Innovative Data Analytics To Inform Pharmacokinetics and Dosing in Pregnancy

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Medication use in Pregnancy – Current Status

Increasing medication use

- In the US, **9 out of 10** women take **medication** during **pregnancy**
- **80% of pregnant women take ≥ 1** medication during first trimester

Off-label use

- **90% of medications** approved do not have labeling for pregnant women
- After **PLLR implementation in 2015**, only **10%** have data for **pregnancy** from **human studies**

Lack of pregnancy drug trials (PDT)

- **Only 0.32%** of the active registered trials are PDT, in a 2014 global survey
- Among active PDTs, **only 4.4%** had **pharmacokinetic** evaluations
- **Only 7%** of the active PDTs were funded by **pharmaceutical industry**

PLLR: Pregnancy & Lactation Labeling Rule

https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html

Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *American Journal of Obstetrics and Gynecology*. 2014;211(6):690.e1-690.e11.;Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2017;124(1):132-140.;Byrne JJ, Saucedo AM, Spong CY. Evaluation of Drug Labels Following the 2015 Pregnancy and Lactation Labeling Rule. *JAMA Network Open*. 2020;3(8):e2015094.

Ren Z, Bremer AA, Pawlyk AC. Drug development research in pregnant and lactating women. *American Journal of Obstetrics and Gynecology*. 2021;225(1):33-42. doi:10.1016/j.ajog.2021.04.227

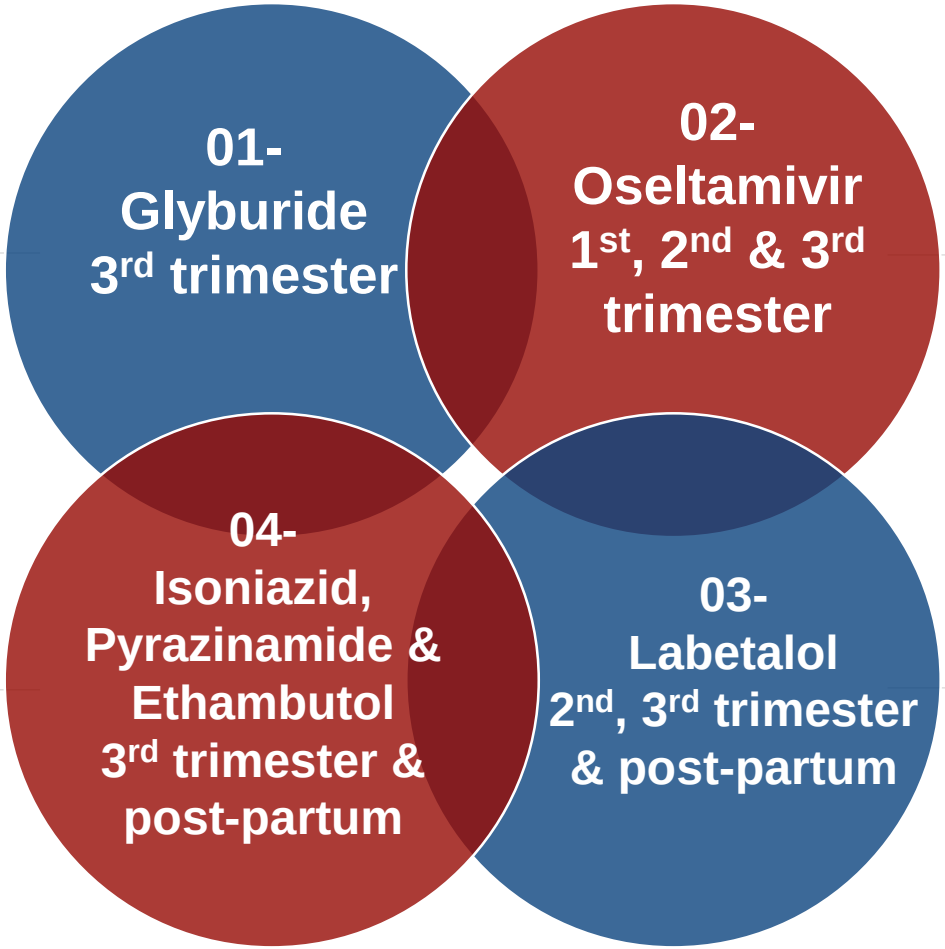
Dedicated PK trials in pregnant women by NICHD – OPRCs and academic researchers has informed clinical practice

