PBPK Modeling Approaches to the Female Reproductive Tract

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FGS Discussion

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Bies Lab – Program Overview

- University at Buffalo, Department of Pharmaceutical Sciences

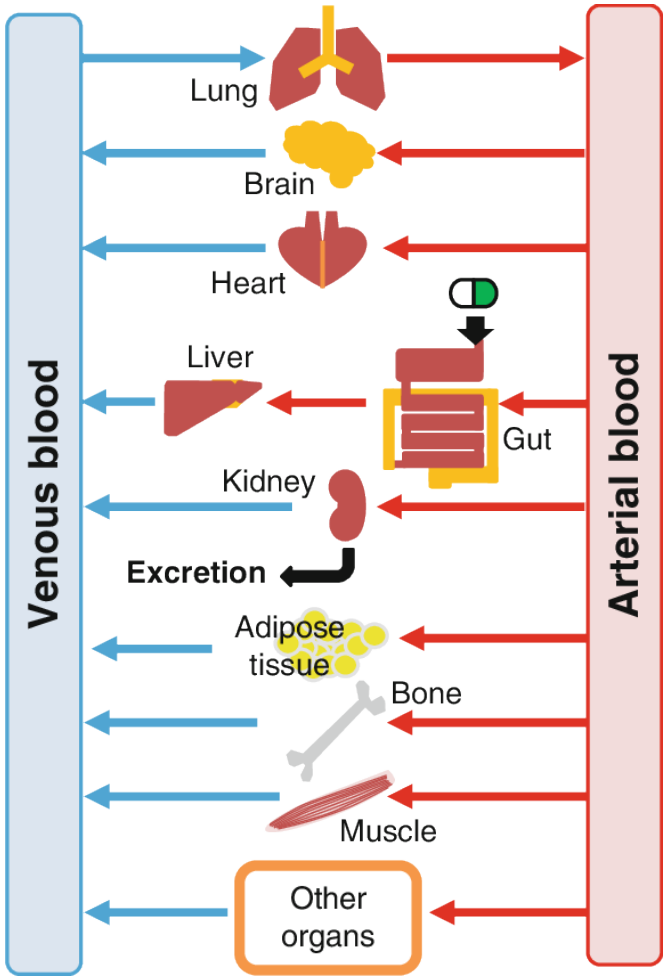
- Projects:
  - complex formulations for HIV prevention (FAME, LATCH, MATRIX) assessing vaginal and cervical administration (collaborations with MWRI Pittsburgh)
  - PBPK model development for female reproductive tract (FDA) collaborations with MWRI Pittsburgh
  - Maternal Pediatric Precision Therapeutics (MPRINT) P30 project, co-lead of Pharmacometrics and Clinical Trial Design Core
  - Machine learning strategies for model selection in population pharmacokinetics (FDA)
  - TAF/TDF population PK model based meta analysis (collaboration with Medstar/Hopkins)
- Local Personnel:
  - 3 Ph.D. candidates
  - 1 MS candidate

Physiologically-Based Pharmacokinetic (PBPK) Modeling

Provides a platform that reflects the constraints of physiological and anatomical characteristics. It can be used to test new compounds on the basis of their specific physiochemical properties

Physiologically-Based Pharmacokinetic (PBPK) Models

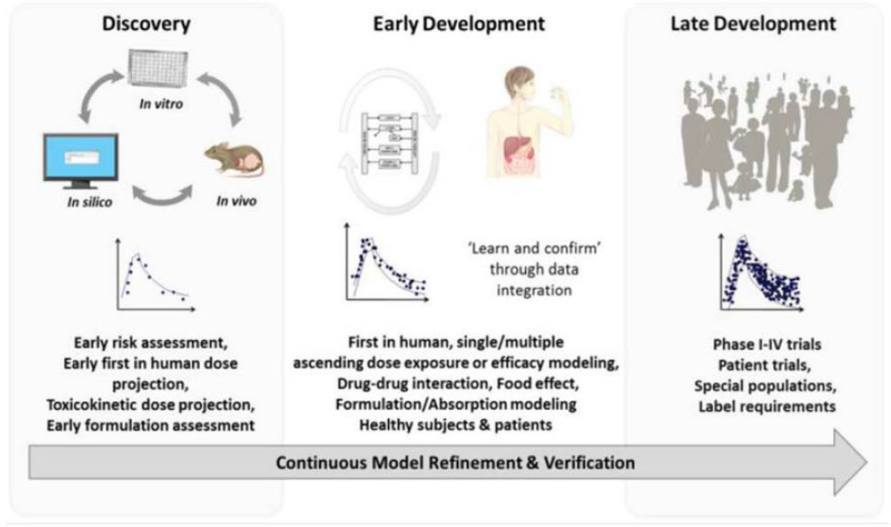
- Mechanistic model of drug behavior
- Incorporates information on:
  - Anatomy
  - Physiology
  - Physicochemical properties
  - In vitro performance
  - In vivo performance
- Allows for a priori predictions of drug concentration over time in tissues and systemic circulation



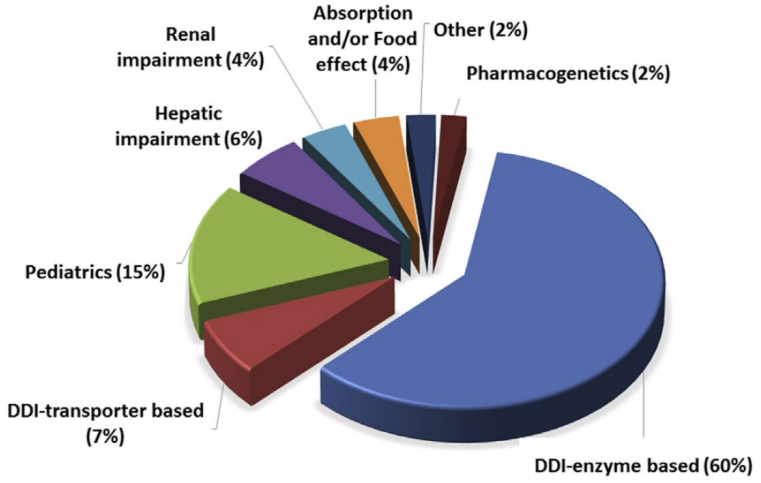
Shin, Hyun Kil & Kang, Young-Mook & No, Kyoung Tai. (2016). Predicting ADME Properties of Chemicals. 10.1007/978-94-007-6169-8_59-1.

PBPK Modeling in New Drug Development

- Drug Development[1,2]
  - Candidate selection
  - Formulation development
  - Clinical study design
  - Dose selection
- Regulatory Decisions[3,4]
  - Potential drug-drug interactions
  - PK in special patient populations
  - Impact of disease states



Jones et al. (2015)

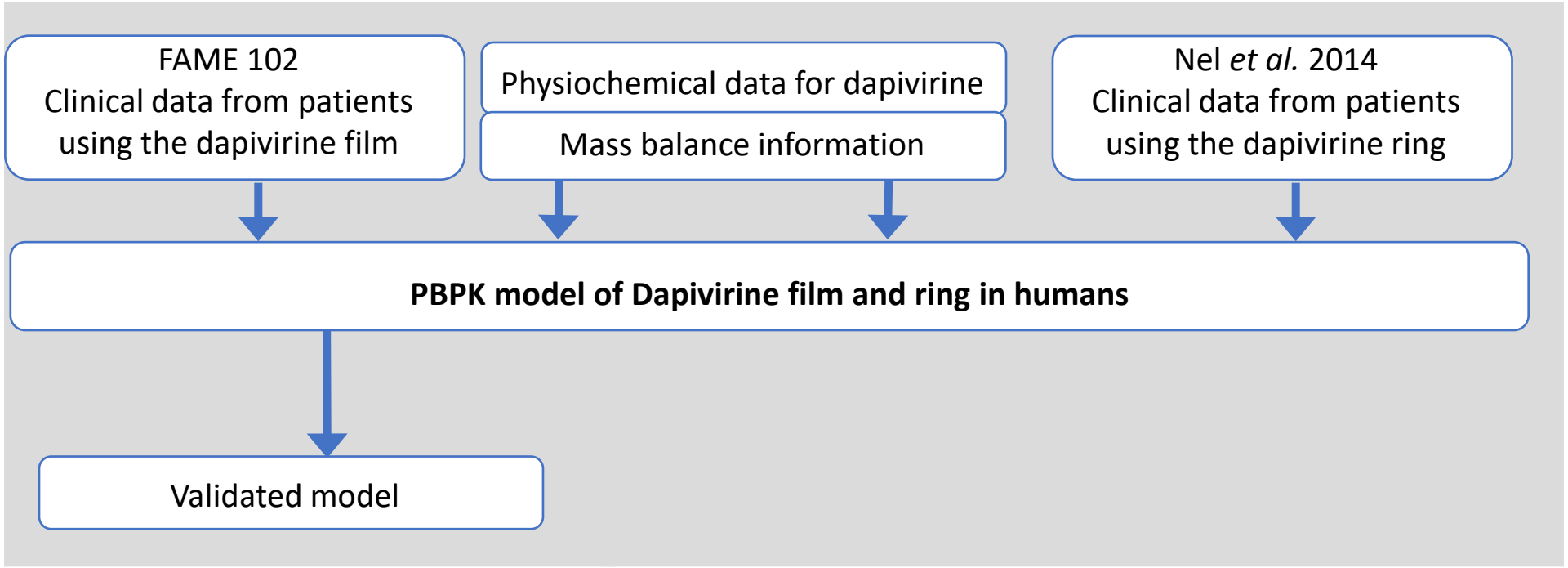


Grimstein et al. (2019)

