



# The role of modelling and trial design considerations – regulatory perspective

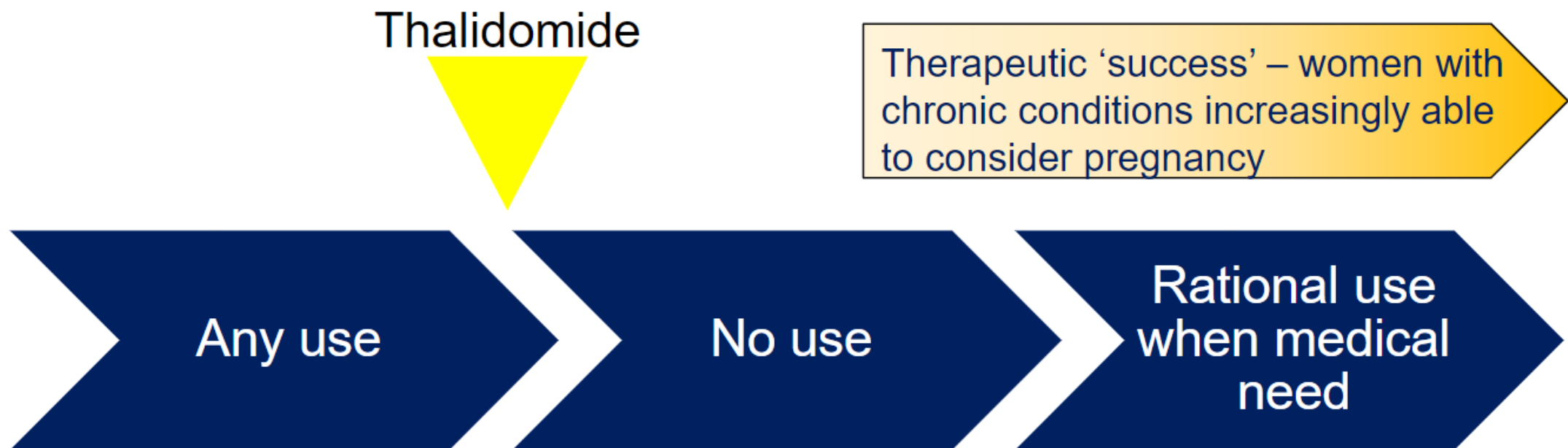
Susan Cole- Expert Pharmacokinetics Assessor- MHRA



# Disclaimer

The views expressed in this presentation are those of the speaker and are not necessarily those of MHRA.

# Evolution of use of medicines during pregnancy



Foetus = 'Innocent bystander'  
Benefits & risks of treatment versus risks of no / alternative treatment

# Drivers for change- limited data for informing on use in pregnancy and lactation

- 80% women used at least one medicinal product during pregnancy, 17% chronic use
- Limited clinical information on use in pregnancy
- Large number of medicines advise avoiding use or contra-indicated due to lack of data
- Pregnant women not included in clinical trials and removed from trial on becoming pregnant
- Physiological changes may affect pharmacokinetics and/or pharmacodynamic responses
- Lack of information can be detrimental to women's health due to under treatment of conditions
- Delayed observation of effects due to foetal development

## Limited medicines with indication for pregnancy

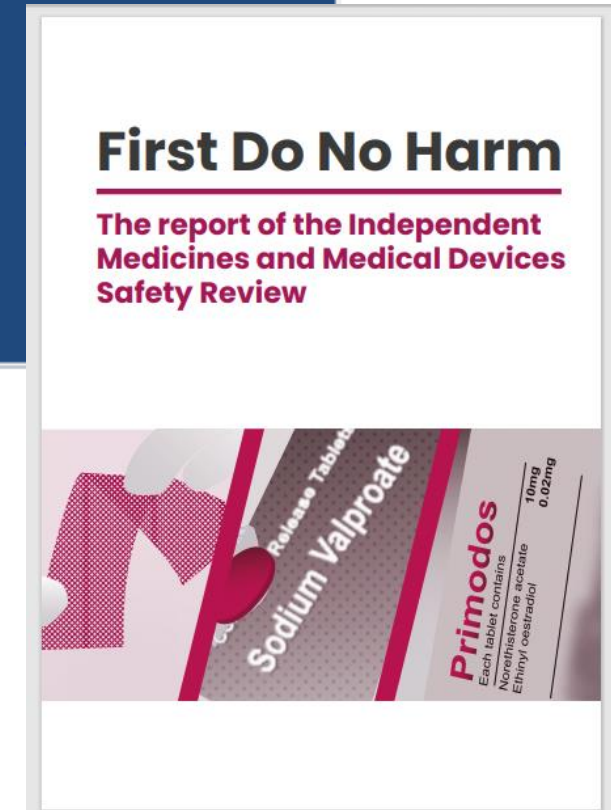
Prescription medicines	Pregnancy indication
Amoxicillin	(asymptomatic) Bacteriuria in pregnancy
Labetalol	hypertension in pregnancy.
Diazoxide injection	hypertensive emergencies: eclampsia or pre-eclampsia.
Doxylamine succinate / pyridoxine hydrochloride	nausea and vomiting of pregnancy
Sodium Feredetate	Iron deficiency anaemia. In pregnancy when other forms of oral iron may not be well tolerated
Non-prescription medicines	
Calcium Gluconate, lactate or carbonate	therapeutic (calcium) supplementation in pregnancy