53% lower AUC in pregnant (N= 40) vs non-pregnant women (N = 40)

- **Higher dose may be needed in pregnant women**
- Umbilical cord levels ~ 70% of maternal plasma

No clinically meaningful change in AUC in pregnant vs post-partum (N = 29)

- **No dose adjustments needed during pregnancy**
- 2 years for study recruitment



Typical study duration: 2 to 5 years

30% lower AUC in pregnant (N= 40) vs non-pregnant women (N = 40)

- **No dosing adjustment needed in pregnant women**
- 5 years for study enrollment

1.4 – 1.6-fold higher apparent clearance in pregnant (N= 57) vs post-partum women

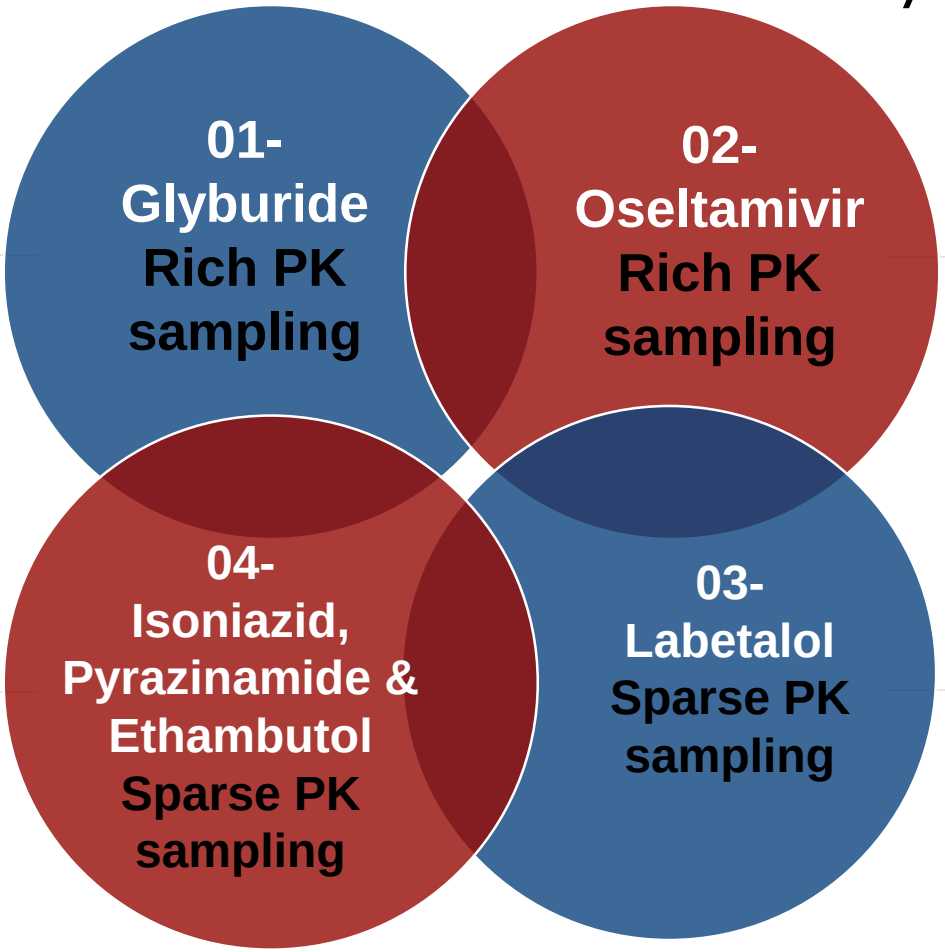
- **Dose adjustments may be needed during pregnancy**

