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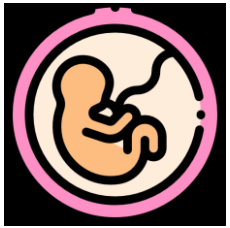

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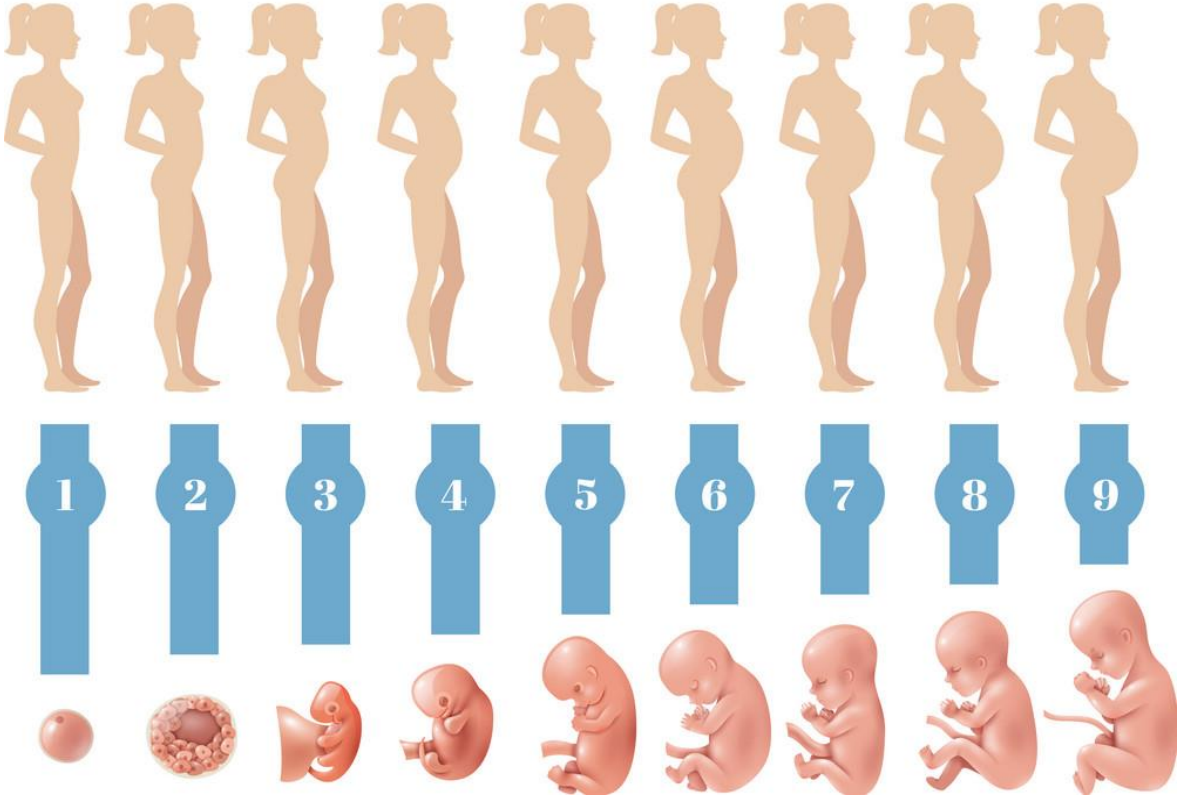
PREGANCY WOMAN STAGES



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Guidance for Industry

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

FDA, 2004

"Introduction to population PK modeling approaches"

"PK studies including pregnant patients, **physiological changes** during and after pregnancy **that are critical for drug absorption and disposition** may need to be considered in the model."

Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

Guidance for Industry

FDA, 2018

EMA, 2006

GUIDELINE ON

THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:

NEED FOR POST-AUTHORISATION DATA

EMA, 2009

GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

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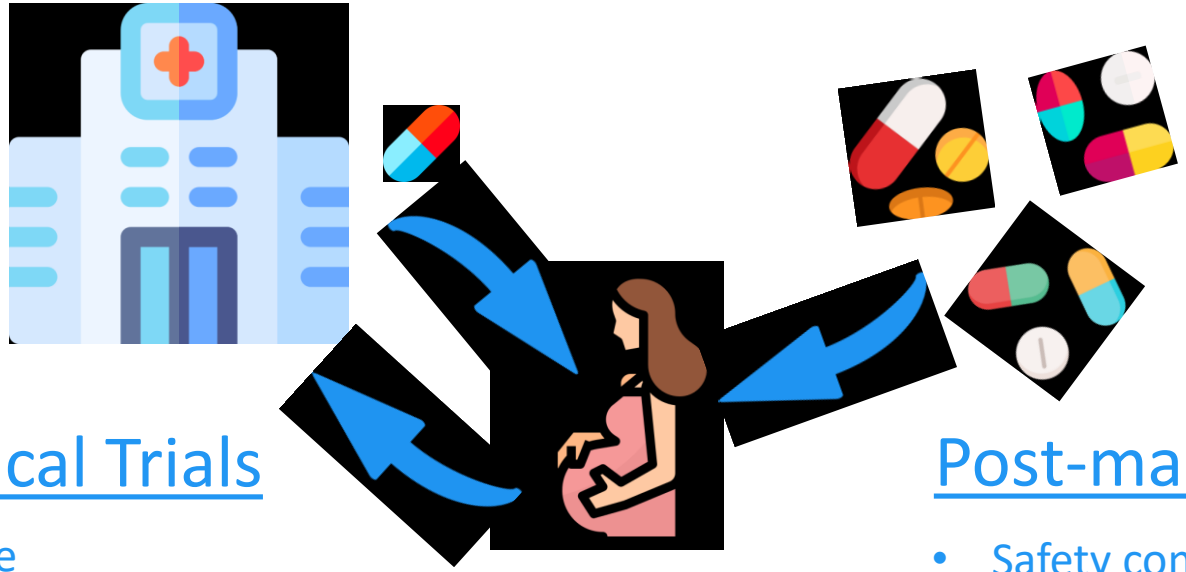

Clinical Trials

- Safe
- Ethical if the drug provides a direct benefit to either the mom or the fetus

Post-marketing

- Safety concerns
- Ethical limitations
- Other approaches are necessary

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"For PK studies including pregnant patients, **physiological changes** during and after pregnancy **that are critical for drug absorption and disposition** may need to be considered in the model."

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-pregnancy-study-design-data-analysis-and-impact-dosing-and-labeling

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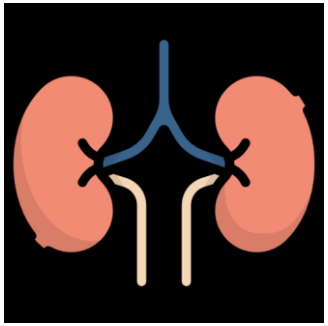

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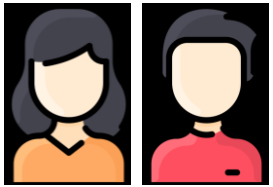
Model development and validation



Model adjustments Postpartum

Pregnancy prediction

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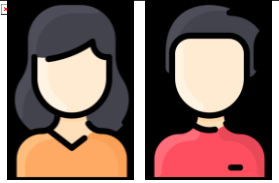

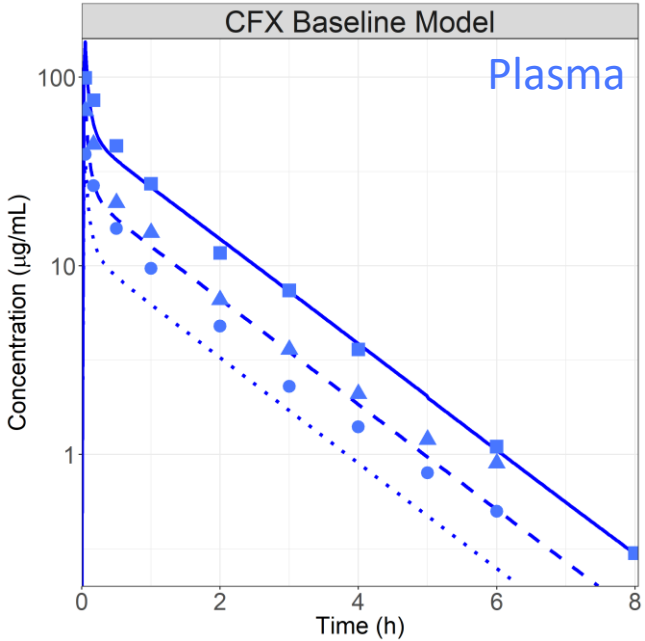

- CFX is cleared by renal filtration and active secretion
- All tissues defined as perfusion limited except the kidney
- Kidney secretion mediated by OAT3 and MRP4. Vmax parameters were fitted

➔ PBPK model can reasonably described the observed concentration following IV administration at 3 doses.

