A Translational Center for Microphysiological Systems-Based Drug Development Tools for Pregnancy and Women's Health

(1U2CTR004868)

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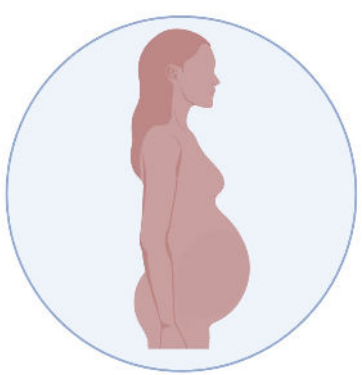
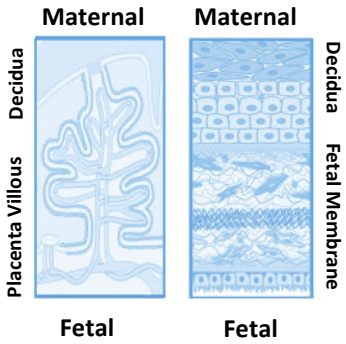
Year 1 & 2 Biological Concept and Workflow

TraCe-R
It's About Saving Babies

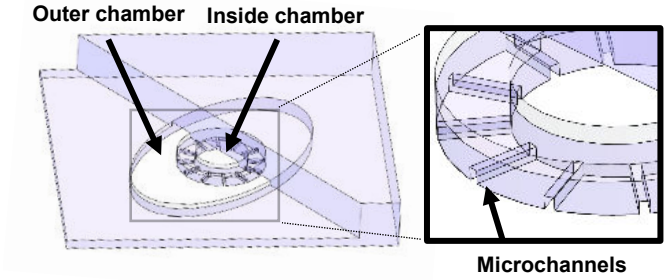
Maternal Drug Administration

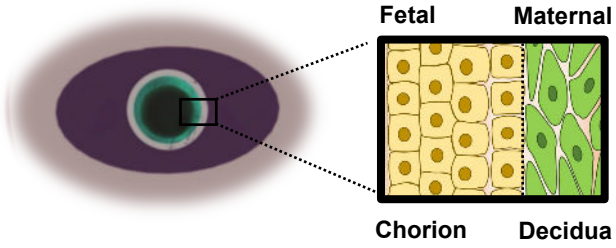


LOI accepted

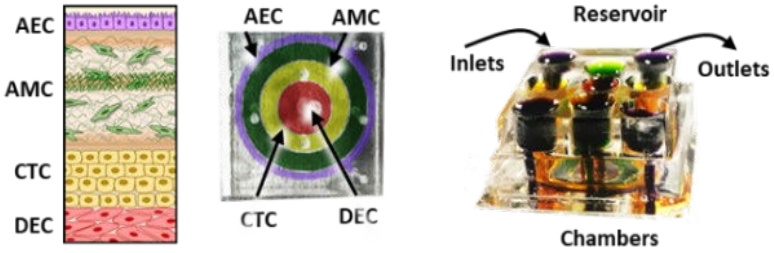


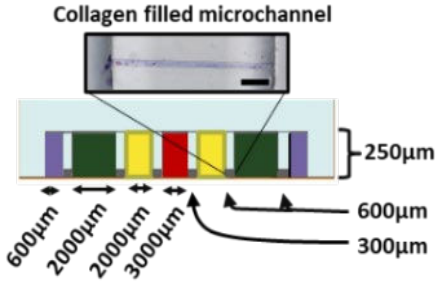
YEAR 1 - Two-Chamber Choriodecidua-OOC





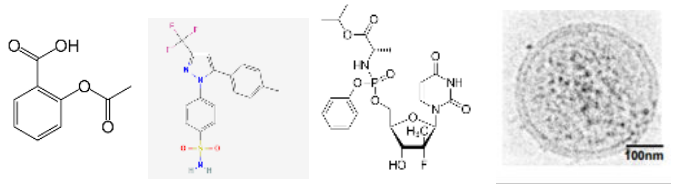
YEAR 2 – Four Chamber FMi – OOC Fetal Membrane - Decidua