OPRC – Obstetric-Fetal Pharmacology Research Center

Pillai VC, Han K, Beigi RH, et al. Population pharmacokinetics of oseltamivir in non-pregnant and pregnant women. *British Journal of Clinical Pharmacology*. 2015;80(5):1042-1050; Hebert MF, Ma X, Naraharisetti SB, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther*. 2009;85(6):607-614; Abdelwahab MT, Leisegang R, Dooley KE, et al. Population Pharmacokinetics of Isoniazid, Pyrazinamide, and Ethambutol in Pregnant South African Women with Tuberculosis and HIV. *Antimicrob Agents Chemother*. 2020;64(3):e01978-19; Fischer JH, Sarto GE, Hardman J, et al. Influence of Gestational Age and Body Weight on the Pharmacokinetics of Labetalol in Pregnancy. *Clin Pharmacokinet*. 2014;53(4):373-383.

Type of study design dictates the type of pharmacokinetic analysis

Non-compartmental analysis (NCA) & Compartmental PK modeling



Non-compartmental analysis (NCA) + Population PK modeling

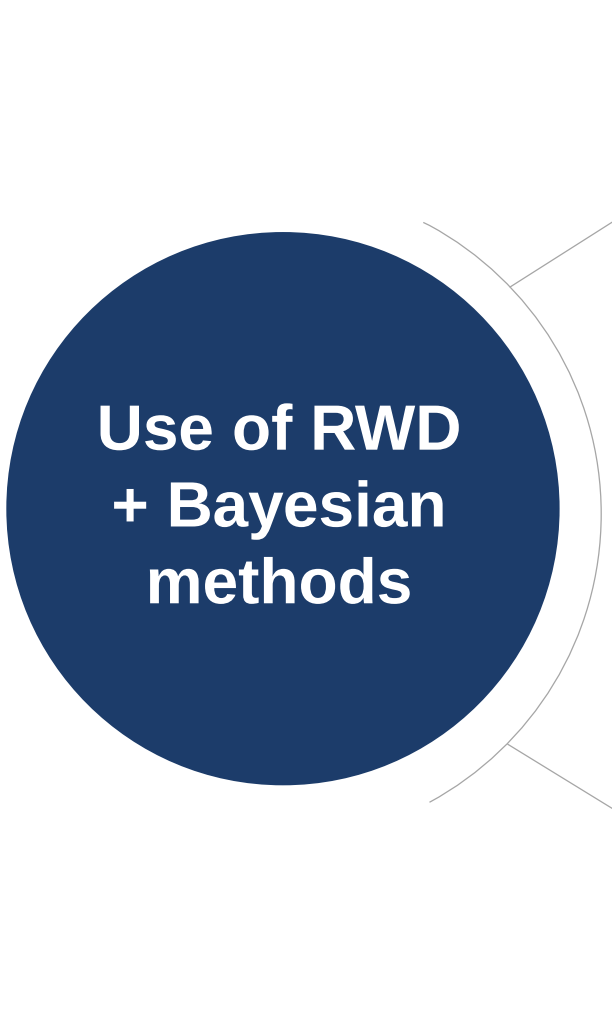
Population PK modeling

Population PK modeling

Recommendations on dosing adjustments may be needed	Recommendations on no dosing adjustments needed
Fold change: $\frac{AUC_{pregnant}}{AUC_{nonpregnant}} \geq$ 2 times lower	Fold change: $\frac{AUC_{pregnant}}{AUC_{nonpregnant}} <$ 2 times lower

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Food and Drug Administration. Published April 27, 2020. Accessed April 24, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-pregnancy-study-design-data-analysis-and-impact-dosing-and-labeling

Alternate strategies to inform PK & dosing in pregnancy with potential to move from "Off-patent to Approval"



Use of electronic health records (EHR) for drugs undergoing TDM

- Create matched datasets (pregnant/non-pregnant)
- Empirical Bayesian/Population PK modeling
- **Case study:** Vancomycin in pregnant women