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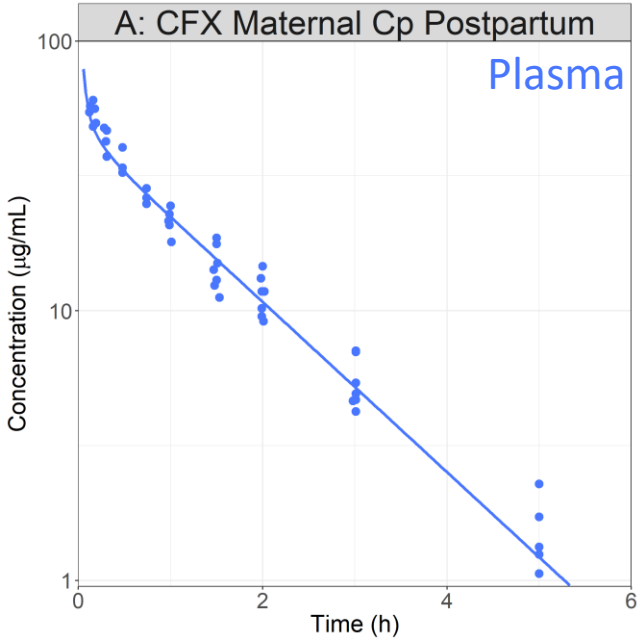

- Transporters Vmax parameters were adjusted to capture the urinary excretion data

➔ PBPK model can reasonably described the observed concentration following IV administration in Postpartum subject.