1. Jones HM, Chen Y, Gibson C, et al. Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. *Clin Pharmacol Ther*. 2015;97(3):247-262. doi:10.1002/cpt.37
2. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther.* 2011;89(2): 259-267.
3. Grimstein M, Yang Y, Zhang X, et al. Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *J Pharm Sci.* 2019;108(1): 21-25.
4. Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making, November 18, 2019. *U.S. Food & Drug Administration*. January, 15, 2020. Available at: https://www.fda.gov/drugs/news-events-human-drugs/development-best-practices-physiologically-based-pharmacokinetic-modeling-support-clinical. Accessed September 21, 2020.

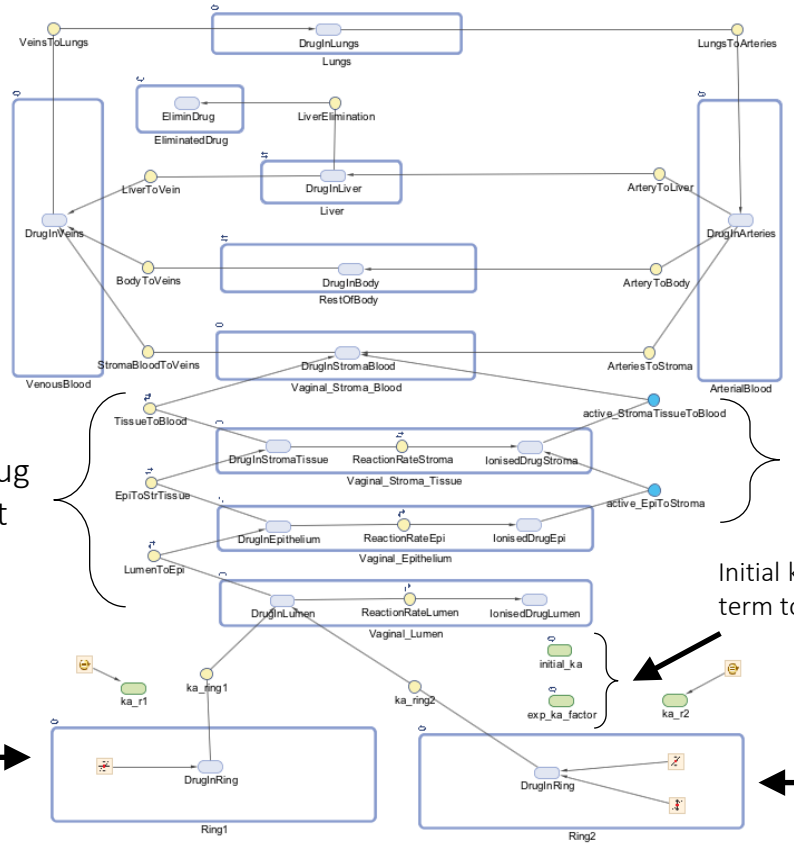
PBPK Model for Dapivirine Cervical Ring

PBPK Model Development



Kay K et al. Br J Clin Pharmacol. 2018 Sep;84(9):1950-1969.

PBPK Model Structure



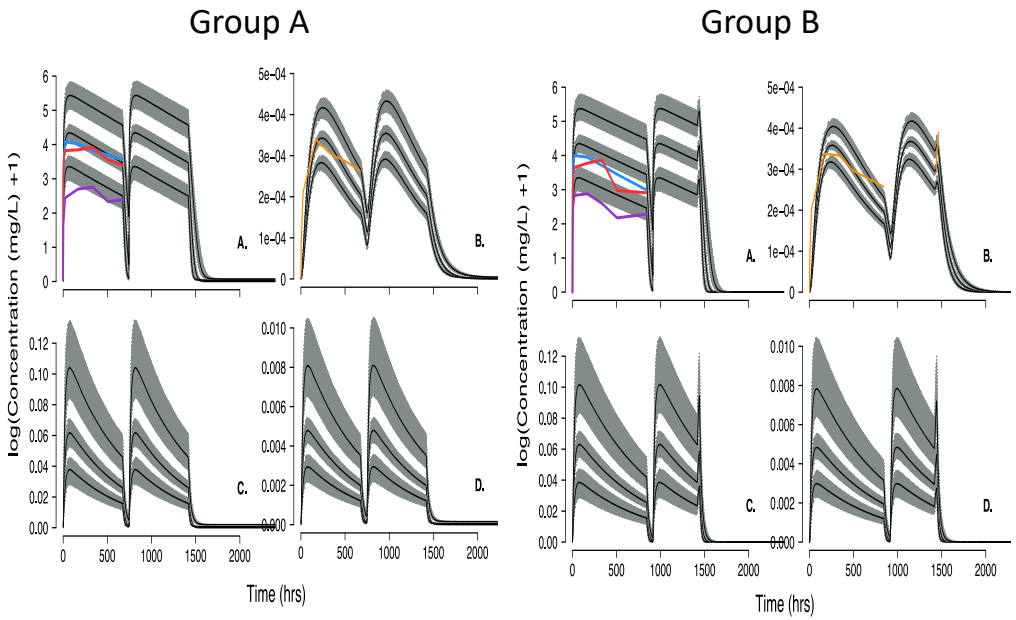
Passive drug transport

Active drug movement

Initial ka and an exponential term to reduce ka over time

Ring 1

Ring 2



Panel A: Vaginal fluid
Panel B: Plasma
Panel C: Epithelium tissue
Panel D: Stromal tissue

- Simulated
- Patient – Ring
- Patient – Cervix
- Patient – Introitus
- Patient – Plasma

Kay K et al. Br J Clin Pharmacol. 2018 Sep;84(9):1950-1969.

GDUFA Research Contract

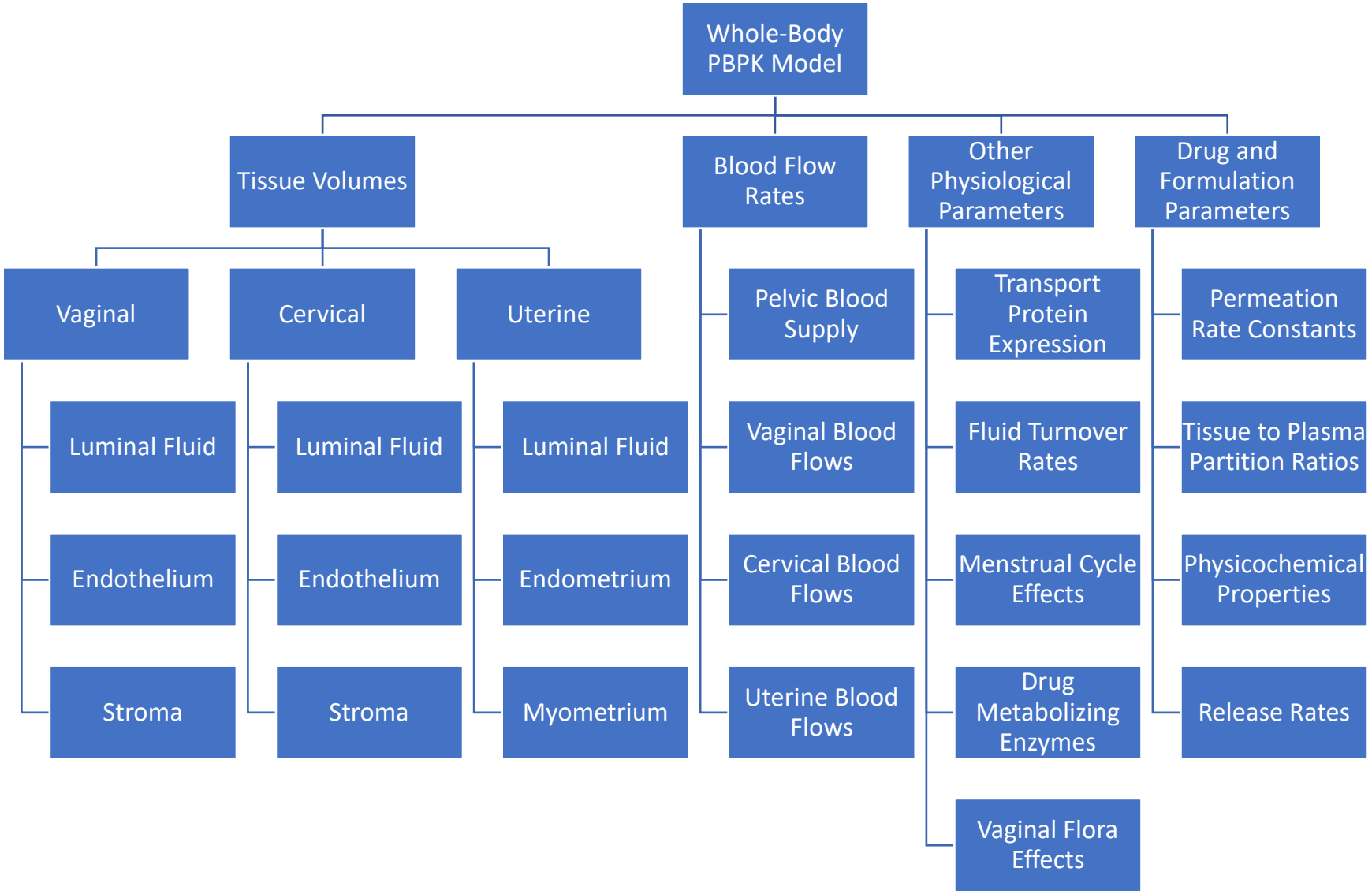
- In 2018, OGD funded a research contract titled: "*Physiologically-based model of the female reproductive tract: vaginal and intrauterine delivery components*" (HHSF223201810188C) with University at Buffalo[1]

