrations-Time profile following insertion of LCS12 (N=7)

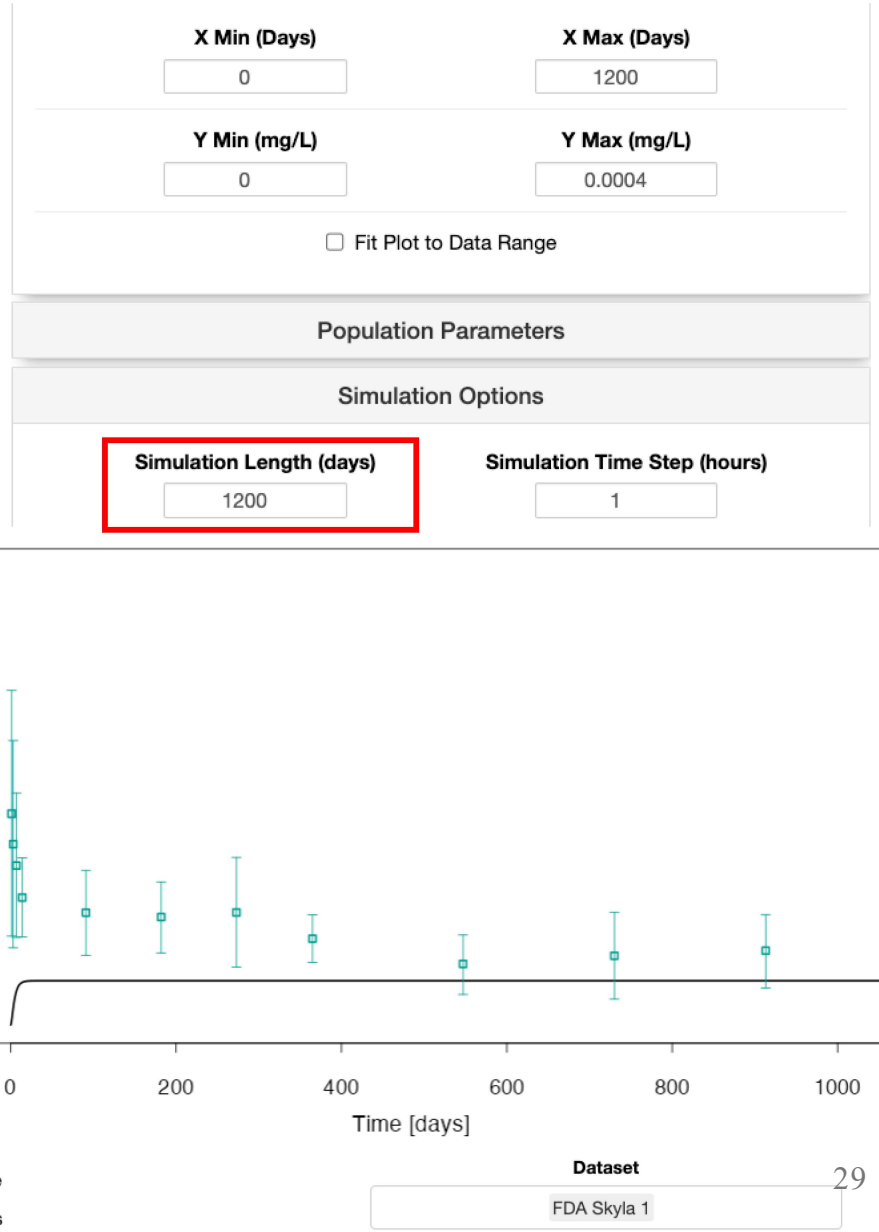


LCS12 contains 13.5 mg LNG.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf

Example 2 – Multiphase Input - Single





https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf

IUD Multiphase Input Rate Constants

In vivo release rate change of the LNG-IUS products approved by the U.S. FDA. (The unit in the table is μg/day).