RWD: Real World Data
TDM: Therapeutic Drug Monitoring

Pregnancy PBPK model informed prior for Bayesian PK modeling & design of pragmatic PK trials

- PBPK model to inform drugs to be studied using pragmatic PK trials using EHR
- PBPK model informed prior for Bayesian PK modeling of drugs with sparse data from RWD

PBPK: Physiologically Based Pharmacokinetics

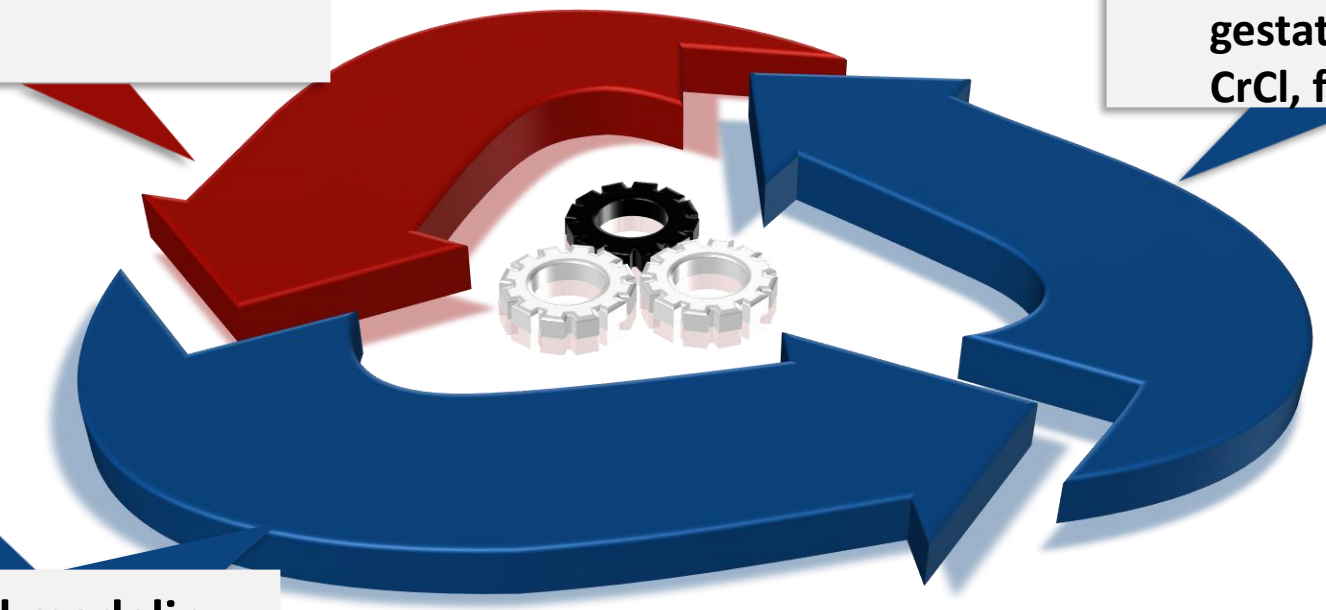
Use of electronic medical records for drugs undergoing TDM – Vancomycin case study

Decision

- **Is there a need to adjust vancomycin dosing in pregnant women?**

Information

- **Retrospective electronic medical records of pregnant women**
- **At least 2 concentrations, dose, gestational age, bodyweight, CrCl, fat free mass**



Analysis

- **Population PK model modeling – prior vancomycin models used as a starting point**

Rahul Goyal, Brady Moffett, Joga Gobburu et al, 2022 – Under consideration for publication: Population Pharmacokinetics of Vancomycin in Pregnant Women