- 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

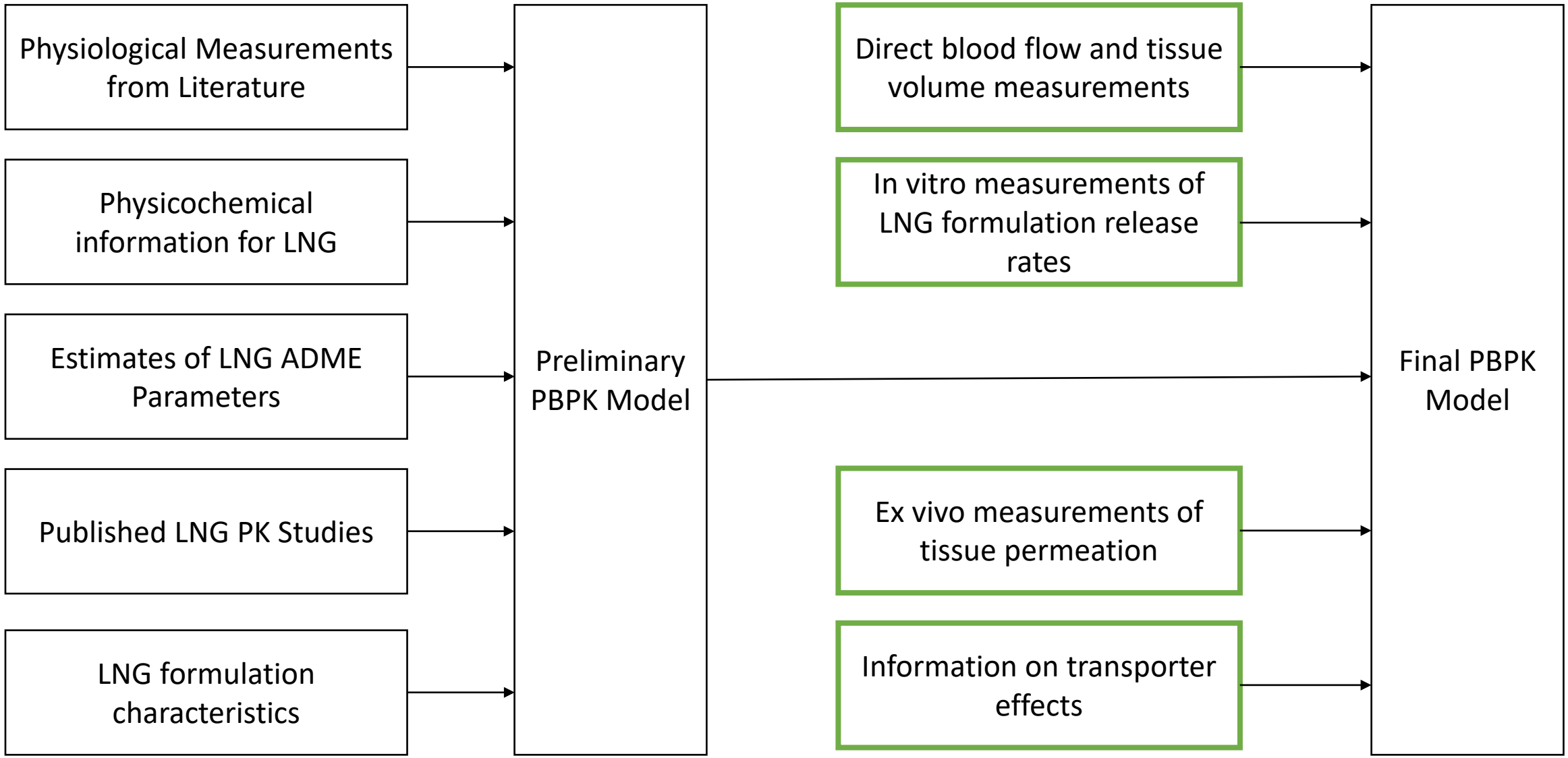
- Supports one of the key scientific initiatives to accelerate access to generic drug products: "***Improve PBPK models of drug absorption via complex routes of delivery"***