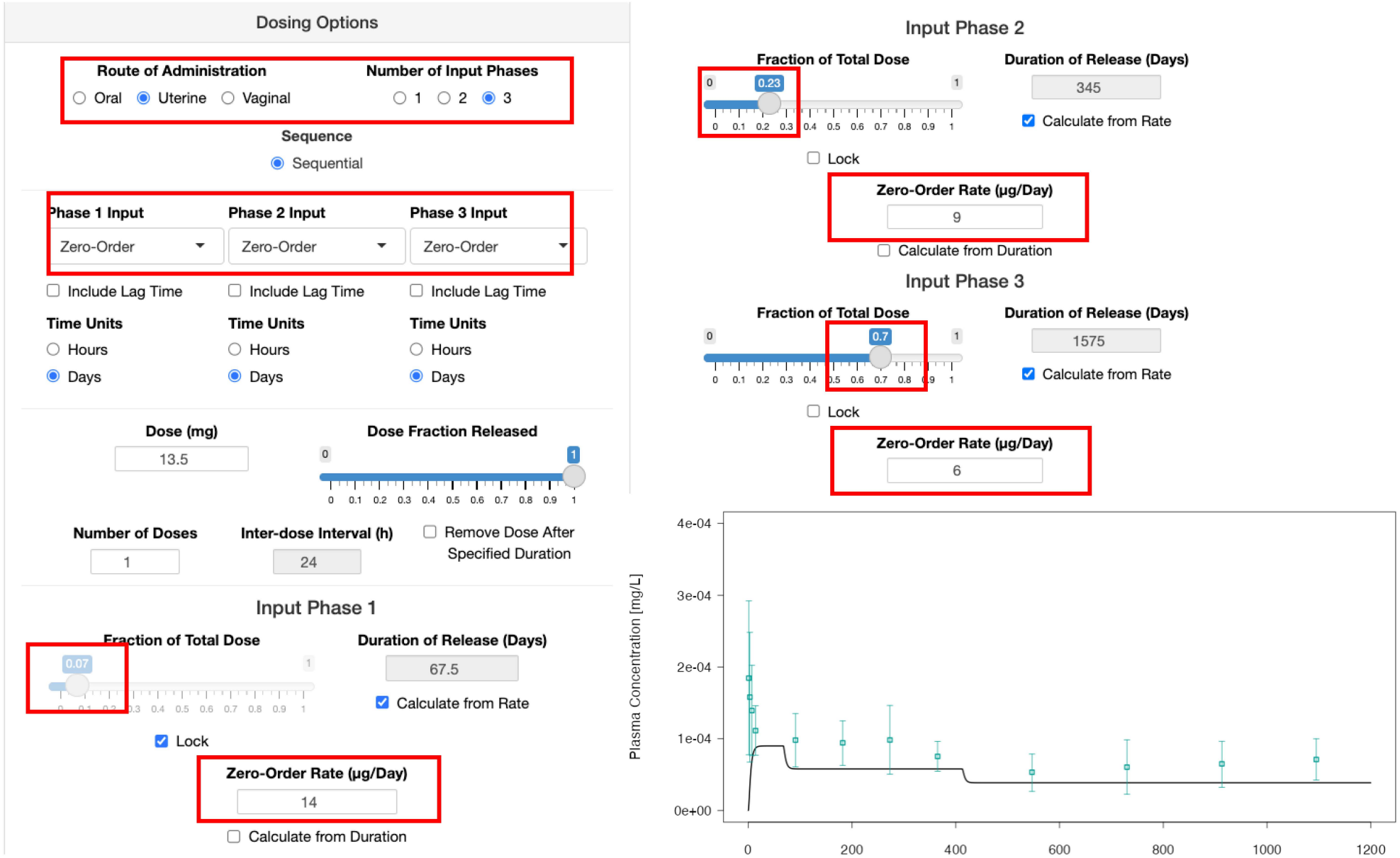
Product (total amount of LNG)	< 1 year	At 1 year	End of approved year for use	Average	Reference
Mirena® (52 mg)	20.0 (3 months)	18.0	10.0 (5 years)	17.1[a]	[7,9,10]
Kyleena® (19.5 mg)	17.5 (24 days)	9.8	7.4 (5 years)	9.0	[11]
Skyla® (13.5mg)	14.0 (24 days)	6.0	5.0 (3 years)	6.0	[12]
Liletta® (52 mg)	19.5 (initial)	17.0	9.8 (5 years)	14.1[a]	[13,14]

Open in a separate window

[a]The average release rate was calculated based on the amount of drug released at the end of the approved 5-year usage (60% cumulative release for Mirena® and 49.4% cumulative release for Liletta® over a 5-year duration). These data were obtained based on the amount remaining in the device after retrieval from patients at the specified amount of time.

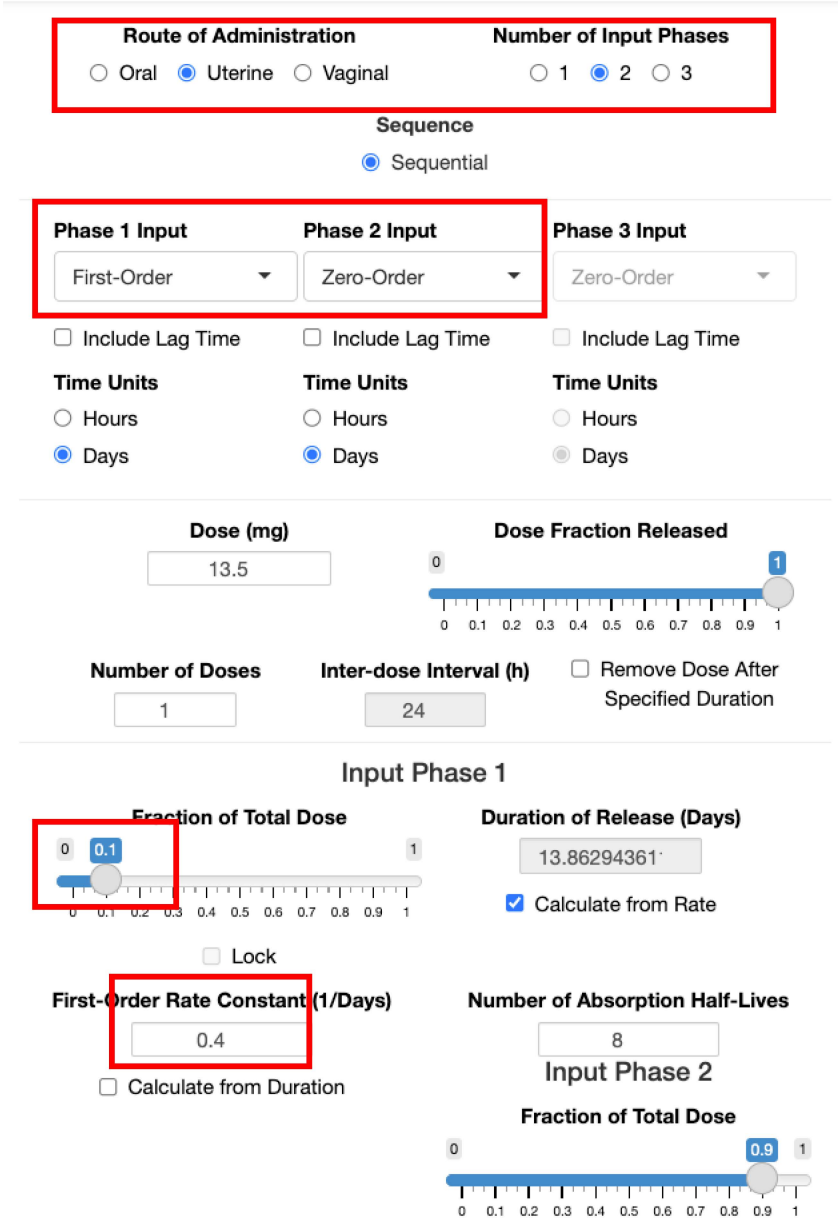
Bao Q et al. Drug release testing of long-acting intrauterine systems. J Control Release. 2019 Dec 28;316:349-358.