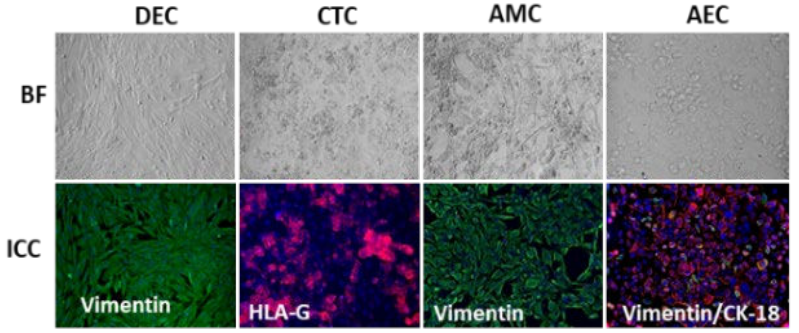




Three Small Molecule Drugs One Biologic

Aspirin, Celecoxib, Sofosbuvir, and tIL-10





utmb Health

FMi – OOC

TraCe-R
It's About Saving Babies

Year 1 completion — May 2025

Retreat @ UTMB CoU defined Preparation of LOI — June 2025

LOI submitted — July 2025

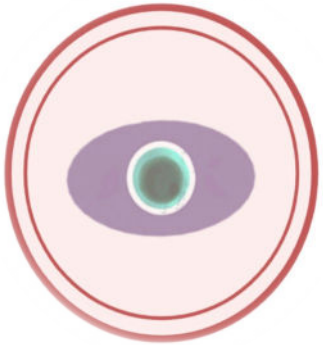
Year 2 FMi-OOC project started — August 2025

LOI accepted — November 2025

QP discussion — January 2026

Year 2 progressing — February 2026

Discussion at Tissue chip consortium Planned QP submission — March 2026



2-chamber CDi-OOC

How to make drug therapy during pregnancy safer?

utmb Health

Description of the Unmet Drug Development Need(s) that the proposed MPS aims to address

- Many "*pregnant women need to use drugs to manage chronic disease conditions or treat acute medical problems*"[1]
- "*Pregnant women are actively excluded from [Phase 3] trials … Consequently, at the time of a drug's initial marketing […] there is seldom human data on the appropriate dosage and frequency of administration during pregnancy… In the absence of [PK/PD] data, the usual adult dose is typically prescribed for pregnant women*"[2]
- "*If there is any labeling information for pregnant women, it is usually based on nonclinical data with or without limited human safety data*"[1]
- "*Information about drug use in pregnancy generally is collected in the post-marketing setting, using data from observational [i.e., not from clinical trials] studies*"[1]
- "[FDA draft] *guidance recommends that PK studies be conducted in pregnant women [when] the drug is known to be prescribed in or used by pregnant women, especially in the 2nd and 3rd trimesters*"[2]
- These considerations are especially relevant for cases of ***first in class*** and ***new modality*** drugs with little historical data on PK/PD

[1] US FDA/CDER/CBER. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials: Guidance for Industry [Draft]. 2018.
[2] US FDA/CDER. Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling [Draft]. 2004.

Preclinical Development		**Clinical Development**			
Nonclinical studies	**IND-Enabling Information**	**Phase 1 Trial**	**Phase 2 Trial**	**Phase 3 Trial**	**Post-marketing**
Pharmacokinetics	Systemic TK →	Complete PK/ADME (prior to Phase 3 Trial) - - - →			
Genotoxicity	In vitro, or Full package →	In vivo micronucleus - - - →			
Safety Pharmacology	CNS, Cardiovasc., Respiratory →				
Repeat dose – Systemic Tox	Duration to support trials →				
Continued Development					
Longer-term/Chronic Tox	Duration to support Phase 3 trials (at least 1 species) →				
DART	Early Fetal Development (2 species) and Fertility (1 species) →				
	Pre- and Post-natal development (1 species) →				
Carcinogenicity	Rodent cancer bioassays →				- - - (PMR) - - - →

Table 1
ICH S5(R3) scenarios identified using Dev Tox NAMS.