1. FY 2018 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.

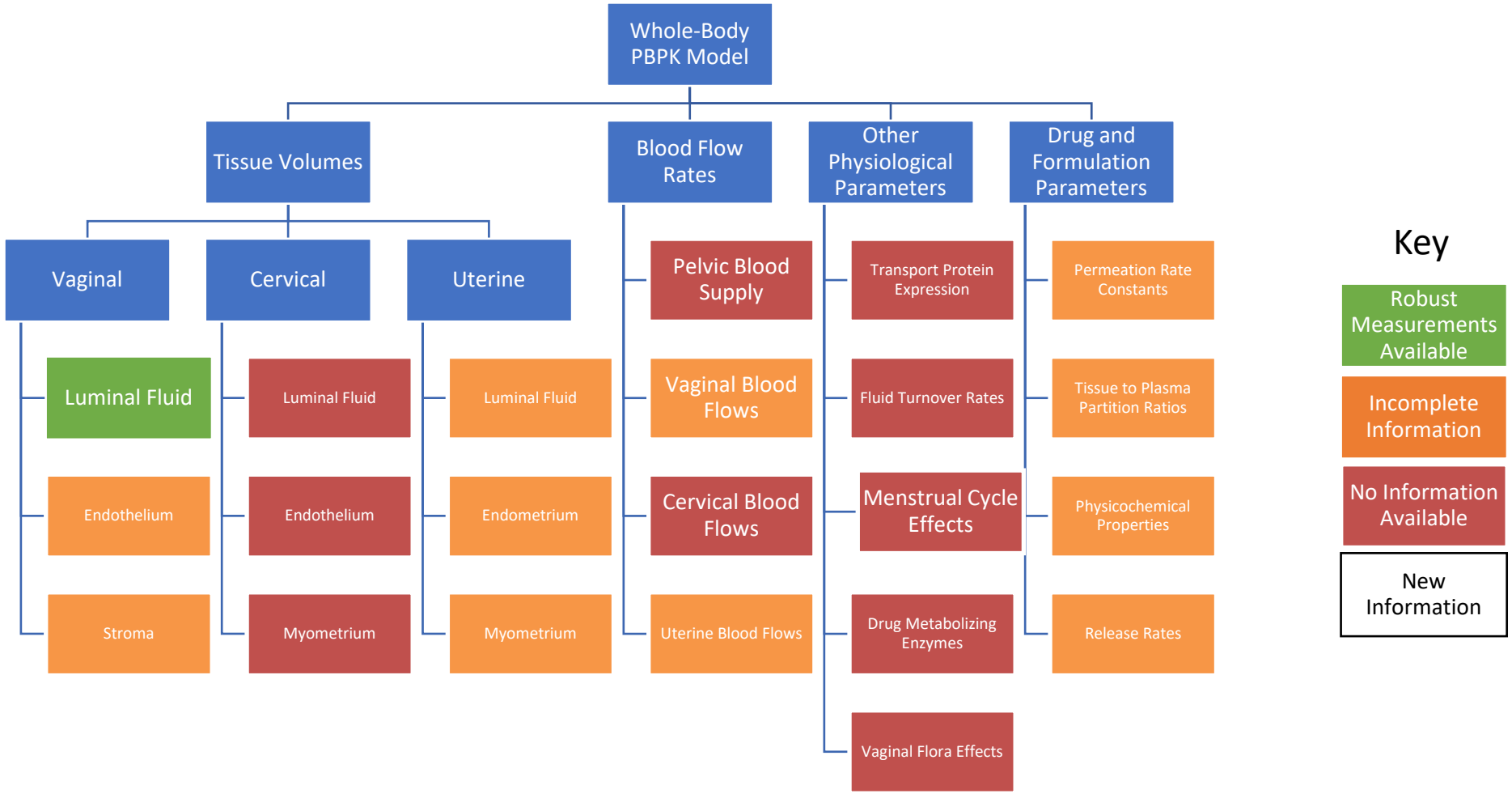
Key Data to Inform Model



Model Development Process

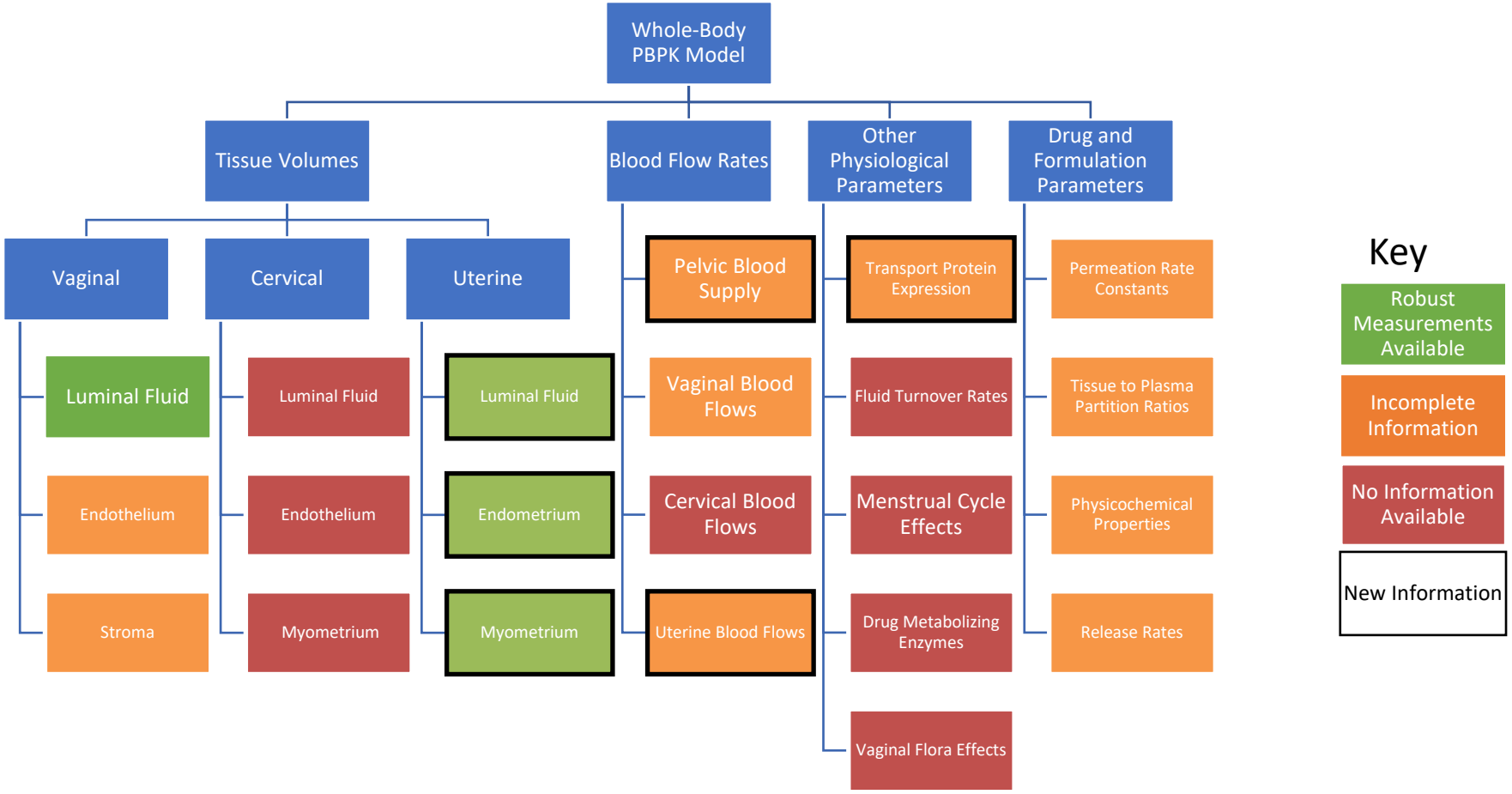


Data from Published Models



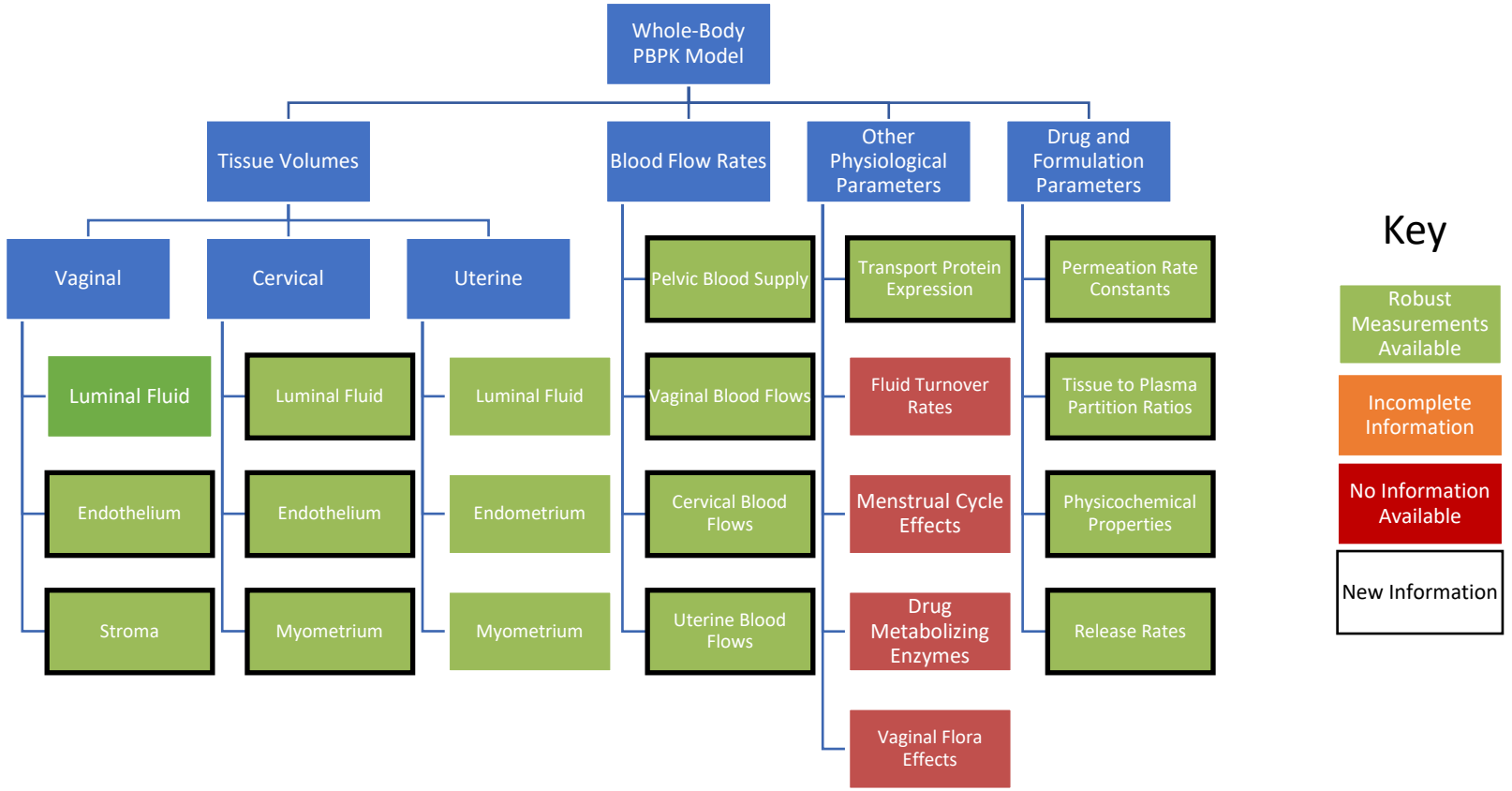
Literature Survey (Complete)

- Completed systematic literature search and summarized data
  - Pubmed, ScienceDirect, Google Scholar, medical texts, etc.