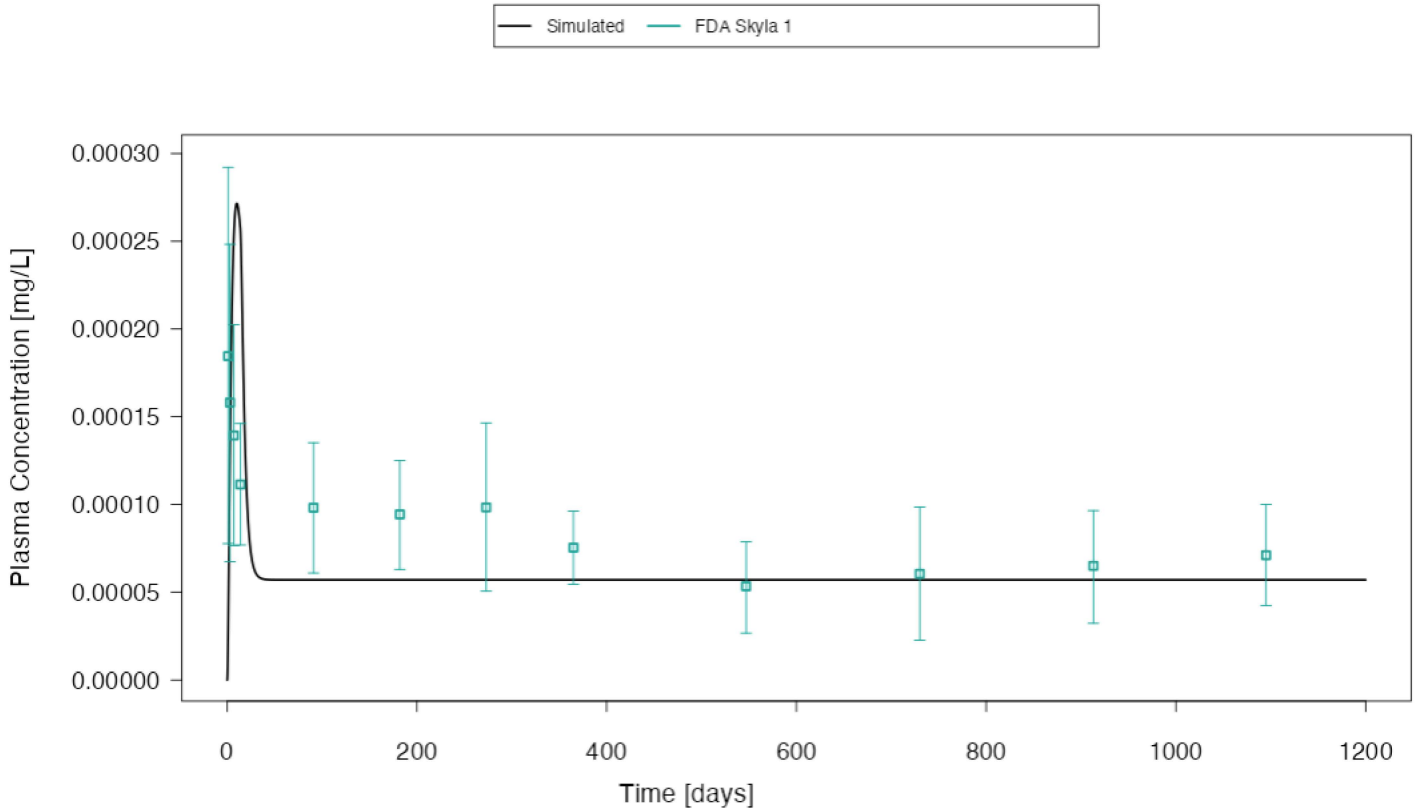
Example 2 – Multiphase Input – Three Zero-order Input