Context	Outcome
Inclusion of women of childbearing potential (WOCBP) (up to 150 WOCBP for up to 3 months) in early phase trials (Section 4.2.3 in ICH S5R3)	• EU, UK, Japan: Use of qualified Dev Tox NAM* which predict outcome in one species in combination with one preliminary EFD in vivo study in 2nd species • US: No assay needed if adequate precautions to prevent pregnancy
In limited circumstances for the inclusion of WOCBP in clinical trials and to support labelling efforts, ICH S5(R3) Annex 2:	
(1) in cases where there is a high likelihood that a pharmaceutical will adversely affect EFD (e.g., class effect, or known role of target biology in EFD)	• If qualified Dev Tox NAM predicts unequivocal MEFL at clinically relevant extrapolated exposures, it can replace in vivo EFD studies • If qualified Dev Tox NAM predicts negative or equivocal, EFD positive for MEFL is only needed in one species. To be considered negative for MEFL requires negative in vivo data from two species
(2) in cases where the pharmaceutical is being developed for certain severely debilitating or life-threatening diseases, or late-life onset diseases	• If qualified Dev Tox NAM* predicts unequivocal MEFL at clinically relevant extrapolated exposures, it can replace in vivo EFD studies on case-by-case basis • If qualified Dev Tox NAM* predicts negative, EFD in 2nd species is needed - If negative, then considered negative - If positive, then considered positive (EFD in 1st species not needed unless would alter risk assessment) • If qualified Dev Tox NAM* predicts equivocal, EFD in other species: - If EFD in 2nd species is positive, then no more studies needed - If EFD in 2nd species is negative, then EFD in 1st species is needed to conclude negative
(3) when toxicity in the animal species precludes attaining systemic exposures relevant to humans under conditions of clinical use	• Qualified Dev Tox NAM data incorporated into Weight of Evidence (WoE) assessment to inform EFD risk
(4) as support for WoE when animal data are equivocal	• If appropriate, qualified Dev Tox NAM(s) could be used rather than additional animal studies to address equivocal animal data

* When a qualified Dev Tox NAM has been shown to predict MEFL in 1st species (rodent or non-rodent).

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New approach methodologies for assessing developmental toxicity of pharmaceuticals: Case examples and future directions

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[l] Medicines Evaluations Board, Utrecht, the Netherlands
[m] Medicines for Malaria Venture (MMV), Geneva, Switzerland
[n] US Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, USA

Table 2
Summary of Dev Tox NAMs currently used in pharmaceutical safety testing within HESI DART pharmaceutical sponsor companies.

	Screening	Prioritization	Mechanistic Study	Regulatory use/ animal replacement
ZEDTA	Yes	Yes	No	No
Stemina Dev Tox quickPredict, Human	Yes	Yes	No	No
Toxys ReproTracker, Human	Yes	Yes	Yes	No
mEST	Yes	Yes	No	No
hEST	Yes	Yes	No	No
rWEC	Yes	Yes	Yes	No

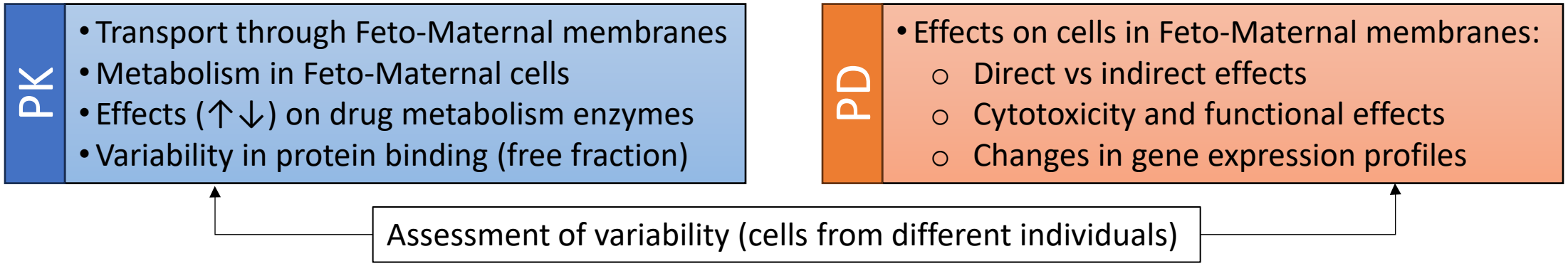
Proposed Context of Use for the Chorio-Decidual Interface MPS