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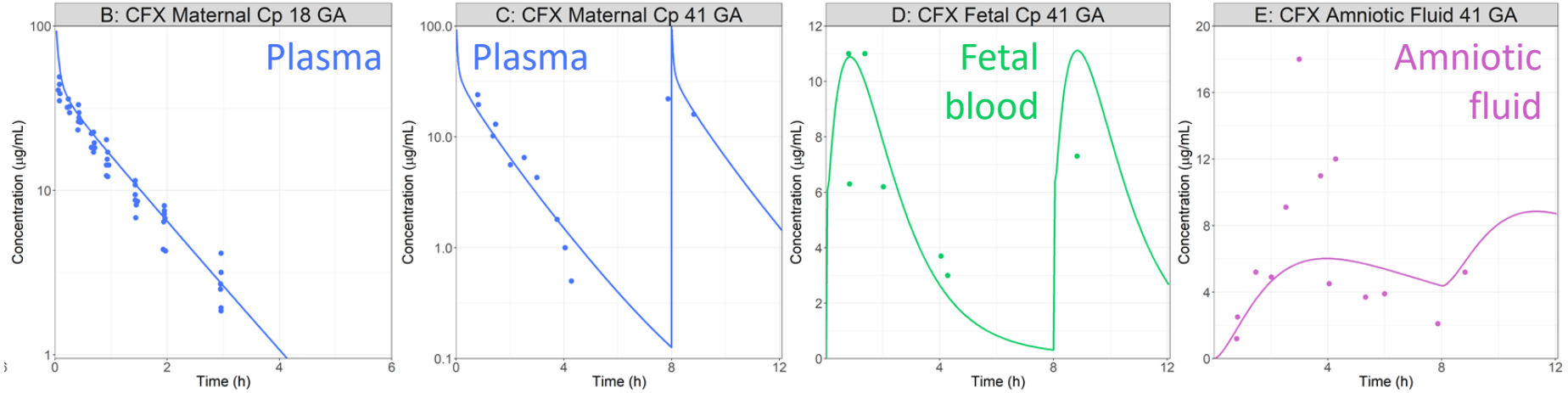
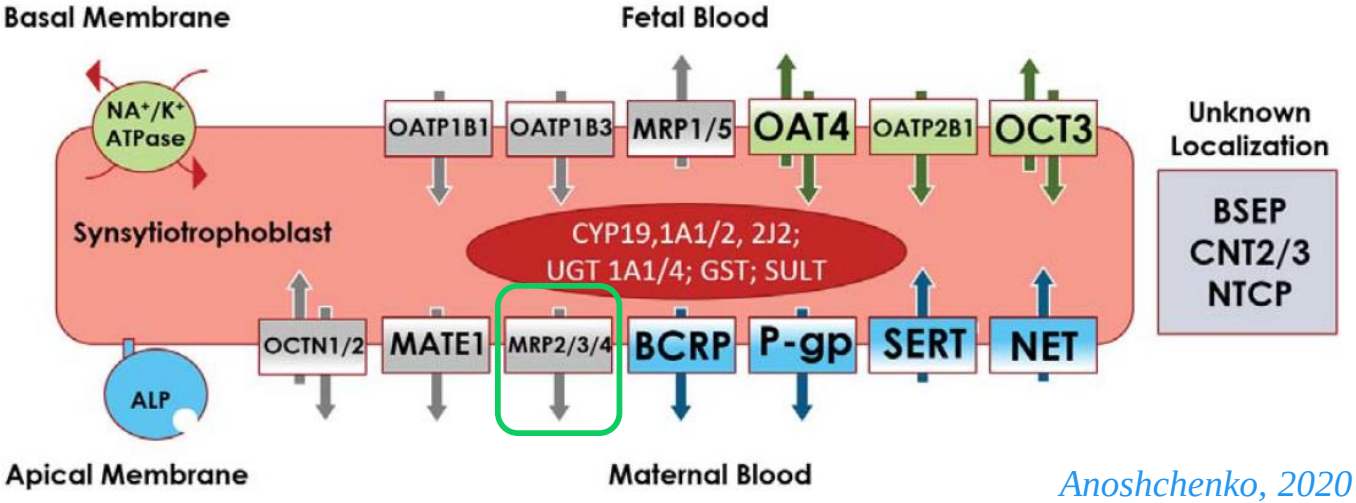
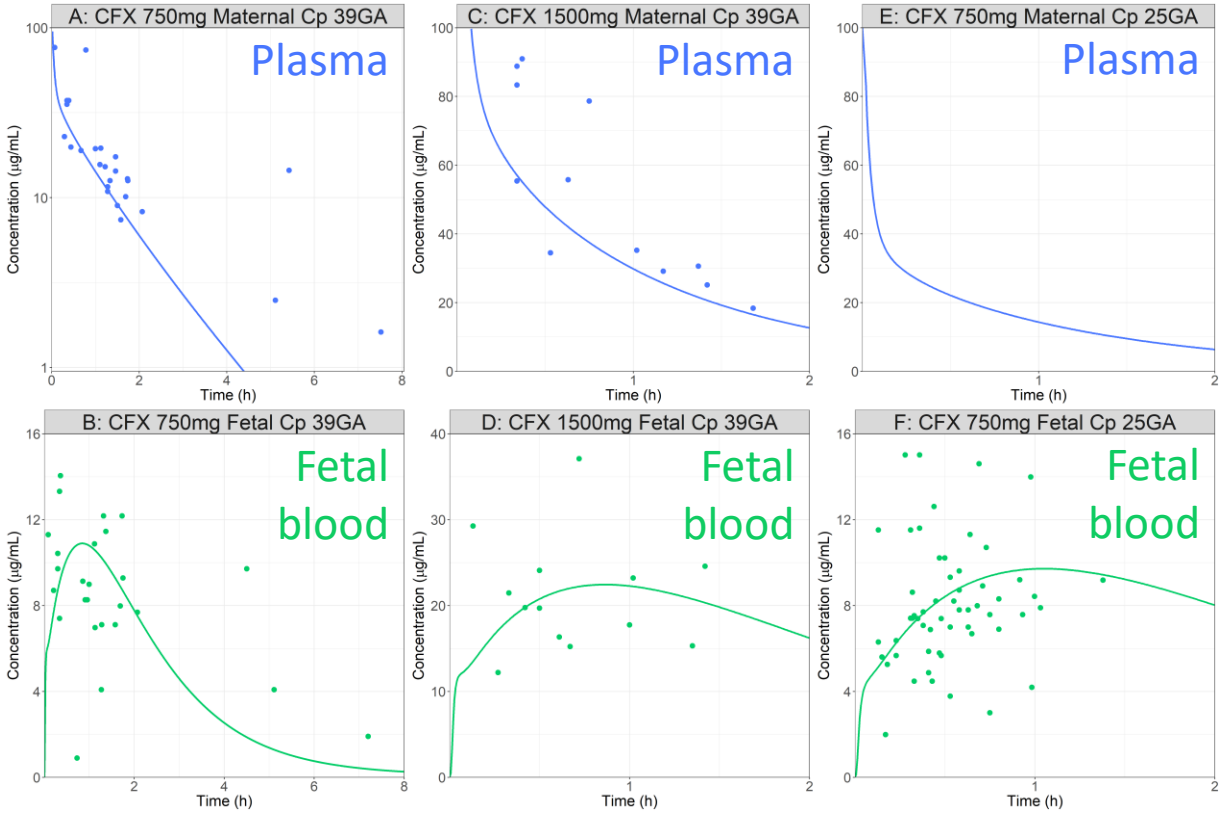