# Drivers for change- UK

UK: Recommendations from Expert Working Group on Hormone Pregnancy Tests to improve evidence base and information for use of medicines in pregnancy.

Experience of key regulatory safety issues relating to medicines in pregnancy - valproate, boosted darunavir.

Cumberlege review



# MHRA/BMGMF

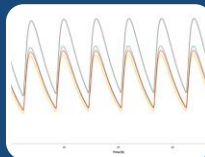
*PBPK Project: Evaluating PBPK modelling and simulation to inform drug dosing in pregnant women*

## Aim

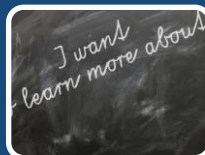
*To improve the knowledge of medicines used during pregnancy, based on changes in systemic exposure, and to evaluate existing PBPK models for their potential to support dosing in pregnant women*



Data collection



Pregnancy PBPK evaluation



Training

# Collection of pregnancy PK data

## Main list

- ~ 200 medicines
- 16 therapeutic areas

## Priority list

- 20 medicines
- e.g. Epilepsy, Antiemetics, Pain, Antidepressants, Antibiotics, Antivirals, Antimalarials, Antipsychotics

- Based on MHRA Medical Assessors' experience

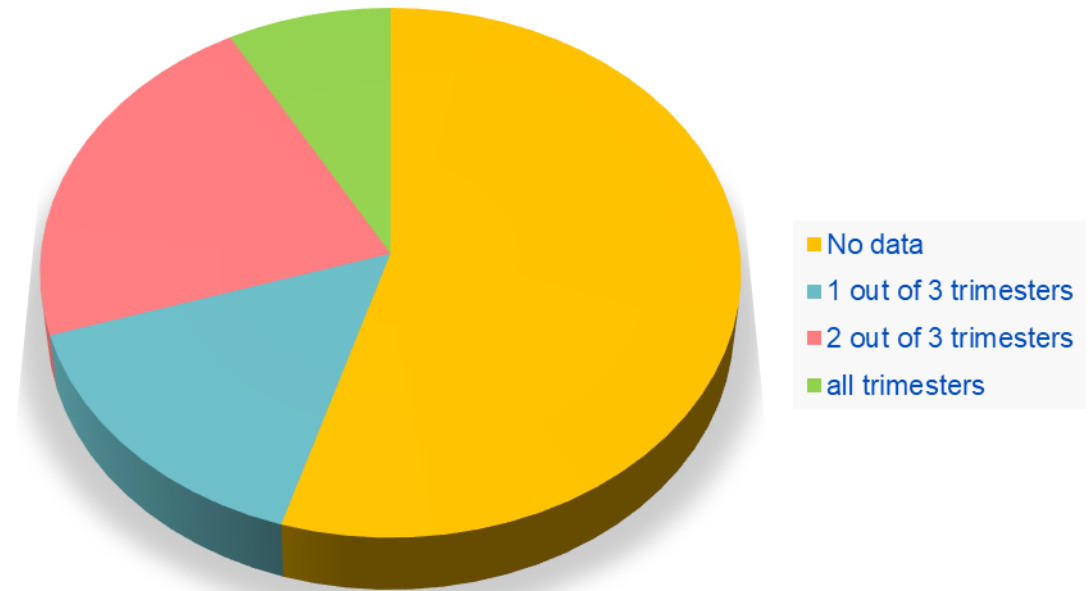
- Endorsed by the CHM, EAGs and UK experts



# Summary- collection of pregnancy PK data

- Pregnancy PK data available < 50 % of identified medicines
- Data in all trimesters only for 19 medicines
- Nonpregnant/postpartum not always available
- Changes in exposure can be significant- up to 5 fold documented metoprolol and lamotrigine.
- Changes can occur very rapidly.
- In some cases numerous studies, results may be contradictory.