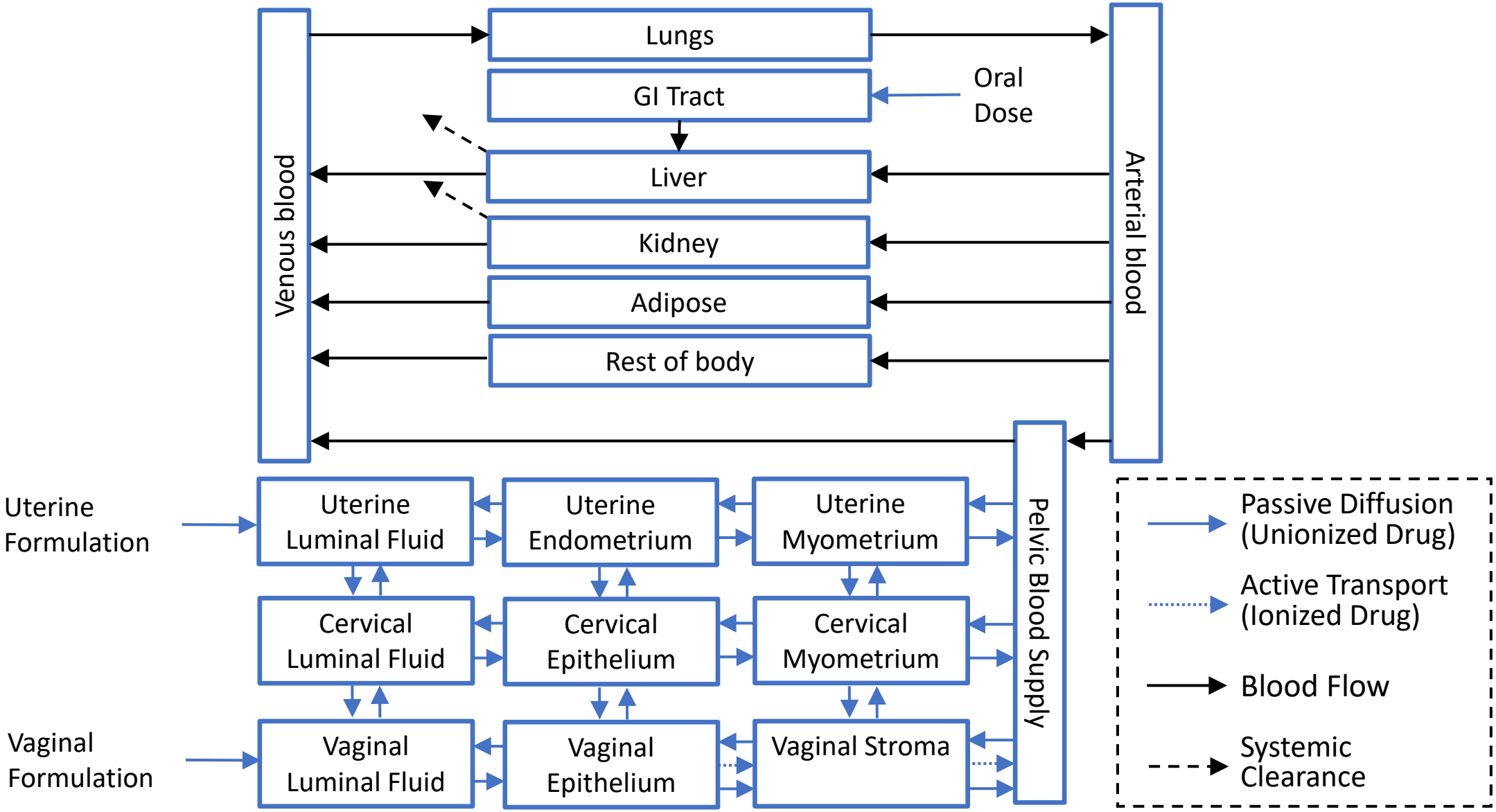


In Vitro/In Vivo/Ex Vivo Studies (In-progress)

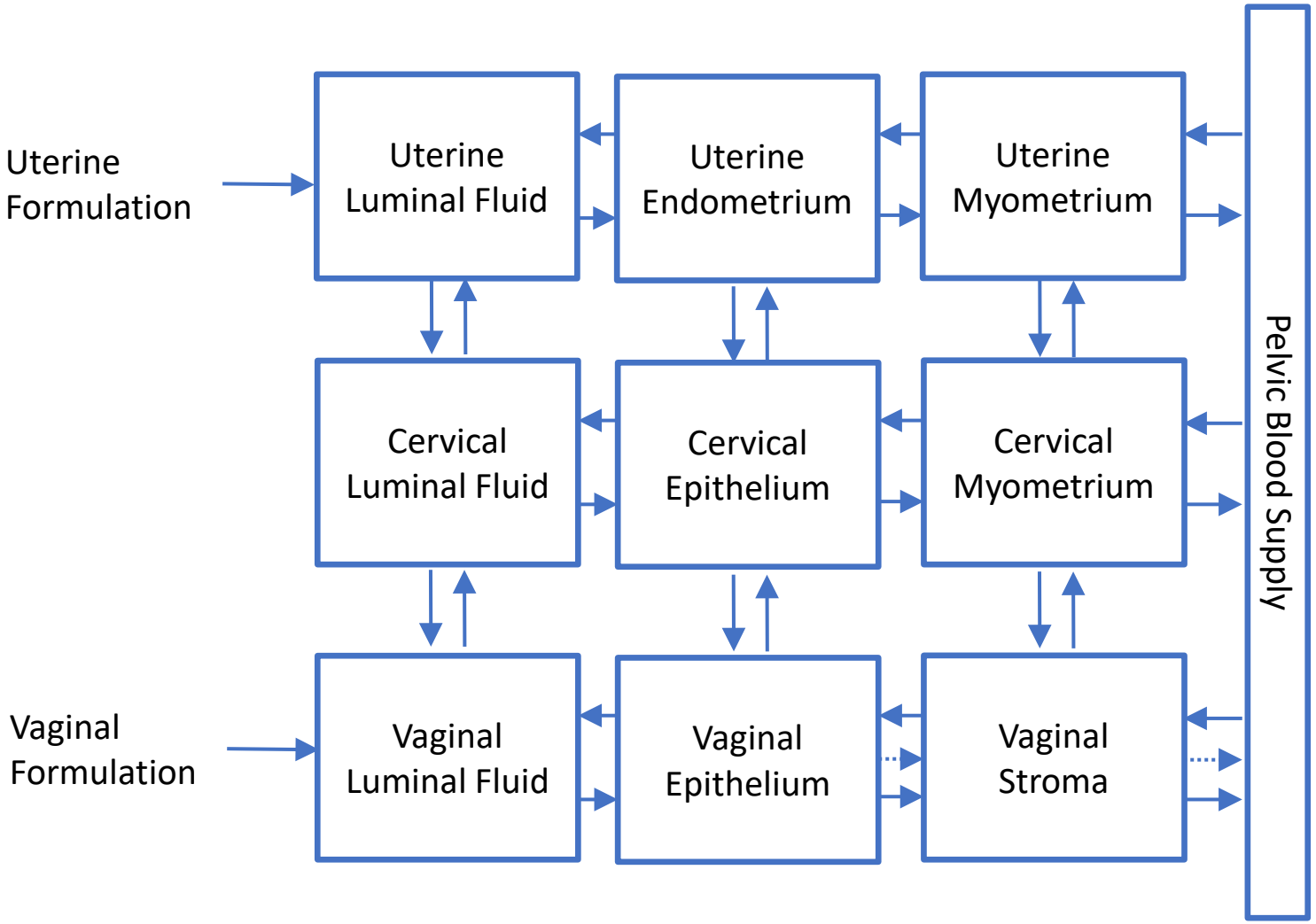
- In vitro studies
  - In vitro release rates in biological fluid simulants
  - Solubility in relevant biological fluids
  - Permeation rates in tissue cultures
- In vivo/ex vivo studies
  - Ultrasound measurements of blood flow rates and tissue volumes
  - Tissue bank samples used to measure transporter expression, permeability, and drug partition coefficients