The proposed MPS can be used "*for **first in class*** and ***new modality drugs** indicated for conditions that occur commonly among females of reproductive potential*"…

- **Concurrent with preclinical DART studies**: To ensure sufficient data is available to inform inclusion of pregnant women in Phase 3 clinical trials [if preclinical DART studies are completed before Phase 3 trial begins]

Context of Use: Human chorio-decidual interface organ on chip (CD-OOC) can be used as a DDT for determining human relevance of a positive rodent DART study of a new modality investigational drug candidate by demonstrating whether the drug candidate can (i) transfer from the maternal decidua to the fetal chorion, and/or (ii) elicit cytotoxic and/or pro-inflammatory effects in either maternal or fetal cells.

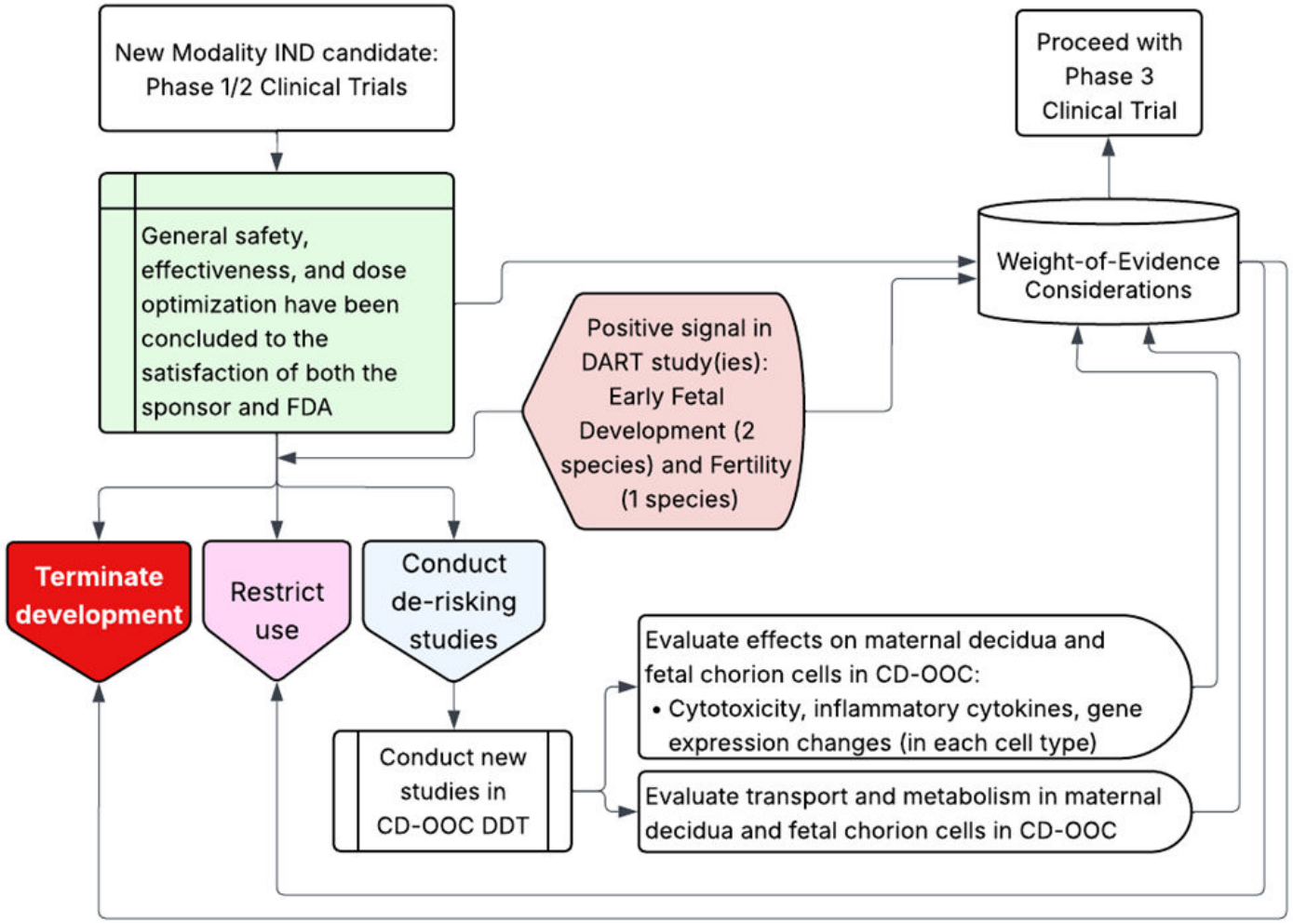
The **USE CASES** for the proposed MPS will be to: provide human-relevant PK and PD *in vitro* data on a drug in pregnancy…