Pharamcokinetics data in pregnancy (up to 2019)





# Factors which may affect reliability of PK studies

Factor	Impact
<b>Controls vs non-pregnant data from the same individuals</b>	Reduce impact of variability between subjects. Each person can serve as their own control.
<b>Non-pregnant or post-partum and time?</b>	Do values represent truly non-pregnant values?
<b>Sufficient number of subjects</b>	Are results significantly different?
<b>Dose route, form and dose adjustments</b>	Route on profile shape. Is dose accurately reported?
<b>Quantity and distribution of blood sampling times</b>	Full profile versus sparse samples, which parameters can be reported?
<b>Bioanalytical methodology</b>	Limit BLQs. Correct entity- active enantiomer/ metabolites.
<b>Free drug levels</b>	Correct understanding for pharmacology
<b>Effects of other factors e.g. disease state</b>	Changes may be due to other factors.
<b>Effect of polymorphisms</b>	Changes in exposure and changes in pregnancy in subjects that are poor or rapid metabolisers.

# Usefulness of platform trials in Pregnancy

## **IMPAACT**

P1026s is a Phase IV, prospective pharmacokinetic (PK) study of selected ARV drugs currently used in the clinical care of HIV-infected pregnant women during pregnancy and postpartum. This study is designed to evaluate the following: the pharmacokinetics of antiretroviral medicines when used alone or co-administered with tuberculosis medicines during pregnancy; the pharmacokinetic parameters of lopinavir/ritonavir and atazanavir/ritonavir/tenofovir in women postpartum before and after starting hormonal contraceptives; and the concentrations of ethinylestradiol, etonogestrel and other progestins in women using hormonal contraceptives and protease inhibitors.

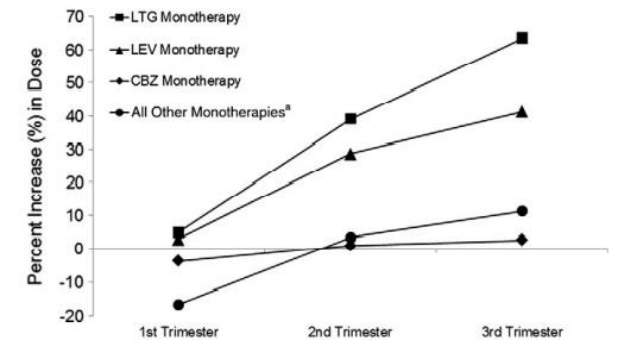
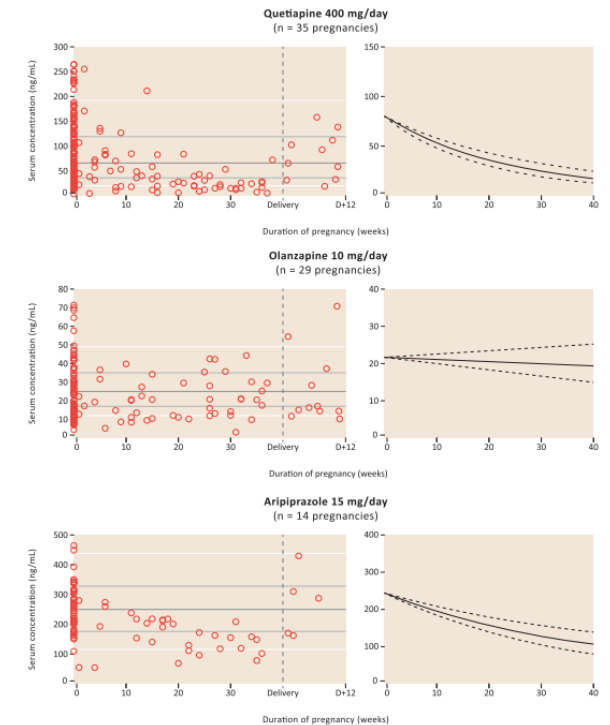
[P1026S / PK in Pregnancy \(impaactnetwork.org\)](http://impaactnetwork.org)

# Use of opportunistic samples

**Westin-** 201 routine therapeutic drug monitoring concentration measurements from a total of 110 pregnancies, and 512 measurements from the same women before and after pregnancy. Serum concentrations in the third trimester were significantly lower than baseline for quetiapine (-76%; confidence interval (CI), -83%, -66%;  $P < 0.001$ ) and aripiprazole (-52%; CI, -62%, -39%;  $P < 0.001$ ), but not for olanzapine (-9%; CI, -28%, +14%;  $P = 0.40$ ).

**Reisinger-** A retrospective analysis was performed for 115 pregnancies. Antiepileptic drug blood levels obtained during routine clinical practice.

Significant changes in clearance during pregnancy were observed for lamotrigine ( $p < 0.001$ ) and levetiracetam ( $p < 0.0060.001$ ).



**Fig. 1.** Percent change in monotherapy antiepileptic drug dosage in each trimester of pregnancy. <sup>a</sup>Other AED monotherapy included topiramate (n = 3), oxcarbazepine (n = 2), valproate (n = 1), zonisamide (n = 1), and ethosuximide (n = 1). Phenytoin was not included because no nonpregnant baseline dose was available. Dosage data for all individual AEDs and for polytherapy regimens are provided in Table e-2. LTG = lamotrigine; LEV = levetiracetam; CBZ = carbamazepine.