https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf

Example 2 – Multiphase Input – First Order+Zero Order





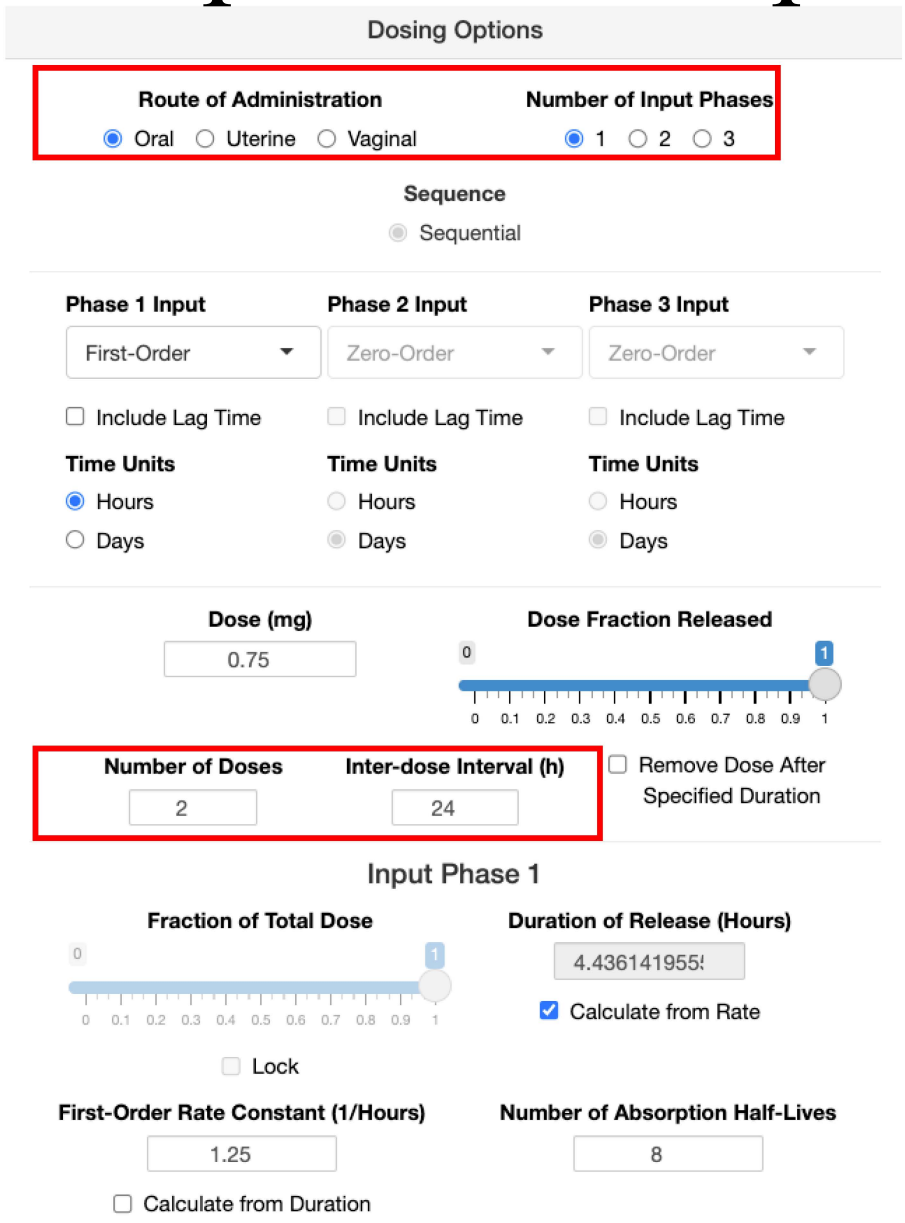
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203159Orig1s000ClinPharmR.pdf