FDA iSTAND Letter of Intent submission (LoI accepted in November 2025):

Human chorio-decidual interface organ on chip for derisking positive rodent DART studies for new modality investigational new drug candidates

Proposed decision tree for de-risking of new modality investigational drug candidates and determining human relevance of a positive rodent DART study



FDA Recommendations for Development of QP for UTMB-TAMU CD-OOC

Drug Development Tool Design

- Elaborate on the Model Design - Explain 24-microchannel design and biological system representation

Suggestions for Context of Use Refinements

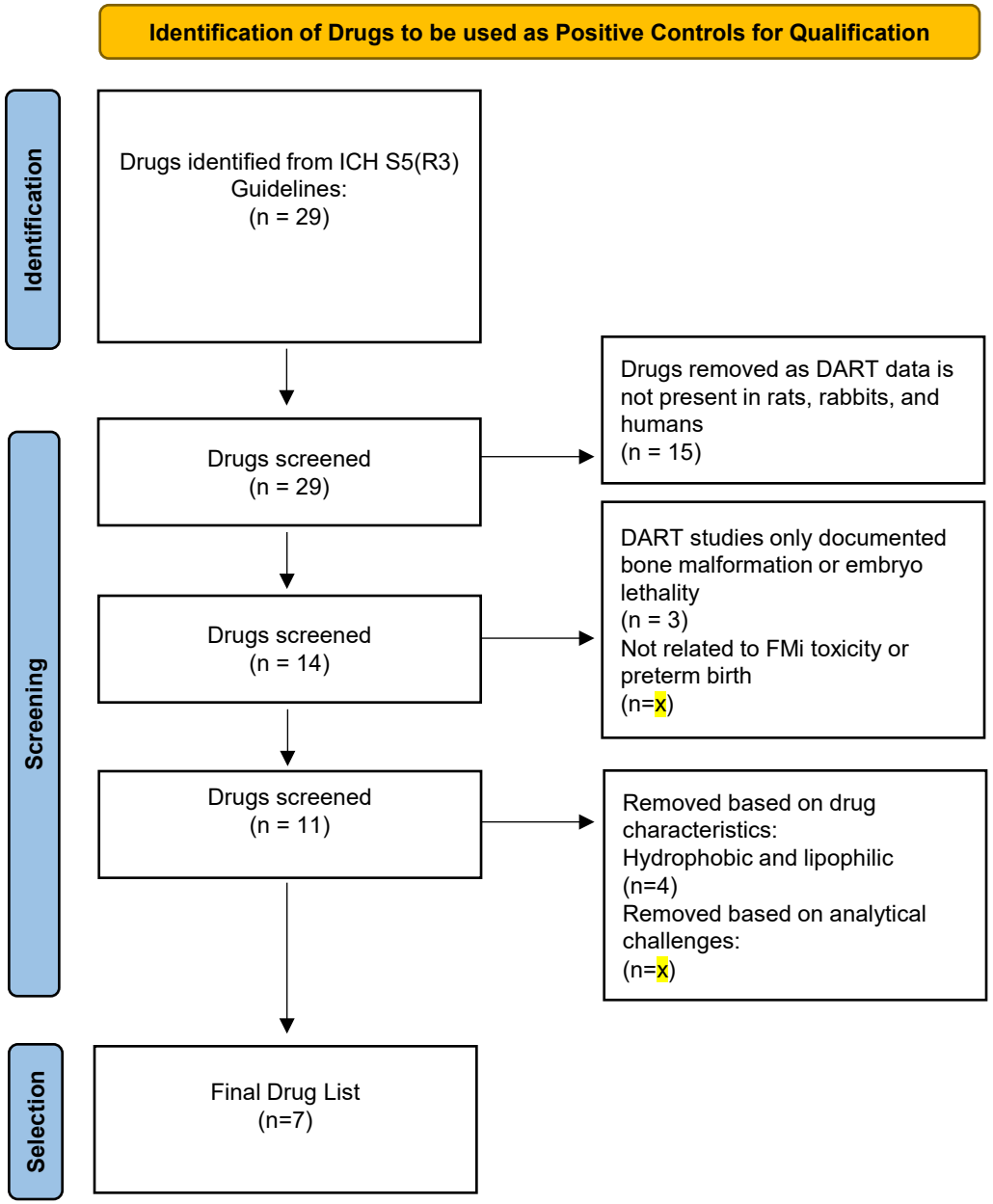
- Gestational timing - Define which pregnancy trimester(s) the model represents
- Study scope - Include both positive AND negative DART studies
- Drug applicability - Specify relevant drug types based on properties and likelihood of fetal exposure