Westin 2018. *Clinical Pharmacology and Therapeutics*. 103, 3, 477- 84  
Reisinger 2013- [Epilepsy & Behavior](#), 29,1 , 13-18

# Drugs with full data sets for PBPK model evaluation

Medicines used for model qualification	
Main clearance pathway	Number of medicines
CYP3A4	3
CYP3A4 + UGT	1
CYP2D6	2 (+1 priority)
Multiple CYPs	2
Multiple CYPs + UGTs	2
Renal (passive transport)	1
Renal (active transport e.g. OCTs, OATs)	4
Biliary	1

# PBPK Modelling in pregnancy

- Ambition versus pragmatic use of models
- Available data are insufficient for qualification of high impact regulatory decision
- Available models evaluated where available for drugs with 'rich' data sets- SIMCYP, Gastroplus, PKSim
- Focus on maternal exposure, recognise importance of fetal exposure
- Reasonable results for changes in pregnancy for renally excreted drugs- ceftazidime, cefuroxime, amoxicillin, metformin, oseltamivir- change in GFR.
- Most have some component of active- transporter updates in progress
- Value of models in clinical trial design and with sparse/ opportunistic samples.

# MHRA/BMGF Trainings

- Training held on January 2020:
  - Importance of PK data in pregnancy and postpartum- promote collection
  - Introduction on the use of modelling to support PK evaluation in pregnancy
- Next training planned on 2022
- Use of PBPK modelling

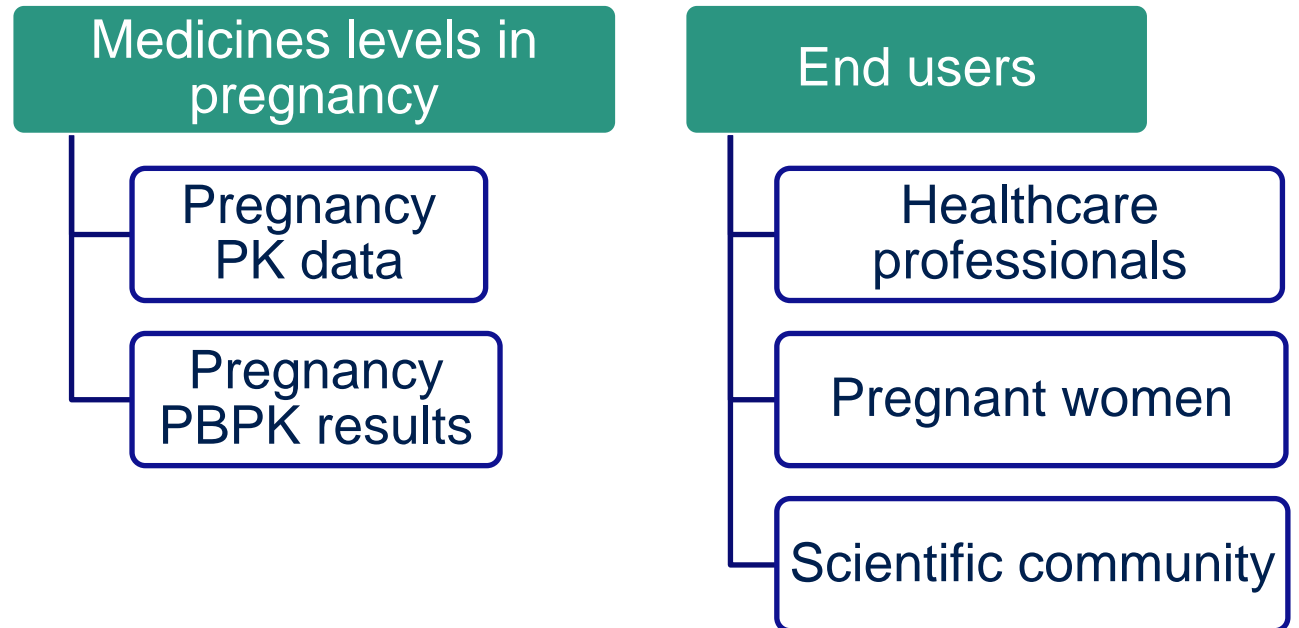


# Medicines levels in pregnancy website

Results of data collection and PBPK modelling will be published on MHRA website and peer reviewed journals

Trainings and events will be advertised on MHRA MedRegs  
<https://medregs.blog.gov.uk/category/medicines-in-pregnancy/>

AIM: Share information about medicines levels in pregnancy to inform dosing





# Medicine levels in pregnancy website

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# Acknowledgements

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