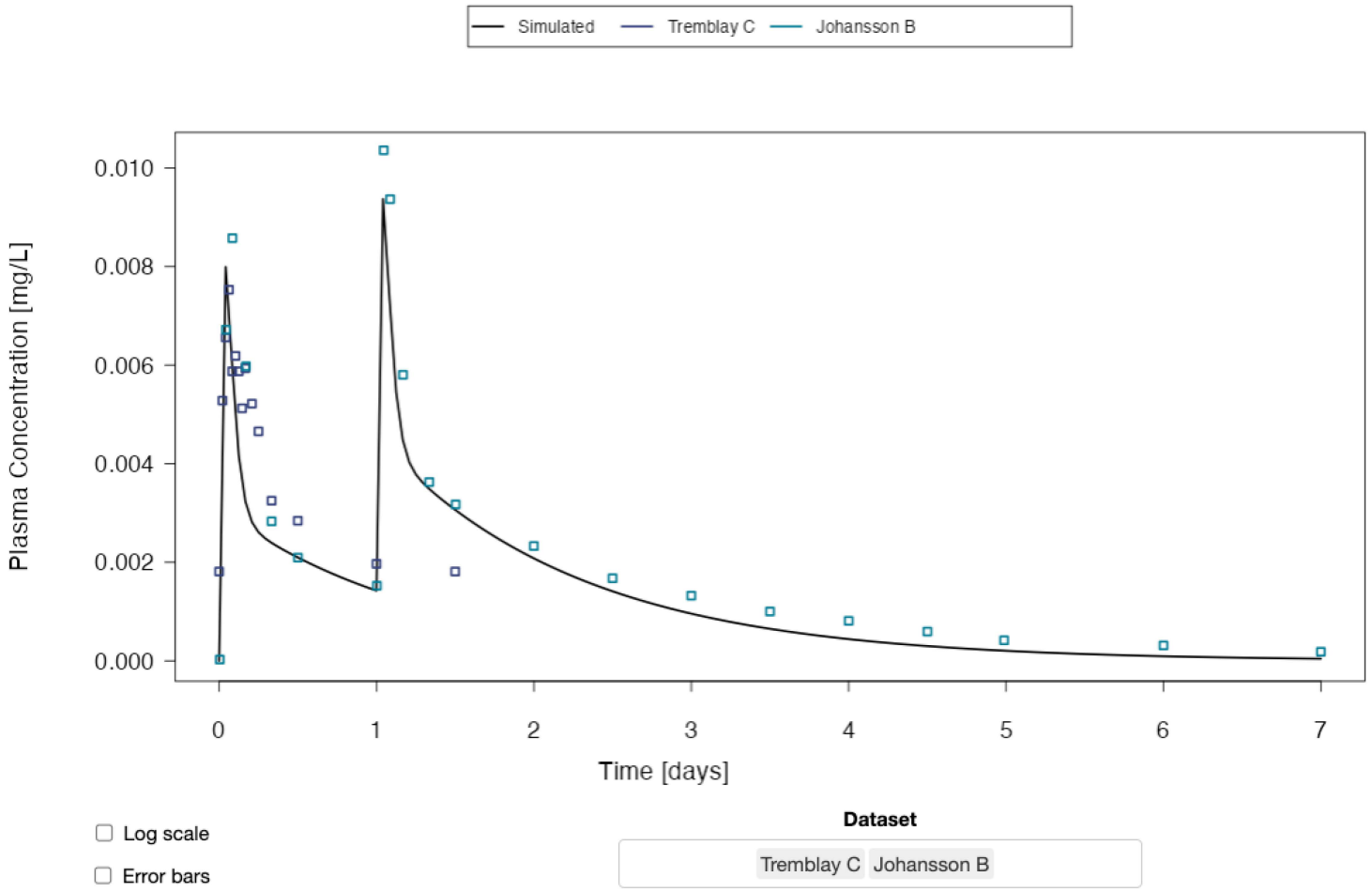
Case Example 3 – Multiple Doses

- Tremblay (N = 8) and Johansson studies (N = 5)
- 2 doses of 0.75 mg LNG, oral administration, dosing interval is 24 h

Tremblay, D. *et al*. *Contraception* **64**, 327–331 (2001).
Johansson, E. *et al. Human Reproduction* **17**, 1472–1476 (2002).

Example 3 – Multiple Doses





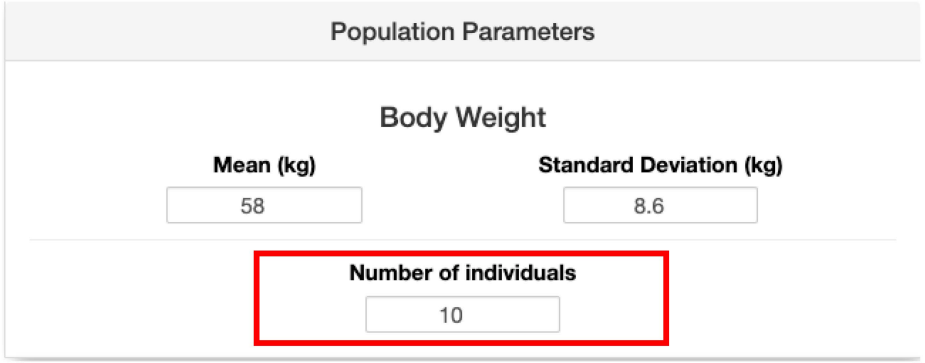
Tremblay, D. *et al*. *Contraception* **64**, 327–331 (2001).
Johansson, E. *et al. Human Reproduction* **17**, 1472–1476 (2002).

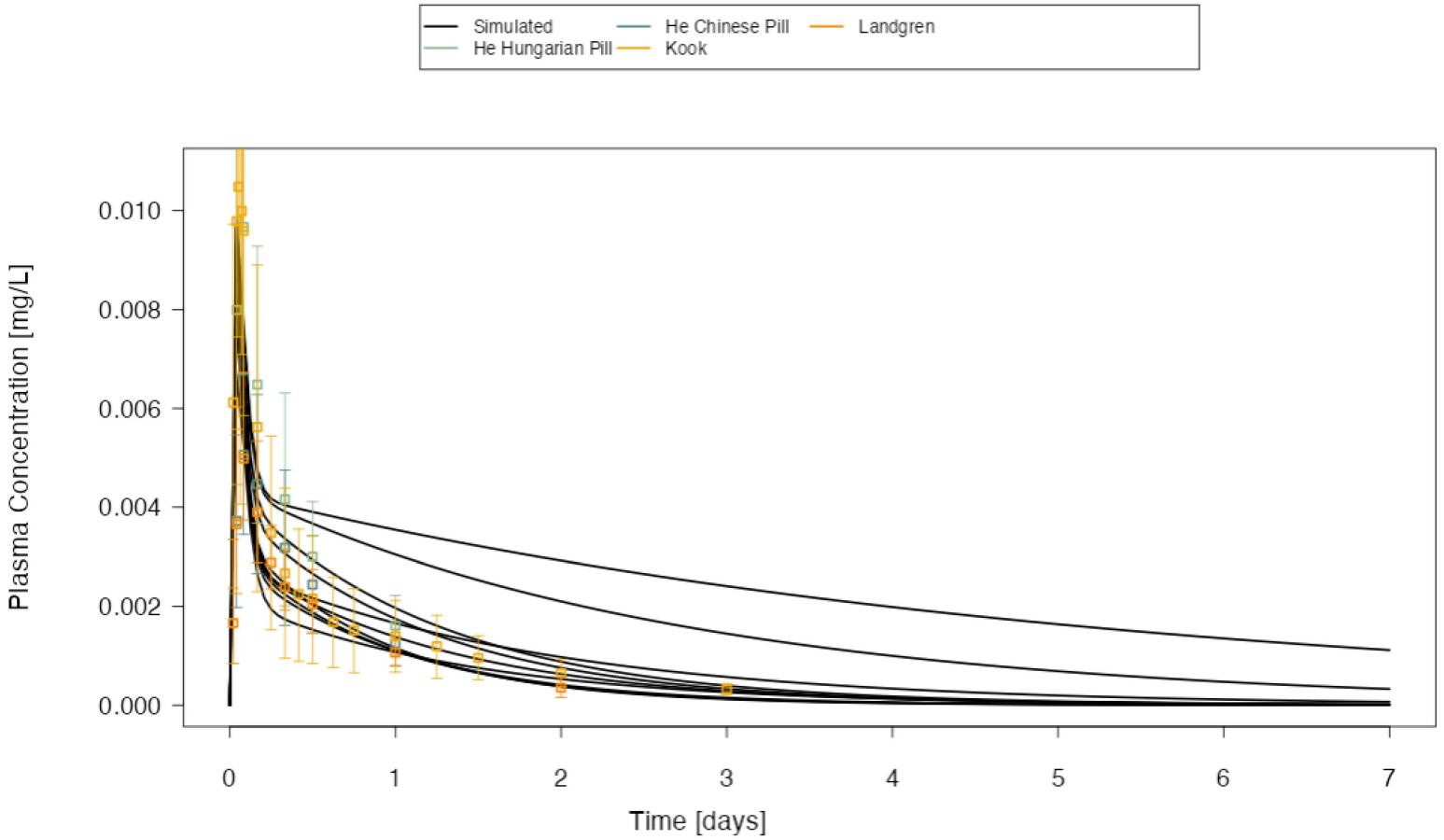
Example 4 – Population Simulation

- 0.75 mg LNG single dose, oral administration
- Observations are from Kook study (N = 16), He study (N = 10) and Landgren study (N = 10)