Vancomycin case study

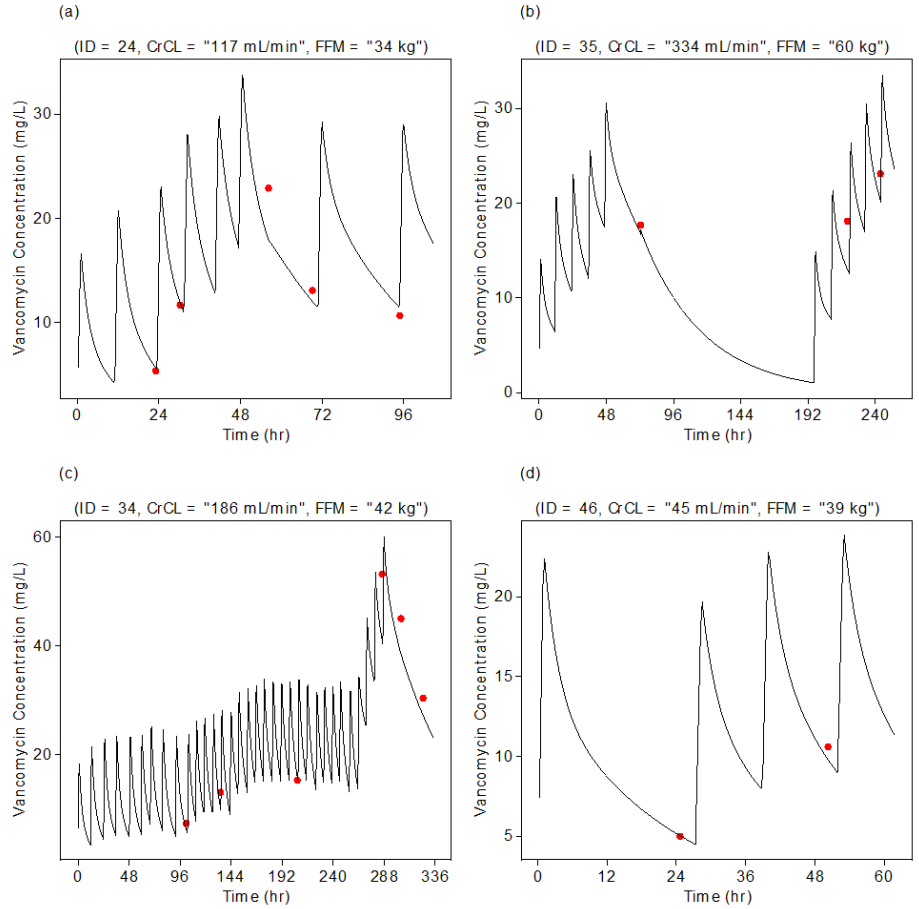
Variable	Value
Number of patients	34
Age (years)	28 (17-38)
Height (cm)	163 (147-173)
Total body weight (kg)	74 (43-157)
Gestational age (weeks)	27 (7-40)
Serum creatinine (mg/dl)	0.56 (0.27-1.97)
Creatinine clearance[2] (ml/min)	176 (43-389)
Fat-free mass[3] (kg)	45 (30-60)
Body mass index (kg/m^2)	28 (19-70)

Population PK model

- Two Compartmental PK model
- Peripheral volume and inter-compartmental clearance fixed based on prior literature

Covariate model

- Creatinine clearance and fat-free mass on clearance
- Fat-free mass on volume

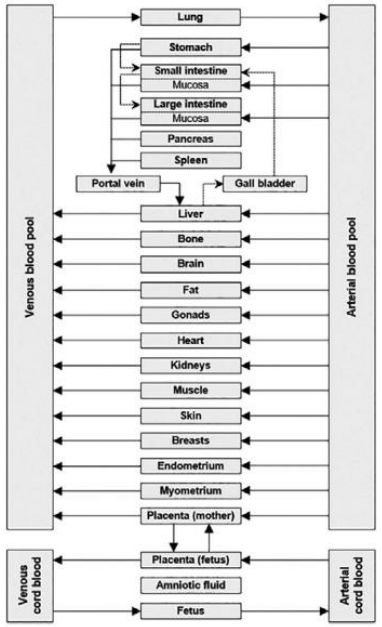


Decision

- **Is there a need to adjust vancomycin dosing in pregnant women?**
  - **No dosing adjustments needed. AUC was similar between pregnant and non-pregnant subjects**