Current PBPK Model Structure



Female Reproductive Tract



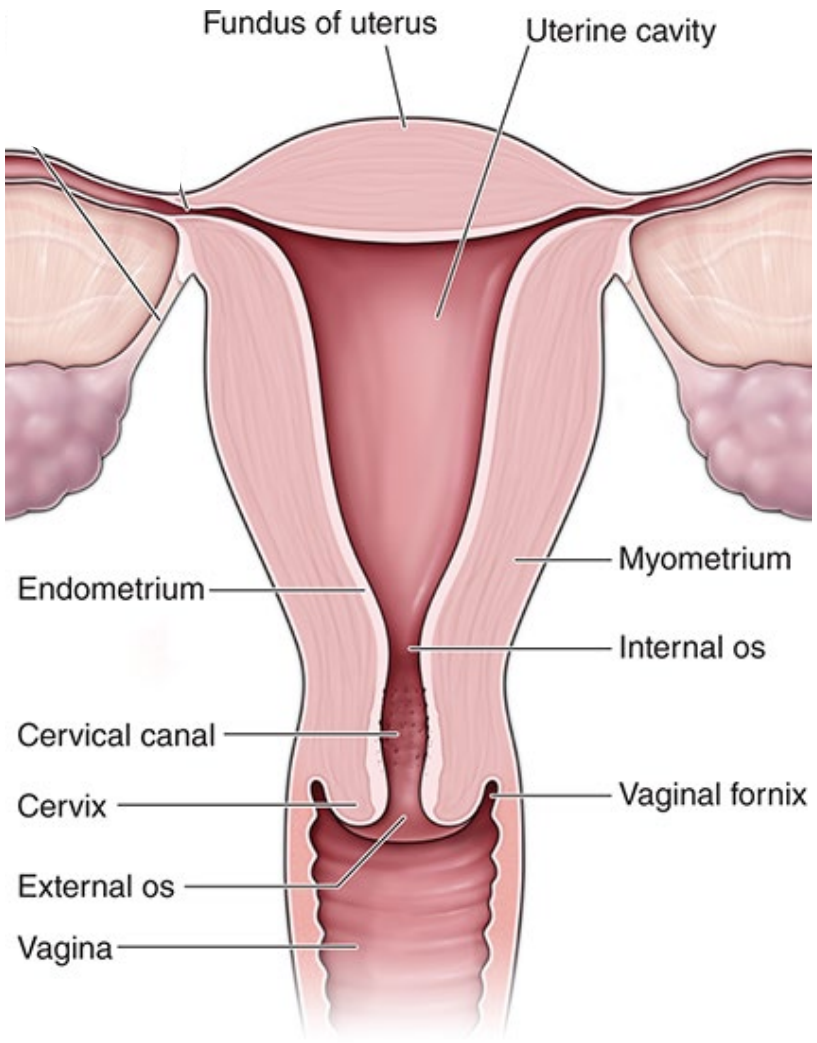
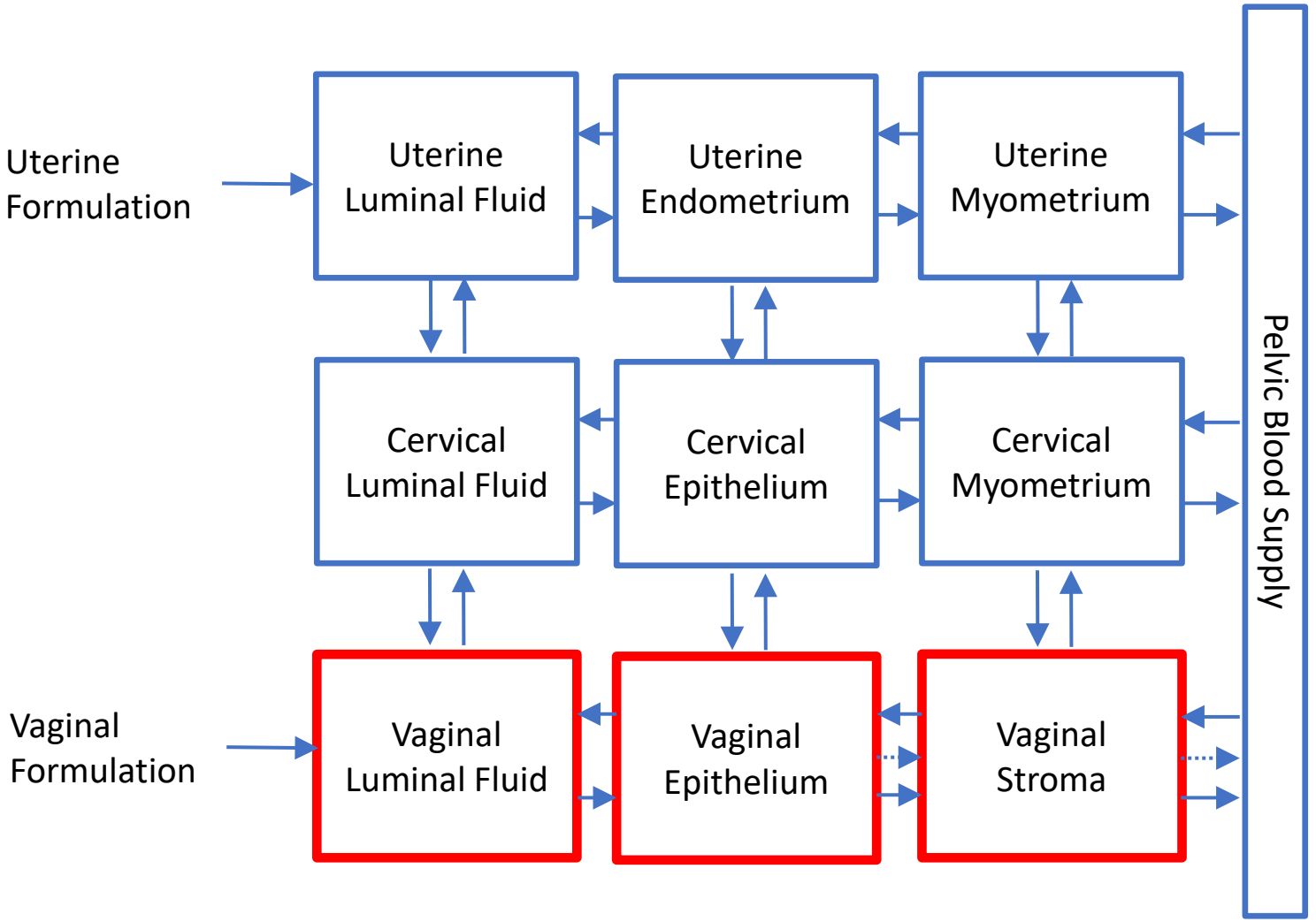
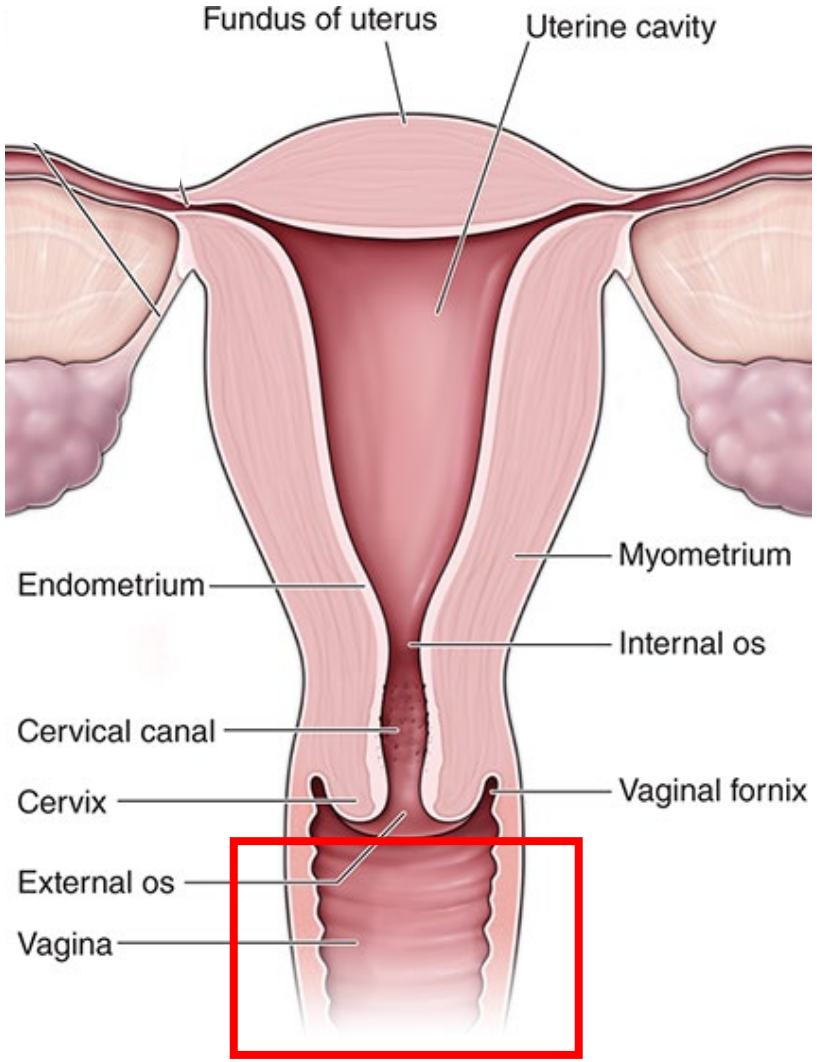


Image Source: CHAPTER 14 Female Reproductive System, Morton DA, Foreman K, Albertine KH. *The Big Picture: Gross Anatomy, 2e;* 2019.
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2478&sectionid=202020761 Accessed: May 14, 2022