Kook, K *et al*. *Contraception* **66**, 73–76 (2002).
He, C. *et al. Contraception* **41**, 557–567 (1990).
Landgren *et al*. *Contraception* **33**, 473–485 (1986).

Example 4 – Population Simulation





Kook, K *et al*. *Contraception* **66**, 73–76 (2002).
He, C. *et al. Contraception* **41**, 557–567 (1990).
Landgren *et al*. *Contraception* **33**, 473–485 (1986).

Example 4 – Population Simulation

Generate median, 5th and 95th percentiles:

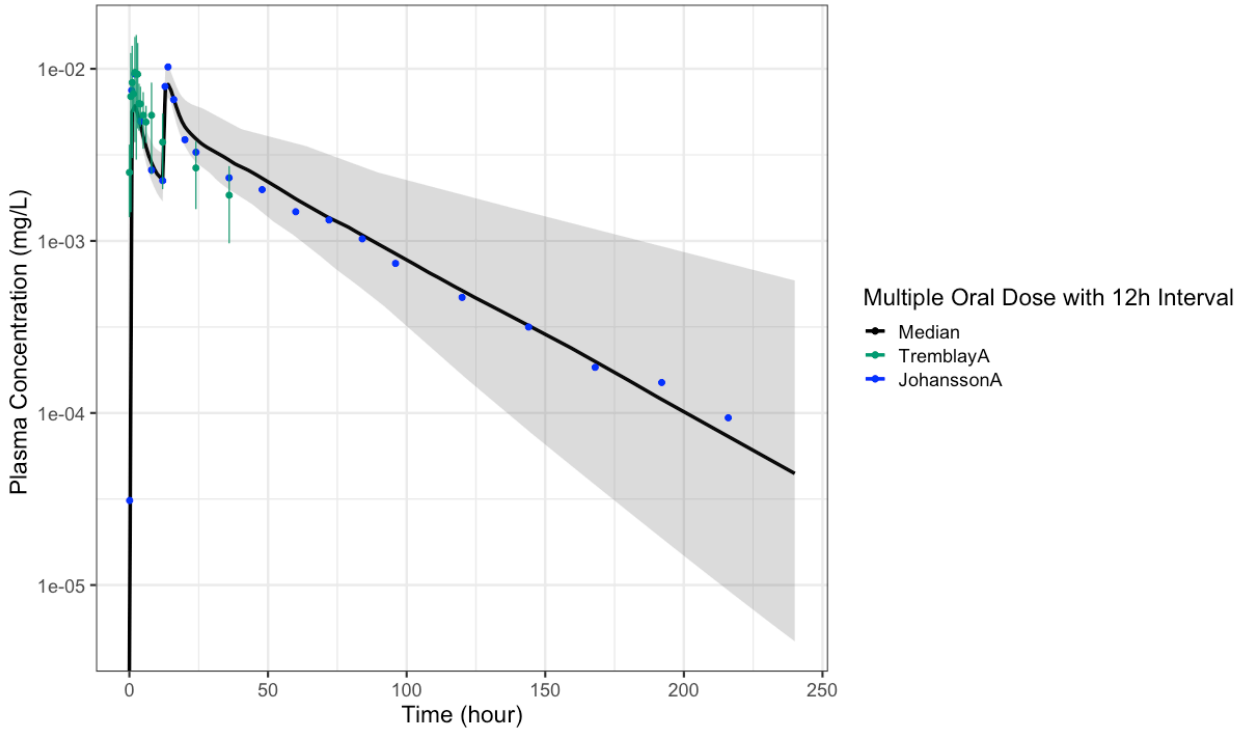
Option 1:

Modify the plot code to make the shiny app generate

Option 2:

1) Download the output
2) Use plotting package to generate the plot

```
p1<-ggplot()+
  theme_bw(base_size=17)+
  geom_line(dat2, linewidth = 1.25, mapping = aes(time, median, color = "Median"))+
  geom_ribbon(dat2, mapping =aes(x= time, ymin = p5, ymax = p95), alpha = 0.2, fill = "grey25")+
  labs(x="Time (hour)")+
  labs(y = "Plasma Concentration (mg/L) ")+
  geom_point(Johansson_2002_A, size = 1.75, mapping = aes(`Dig Time (h)`, `Conc (ng/mL)`*1e-3,color =
  geom_point(Tremblay_2001_A, size = 1.75, mapping = aes(`Time (h)`, `Mean (ng/mL)`*1e-3,color = "Trem
  geom_errorbar(Tremblay_2001_A,mapping = aes(x=`Time (h)`, ymin =lower*1e-3, ymax=upper*1e-3, color="
  #geom_errorbar(Johansson_2002_B, mapping = aes(x=`Nom Time (h)`, ymin =lower*1e-6, ymax=upper*1e-6,
  scale_color_manual(name ='Multiple Oral Dose with 12h Interval',
                     breaks = c('Median','TremblayA','JohanssonA'),
                     values = c('TremblayA' = '#009E73','Median' = 'black','JohanssonA' = 'blue'))+
  scale_y_log10()
#scale_y_log10()
```