Model Validation Requirements

- Analytical validation – Approaches to quantify accuracy, predictive values, repeatability, reproducibility?
- Study design plan - Statistical approach, drug selection, +/- controls, concentrations, time of exposure
- Clinical integration - Define use of the tool during Phase 1/2 trials and role in overall weight-of-evidence

Model Output Interpretation

- Result interpretation – Will the model yield a binary (go/no-go) or continuous score for decision-making
- Future use workflow – Need a clear flowchart showing when/how model to be used in drug development


Identification of Drugs to be used as Positive Controls for Qualification
Identification
Drugs identified from ICH S5(R3) Guidelines:
(n = 29)
Screening
Drugs screened
(n = 29)
Drugs removed as DART data is not present in rats, rabbits, and humans
(n = 15)
Drugs screened
(n = 14)
DART studies only documented bone malformation or embryo lethality
(n = 3)
Not related to FMi toxicity or preterm birth
(n=x)
Drugs screened
(n = 11)
Removed based on drug characteristics:
Hydrophobic and lipophilic
(n=4)
Removed based on analytical challenges:
(n=x)
Selection
Final Drug List
(n=7)

Positive controls (Positive DART Compounds with Adverse Pregnancy Outcome Context)

Compound (ICH list)	Therapeutic class	One-line justification (DART relevance)	Association with adverse pregnancy outcomes	References	Cmax	References
Busulfan	Alkylating agent	Classic embryo-fetal toxicant; listed MEFL-positive control (rat/rabbit/human marker).	Bone malformations; increased resorptions and decreased live young; Placental apoptosis; No reported effects on gestational length or preterm labor	Busulfan-induced apoptosis in rat placenta – ScienceDirect --	0.128 ug/mL	Ehrsson H, Hassan M, Ehrnebo M, Beran M. Busulfan kinetics. Clin Pharmacol Ther. 1983;34:86-89.
Cyclophosphamide	Alkylating agent	Listed MEFL-positive control (rat/rabbit/human marker).	Bone malformations; embryo-fetal resorptions; embryo lethal	-	Cytoxan : 106 ug/mL	Chan KK, Hong PS, Tutsch K, Trump DL. Clinical pharmacokinetics of cyclophosphamide and metabolites with and without SR2508. Cancer Res. 1994;54:6421-6429.
Fluconazole	Antifungal	Listed MEFL-positive control (rat/rabbit/human marker).	Embryo lethal; abortions	---	9.07 ug/mL	FDA, United States. Pharmacology Review NDA 019949 (26 Jan 1990a), p. 7, 13. FDA, United States. Clinical Pharmacology Review NDA 019949 (17 Apr 1990b), p. 7, 50 – 52.
5-Fluorouracil	Antimetabolite	Listed MEFL-positive control (rat/rabbit/human marker).	Bone malformations; embryo-fetal resorptions	---	29 ug/mL	Schaaf LJ, Dobbs BR, Edwards IR, Perrier DG. Nonlinear pharmacokinetic characteristics of 5-fluorouracil (5-FU) in colorectal cancer patients. Eur J Clin Pharmacol. 1987;32:411-418. Bocci G, Danesi R, Di Paolo AD, Innocenti F, Allegrini G, Falcone A, et al. Comparative pharmacokinetic analysis of 5-fluorouracil and its major metabolite 5-fluoro-5,6-dihydrouracil after conventional and reduced test dose in cancer patients. Clin Cancer Res. 2000;6:3032-3037.
Hydroxyurea	Antimetabolite	Listed MEFL-positive control (rat/rabbit/human marker).	Bone malformations; embryo-fetal resorptions	---	52 ug/mL	MHRA Public Assessment Report PL 10880/128-9, page 48.
Methotrexate	Antimetabolite	Classic embryo-fetal toxicant; MEFL-positive control (rat/rabbit/human marker).	Bone malformations; increased resorptions; embryo lethal	---	2.14 ug/mL	Campbell MA, Perrier DG, Dorr RT, Alberts DS, Finley PR. Methotrexate: bioavailability and pharmacokinetics. Cancer Treat Rep. 1985;69:833-838.
Valproic acid	Antiepileptic	Listed MEFL-positive control (rat/rabbit/human marker).	Bone/organ malformations; resorptions	--	205 ug/mL	Nitsche V, Mascher H. The pharmacokinetics of valproic acid after oral and parenteral administration in healthy volunteers. Epilepsia. 1982;23:153-162