Female Reproductive Tract: Vaginal Compartment





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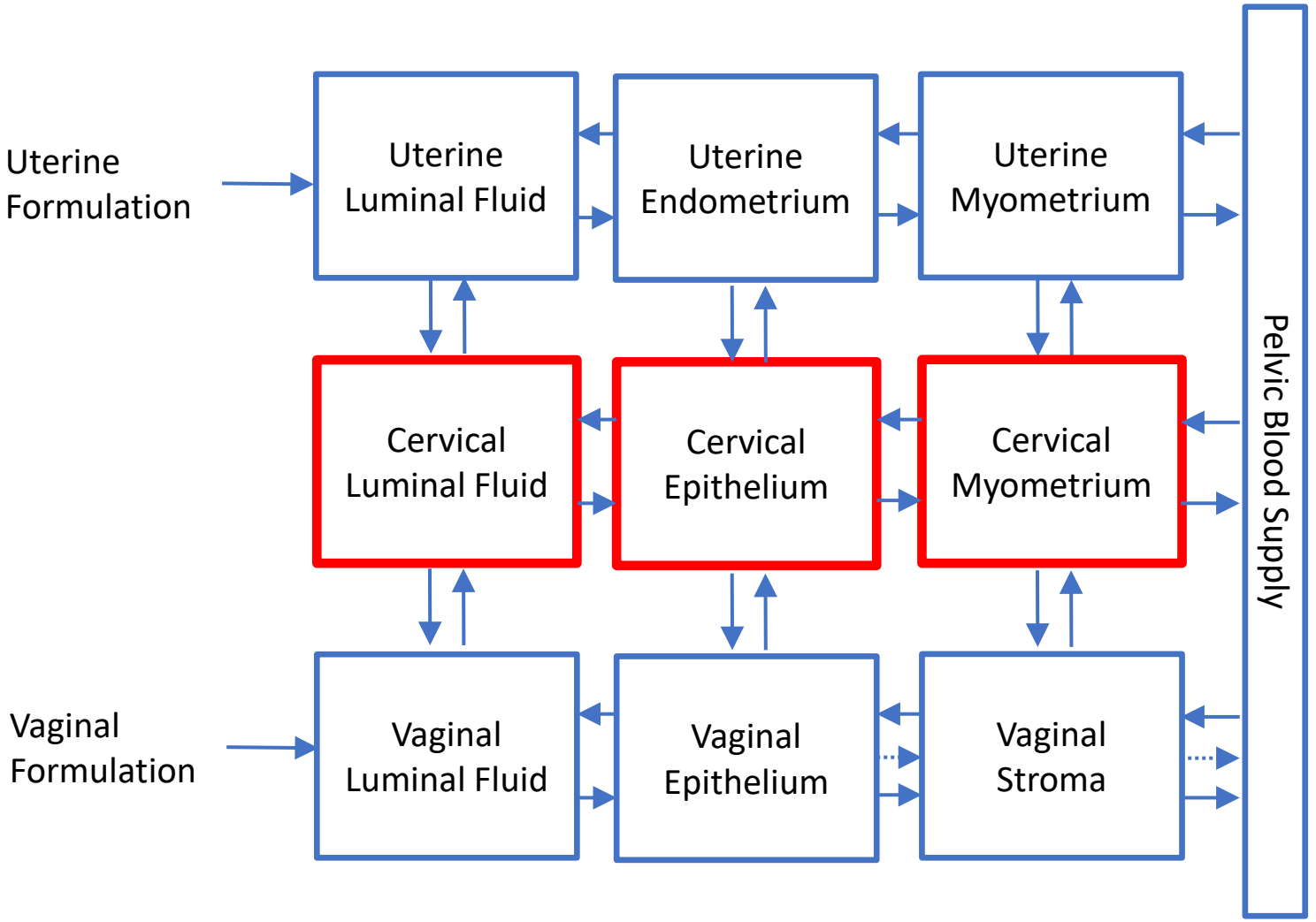
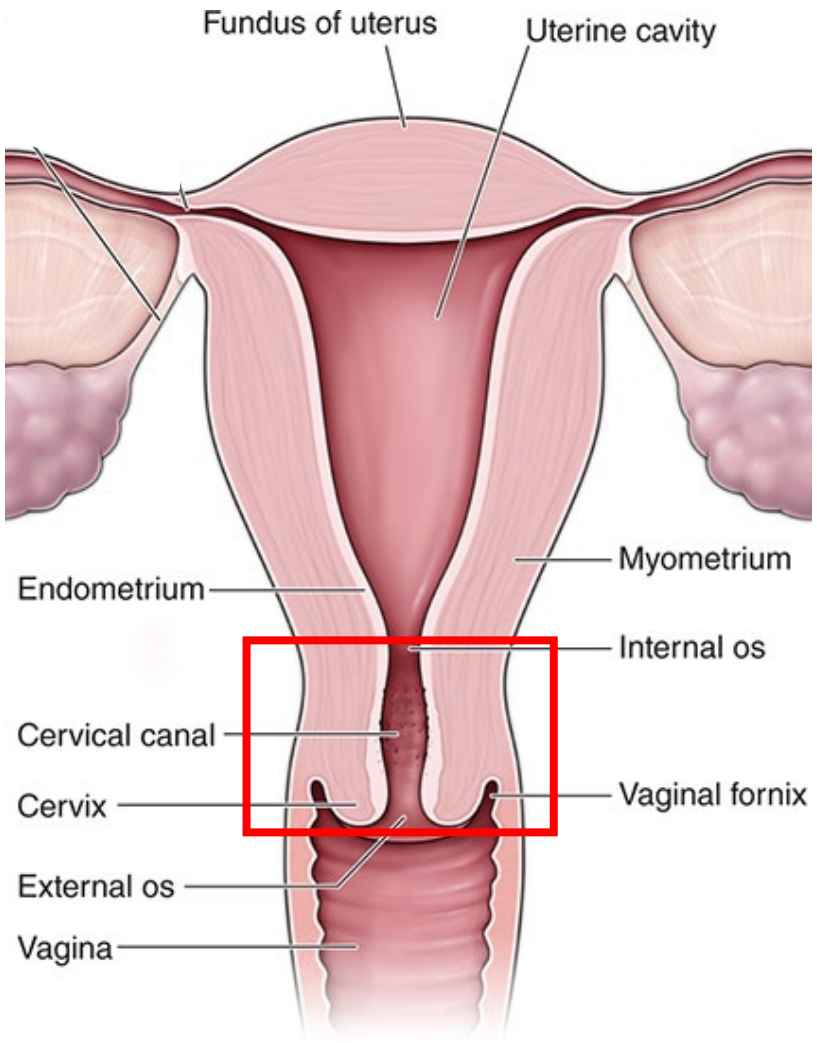
Female Reproductive Tract: Cervical Compartment