Pregnancy PBPK model informed Bayesian framework to prioritize study of drugs, design and analysis

List of drugs



Apply Pregnancy PBPK model

Clinically meaningful lower exposure in pregnant subjects

High priority for drugs to be studied

Prioritize drugs based on evidence of need

Pragmatic PK/PD trial – informative sampling with Bayesian features to update as data is accrued

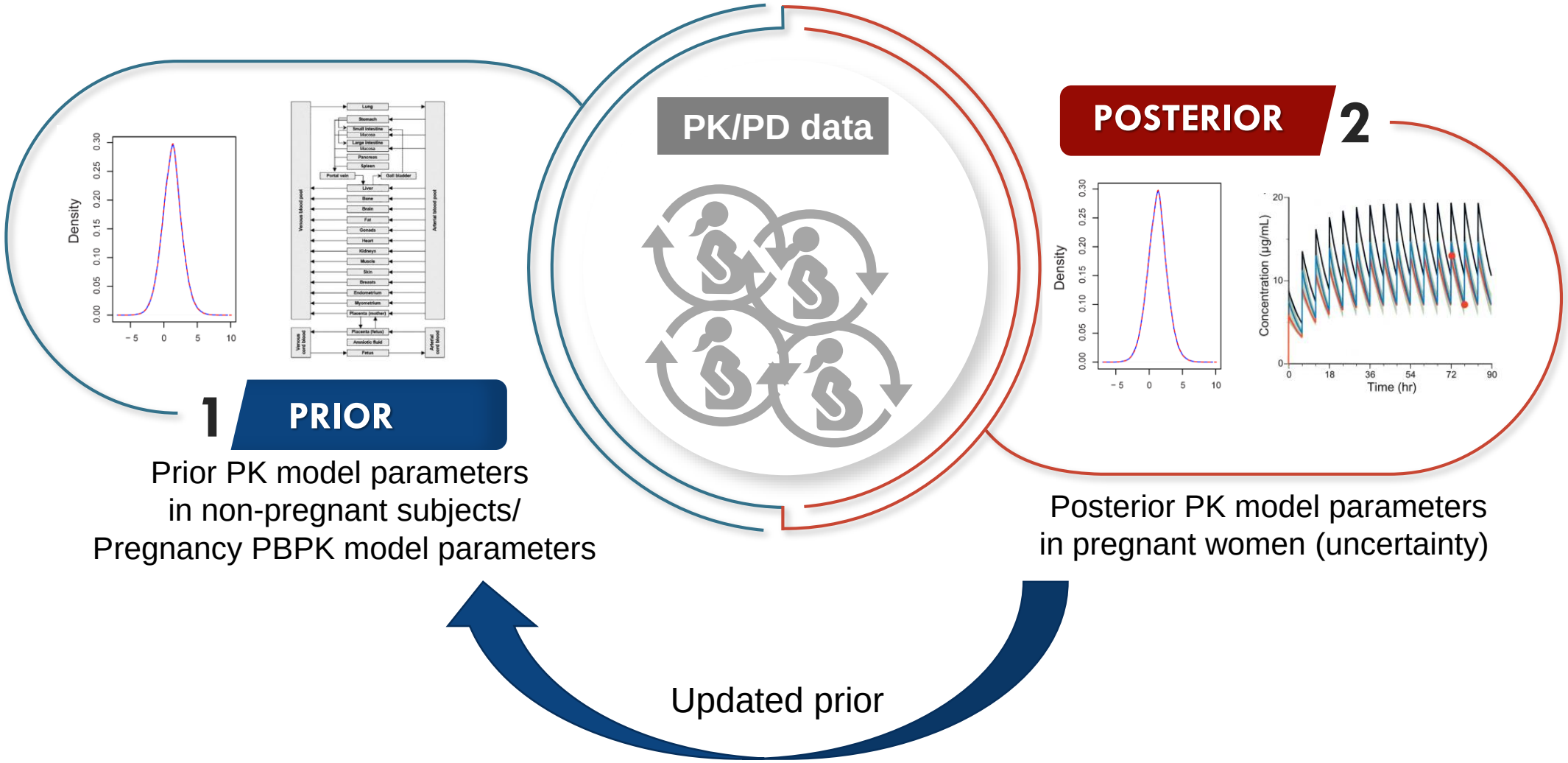
No clinically meaningful change in exposure in pregnant subjects