Negative control (Negative DART Compounds)

Compound (ICH list)	Therapeutic class	Cmax	References
Sax gliptin	Antihyperglycemic	0.024 ug/mL	U.S. Label Onglyza.
Vildagliptin	Antidiabetic	245 ng/mL (oral), 525 ng/mL (IV)	He YL. Clinical pharmacokinetics and pharmacodynamics of vildagliptin. Clin Pharmacokinet. 2012 Mar 1;51(3):147-62. doi: 10.2165/11598080-000000000-00000. PMID: 22339447.
Cetirizine	Antihistamine	0.33 ug/mL	FDA, United States. Clinical Pharmacology and Biopharmaceutics Review of NDA 021621/S-000 (31 Oct 2003) (Clinical AUC, single dose, page 11).
Acetaminophen	NSAID	23.7 ug/mL	Rayburn W, Shukla U, Stetson P, Piehl E. Acetaminophen pharmacokinetics: comparison between pregnant and nonpregnant women. Am J Obstet Gynecol. 1986 Dec;155(6):1353-6. doi: 10.1016/0002-9378(86)90173-0. PMID: 3789044.
Metformin	Antihyperglycemic	1.5 ug/mL	Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 1996 May;30(5):359-71. doi: 10.2165/00003088-199630050-00003. PMID: 8743335.

Clinically Used Drug

Compound (ICH list)	Therapeutic class	Cmax	References
Pravastatin	HMG-CoA	0.038 ug/mL	Quion JA, Jones PH. Clinical pharmacokinetics of pravastatin. Clin Pharmacokinet. 1994 Aug;27(2):94-103. doi: 10.2165/00003088-199427020-00002. PMID: 7955780.
Indomethacin	NSAID	3 ug/mL	Helleberg, L. Clinical Pharmacokinetics of Indomethacin. Clin Pharmacokinet 6, 245–258 (1981). https://doi.org/10.2165/00003088-198106040-00001
Mifepristone	Antiprogesterone steroid	2 ug/mL	Heikinheimo O. Clinical pharmacokinetics of mifepristone. Clin Pharmacokinet. 1997 Jul;33(1):7-17. doi: 10.2165/00003088-199733010-00002. PMID: 9250420.
Aspirin	NSAID	4 ug/mL	Boelig RC, Kaushal G, Rochani A, McKenzie SE, Kraft WK. Aspirin pharmacokinetics and pharmacodynamics through gestation. Am J Obstet Gynecol. 2024 Sep;231(3):344.e1-344.e16. doi: 10.1016/j.ajog.2023.12.028. Epub 2023 Dec 23. PMID: 38145726; PMCID: PMC11193839.