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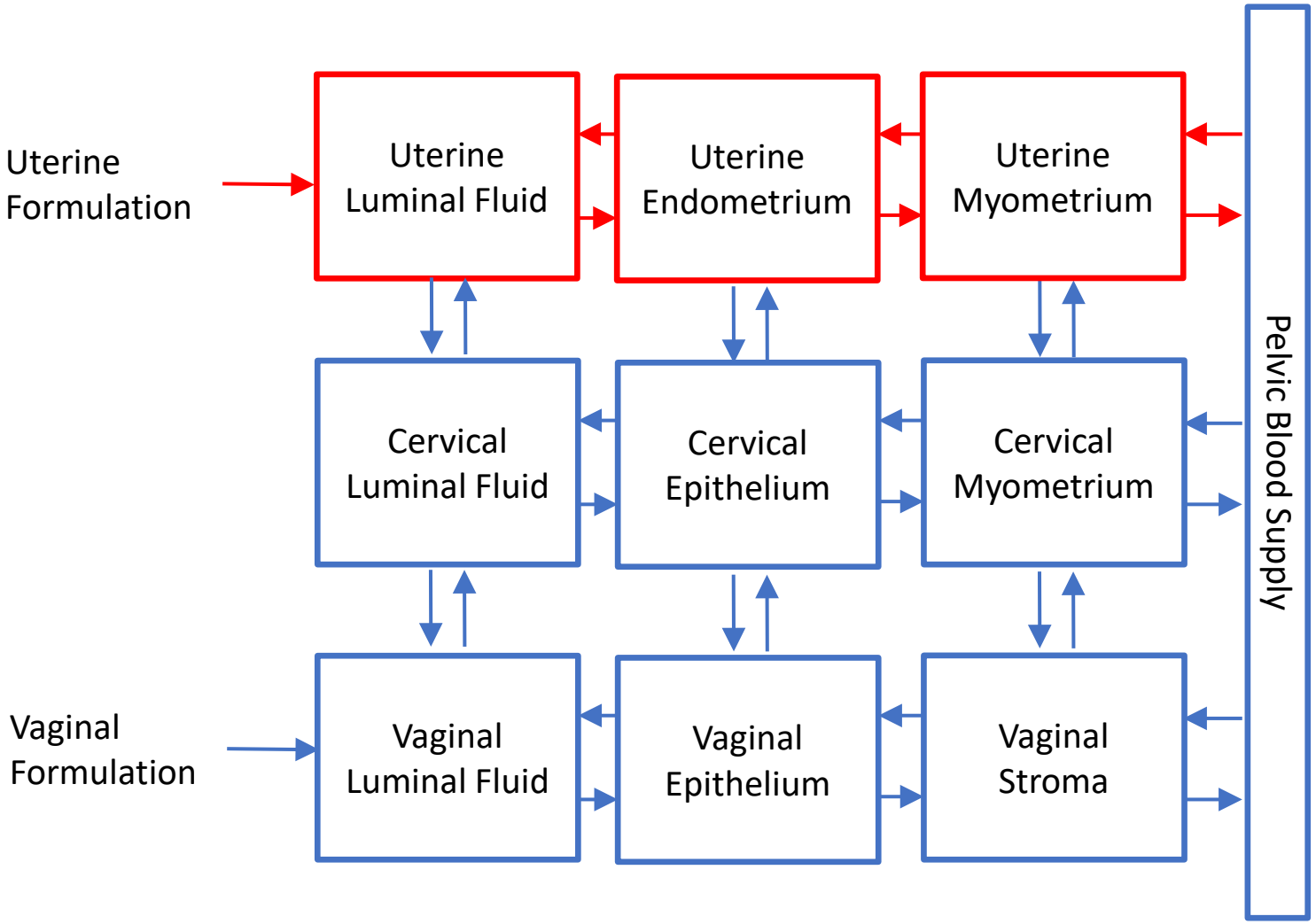
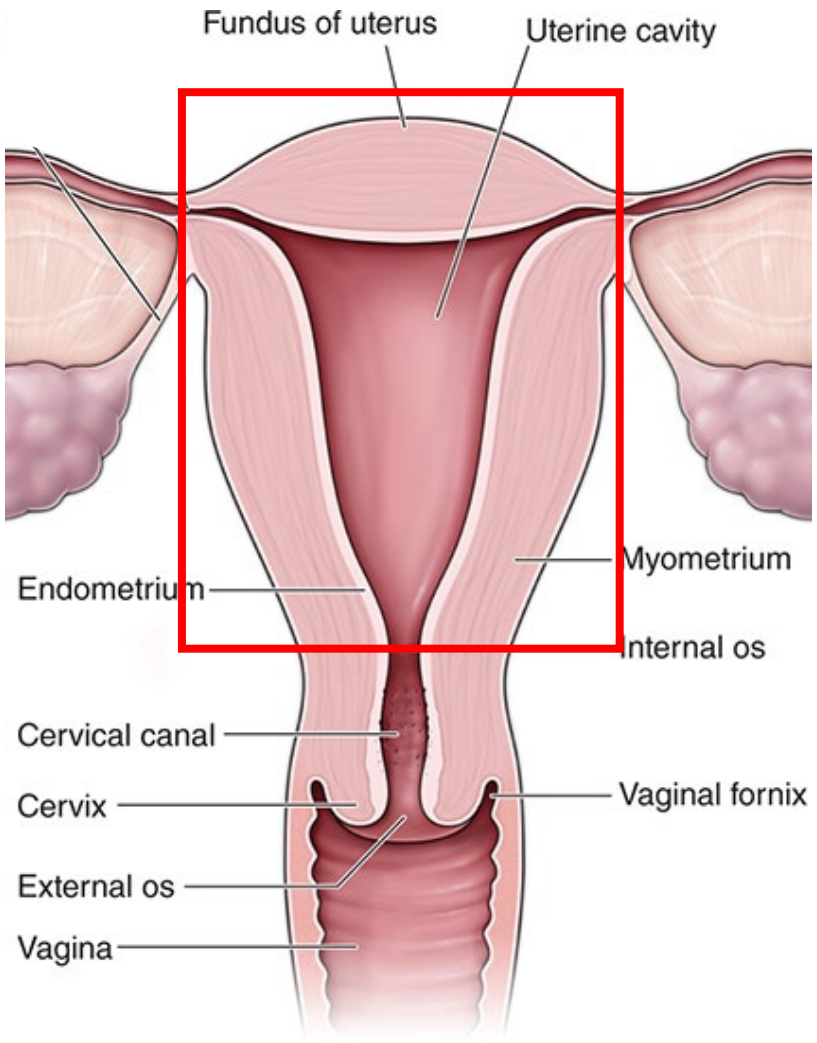
Female Reproductive Tract: Uterine Compartment





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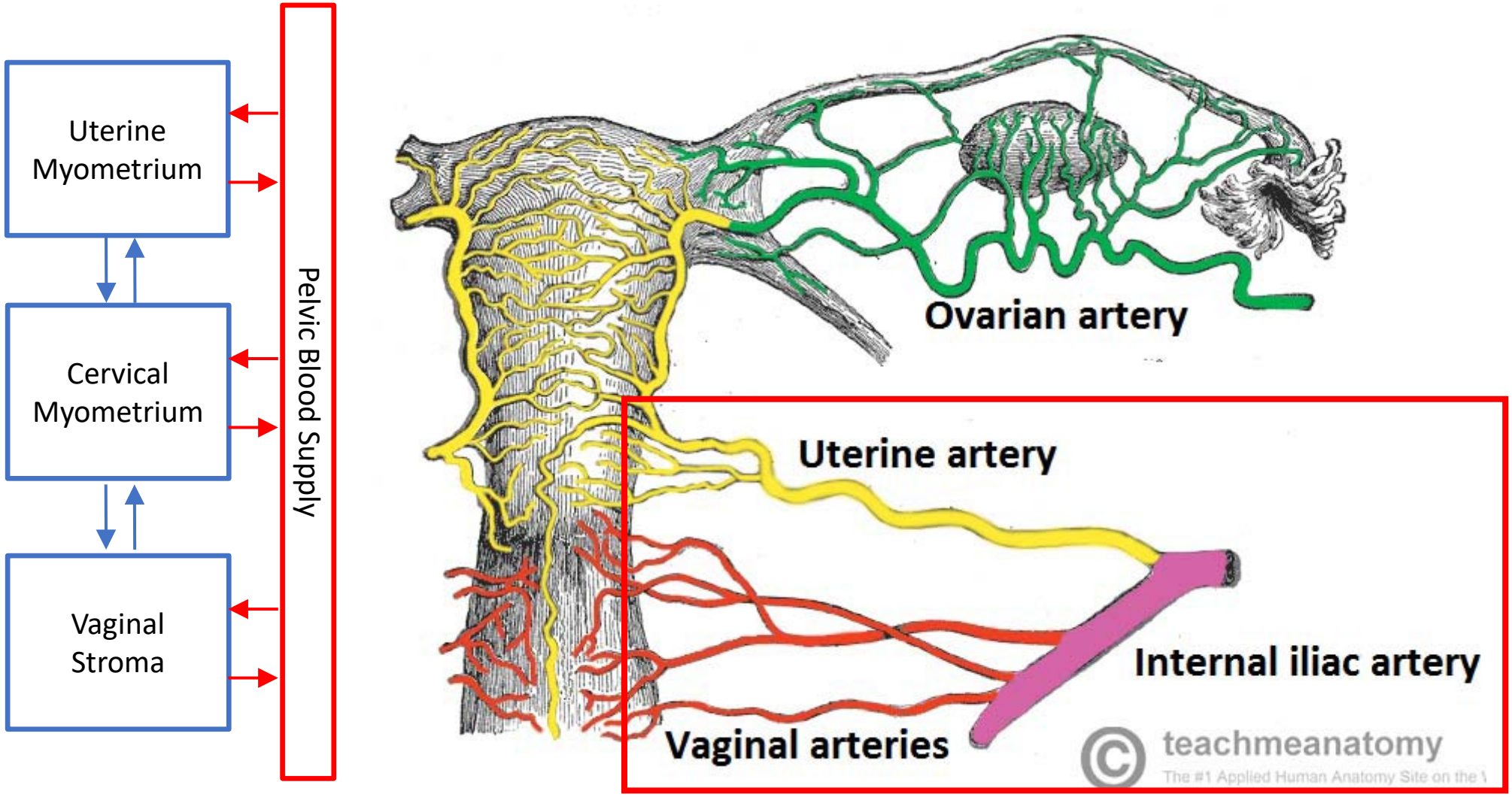
Common Blood Supply



PBPK Model Application to FGS

- Facilitates virtual administration of compounds through various routes of administration (IV, IM, vaginal, uterine)
- Provides predictions of concentration of compound of interest in different target tissues (eg. vaginal/cervical/uterine tissue/fluids)
- Can be linked with pharmacodynamic models to assess effect on biomarkers/receptors/cells of interest

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- Doaa Alantary
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- Sravan Patel

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