Low priority for drugs to be studied

Bayesian PK/PD modeling using pregnancy PBPK model informed prior/literature

- Sparsely collected data from real-world studies
- Dose individualization

Bayesian PK/PD modeling framework



Opportunities & Challenges

Use of RWD + Bayesian methods

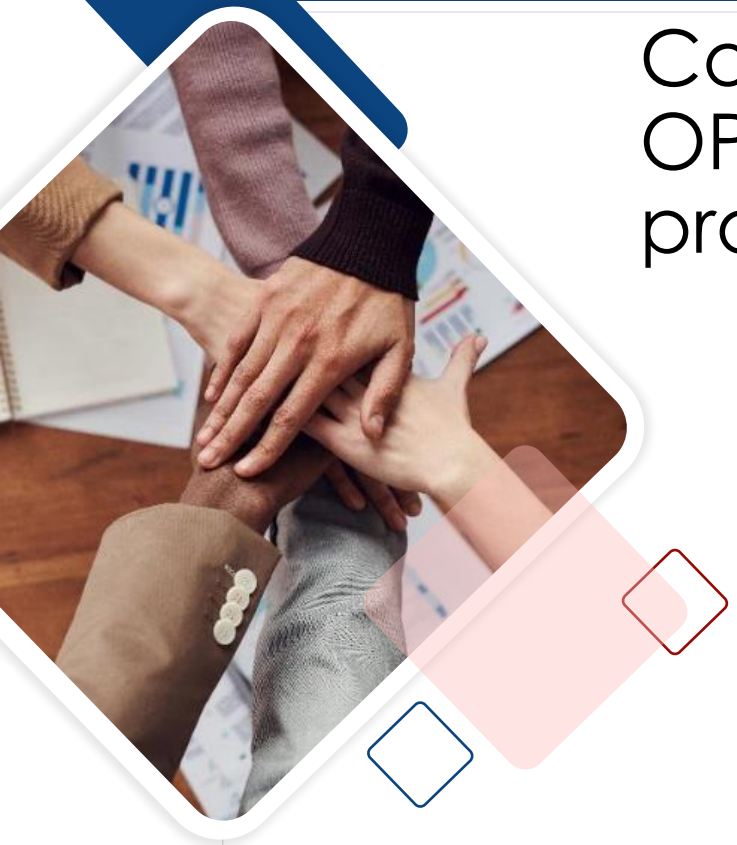
RWD

Opportunities	Challenges
Reflects real world clinical practice	Lack of information on relevant variable, not part of routine care
Heterogeneous, generalizable	Data quality – careful curation needed

PBPK + Bayesian

Opportunities	Challenges
Incorporation of prior knowledge for design/analysis	Ensure validity of the pregnancy PBPK model
PBPK model informed prior or prior from drug literature for sparse data	Availability of trained personnel to implement Bayesian methods & PBPK models

Consortium of multiple stake holders (academia, OPRCs, FDA, pregnancy community) needed to promote "Off-label to approval" pipeline



Goal

By 2030, aspire to renew labeling information of 10 priority off-patent medications used in pregnancy

1. **CALL TO ACTION**
   Establish the collaboration between stakeholders & pregnancy community
2. **PILOT PROJECT**
   Demonstrate the process from inception to approval for 2 drug products
3. **REVIEW**
   Evaluate results of pilot product to ensure that a repeatable process is feasible
4. **FACILITATE SCALE UP**
   Finalize the systematic, reproducible process to achieve pregnancy labeling
5. **PROMOTE**
   Offer training to encourage other clinical pharmacology fellows to undertake such projects