- Placenta model was changed to permeability limited

➔ PBPK model can reasonably described the observed maternal and fetal concentrations following IV administration.



Anoshchenko, 2020


A: CFX 750mg Maternal Cp 39GA
Plasma
C: CFX 1500mg Maternal Cp 39GA
Plasma
E: CFX 750mg Maternal Cp 25GA
Plasma
B: CFX 750mg Fetal Cp 39GA
Fetal blood
D: CFX 1500mg Fetal Cp 39GA
Fetal blood
F: CFX 750mg Fetal Cp 25GA
Fetal blood
Concentration (µg/mL)
Time (h)

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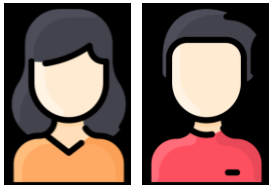
Model development and validation



Model adjustments Postpartum

Pregnancy prediction

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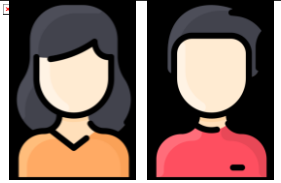

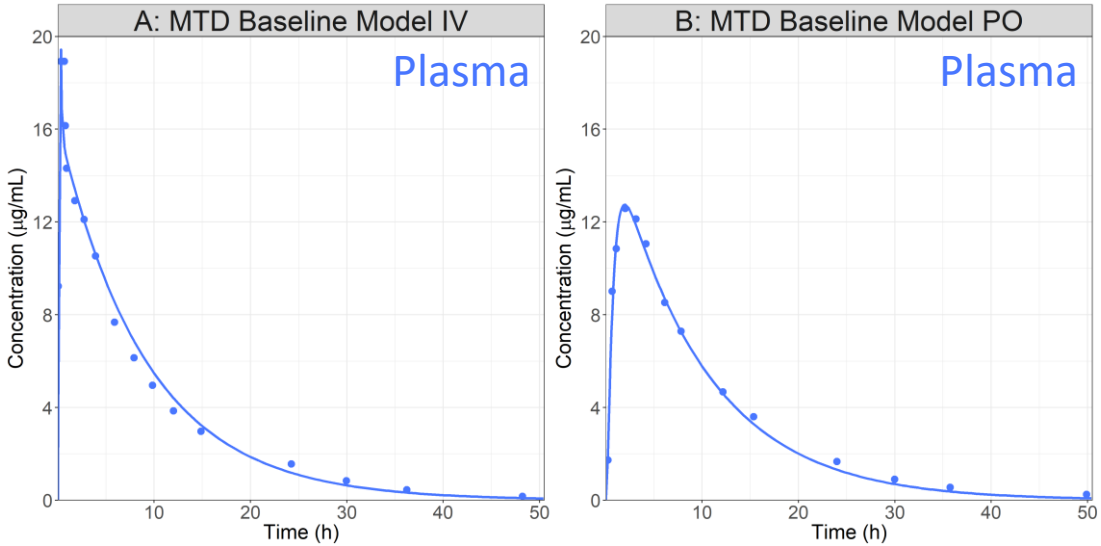

- MTD is metabolized by the CYPs 3A4, 2A6, 2E1 and UGT
- All tissues defined as perfusion limited

➔ PBPK model can reasonably described the observed concentration following IV/PO administrations.

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Plasma

- No model adjustment was made based on Postpartum data at 2 doses (0.25/1g PO)

➔ PBPK model can reasonably described the observed concentration following PO administration in Postpartum subject.

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Plasma Plasma Plasma Plasma

➔ PBPK model can reasonably described the observed maternal Cp concentrations following PO administration at different stages of pregnancy.

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Plasma

Plasma

Plasma

Fetal blood

Fetal
Placenta

Fetal
Placenta

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