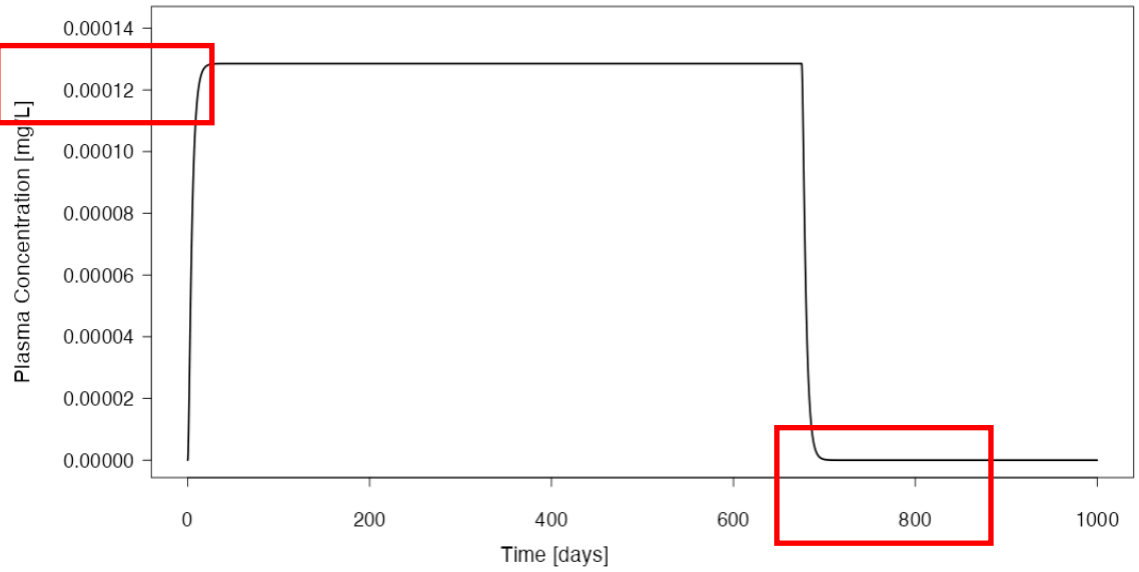


Example 5 – Comparison Between Formulations

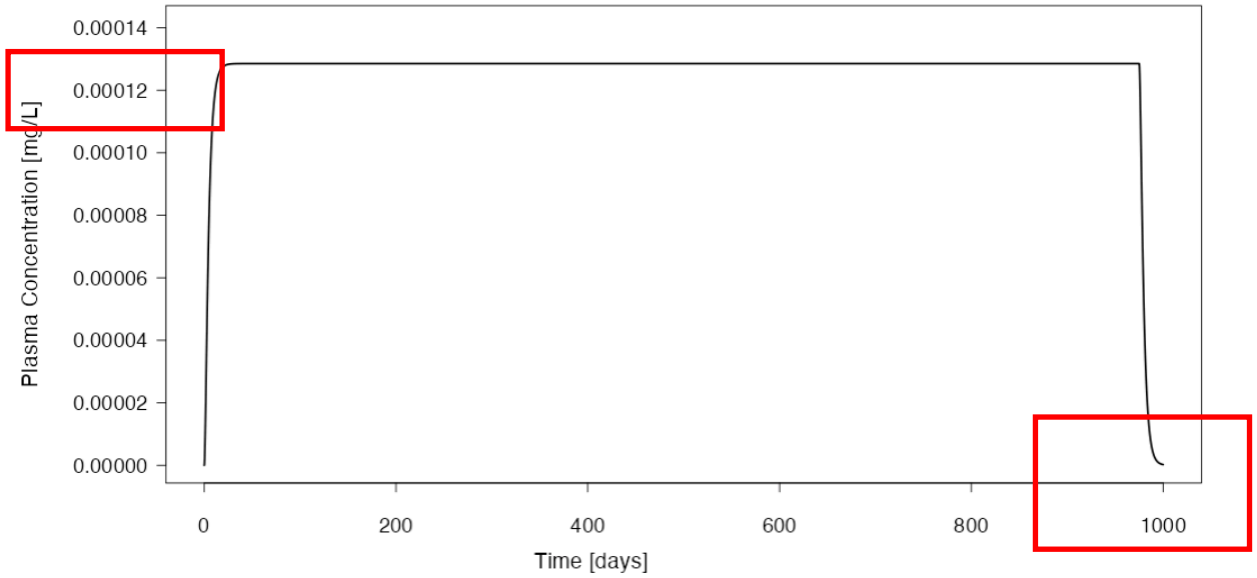
- Different drug load
- Different input rate

Example 5 – Comparison Between Formulations – Different Drug Load

13.5 mg LNG
Zero-order input (20 μg/day)

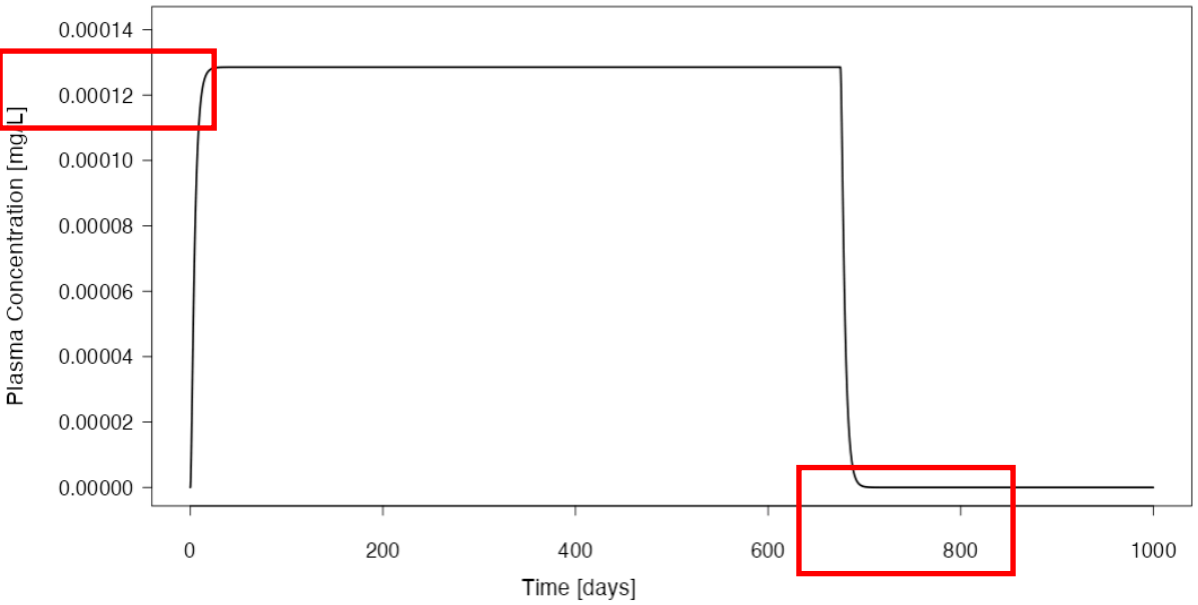


19.5 mg LNG
Zero-order input (20 μg/day)

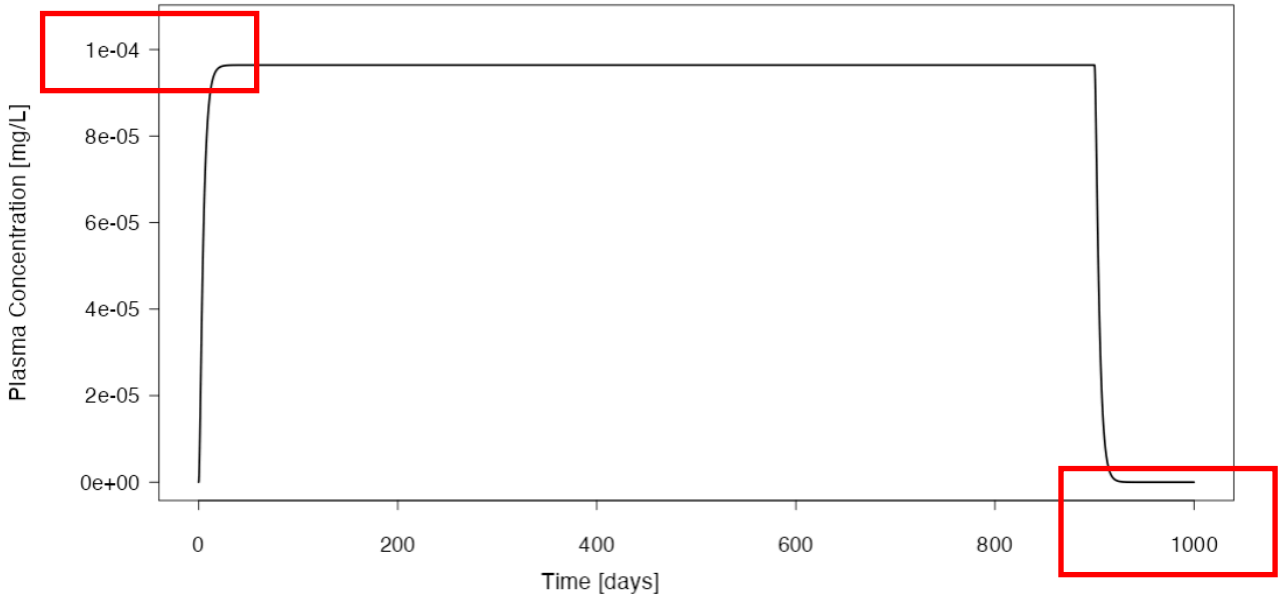


Example 5 – Comparison Between Formulations – Different Input Rate

13.5 mg LNG
Zero-order input (20 μg/day)



13.5 mg LNG
Zero-order input (15 μg/day)



Acknowledgments

FDA/CDER/OGD/ORS IO

- Rob Lionberger
- Lei Zhang

FDA/CDER/OGD/ORS/DQMM

- Mark Donnelly
- Liang Zhao
- Eleftheria Tsakalozou
- Meng Hu
- Fenggong Wang
- Kairui Feng
- Miyoung Yoon
- Lanyan (Lucy) Fang
- Andrew Babiskin

FDA/CDER/OGD/ORS/DTPII

- Minori Kinjo

"Physiologically-based model of the female reproductive tract: vaginal and intrauterine delivery components" (HHSF223201810188C)

University at Buffalo

- Robert Bies (PI)
- Xinnong Li
- Tom Straubinger

Magee Women's Research Institute

- Lisa Rohan (co-PI)
- Beatrice Chen
- Sharon Achilles (currently Gates Foundation)
- Doaa Alantary
- Zhongfang Zhang
- Guru Valicheria
- Lin Wang

Certara

- Mark Sale (PI)
- James Craig
- Keith Nieforth

National Institute of Allergy and Infectious Diseases, National Institutes of Health, IPCP Grant U19-AI120249

Bayer US, Pharmaceuticals Division

"Development of a model selection method for population pharmacokinetics analysis by deep-learning based reinforcement learning" (1U01FD007355)