Nonclinical Studies – What animal studies can (and can't) tell us about drugs in milk

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Disclosure

I am a regulatory toxicology consultant, advising pharmaceutical companies on non-clinical testing strategies during drug development

Presentation Outline

- DART Testing Requirements
- Studies with lactational animals
- Extrapolation to human risk
  - Drugs in milk across species
- Concluding remarks

PLLR Requirements

- Risk Summary – Lactation
  - Effects on milk production
  - Presence of drug in human milk
  - Effects on the breastfed child
  - *Animal data not included if human data exist*
  - *Animal data, when included, should only state presence or absence of drug in milk*

ICH S5(R2): Reprotox Testing Guidelines

Evaluate the entire reproductive life cycle, including the following….

A. **Premating to conception** - adult male and female reproductive functions, development and maturation of gametes, mating behavior, fertilization

B. **Conception to implantation** - adult female reproductive functions, preimplantation development, implantation

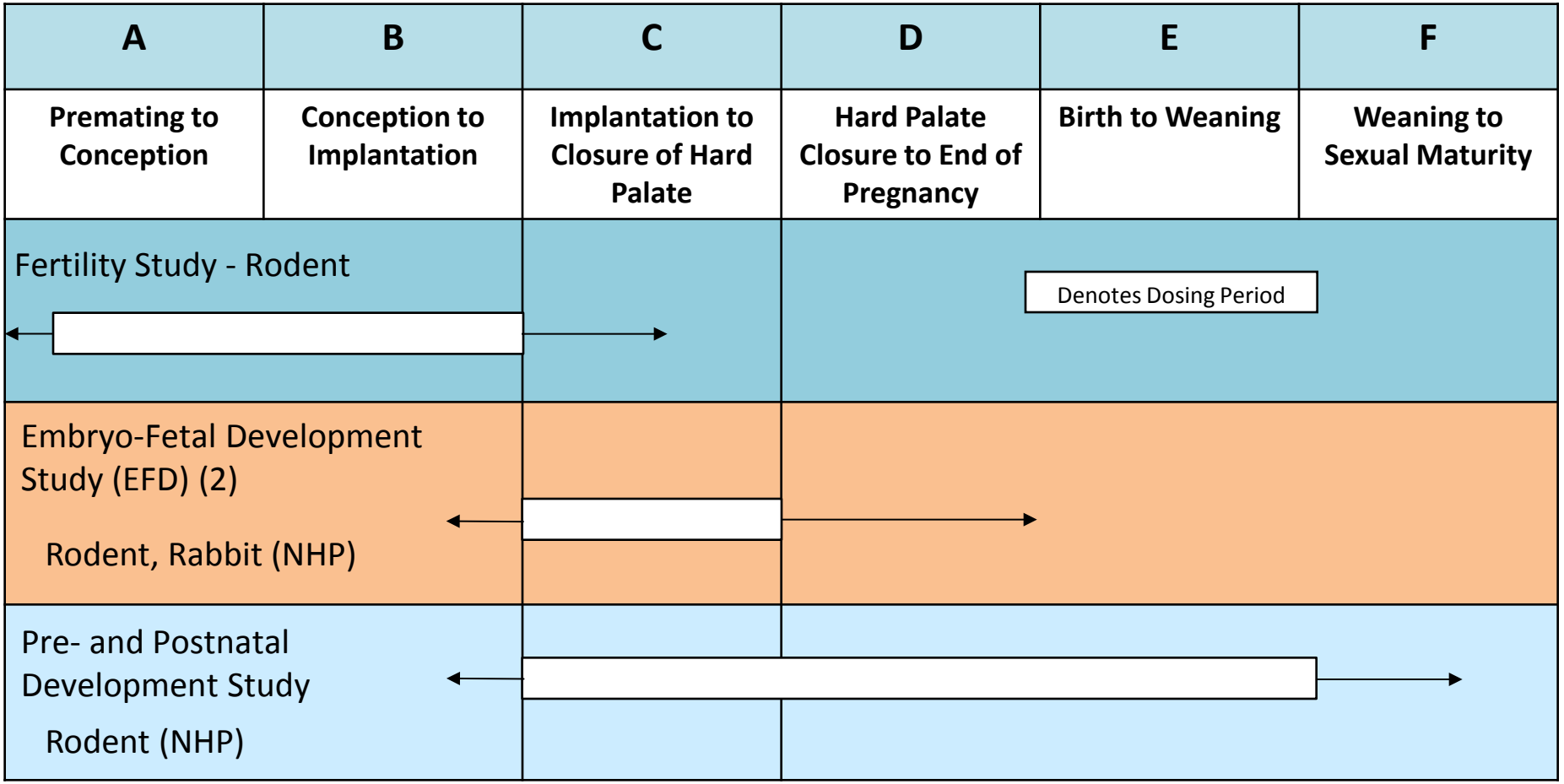
C. **Implantation to closure of the hard palate** - adult female reproductive functions, embryonic development, major organ formation

D. **Closure of the hard palate to the end of pregnancy** - adult female reproductive functions, fetal development and growth, organ development and growth

E. **Birth to weaning** - adult female reproductive functions, neonate adaptation to extrauterine life, preweaning development and growth

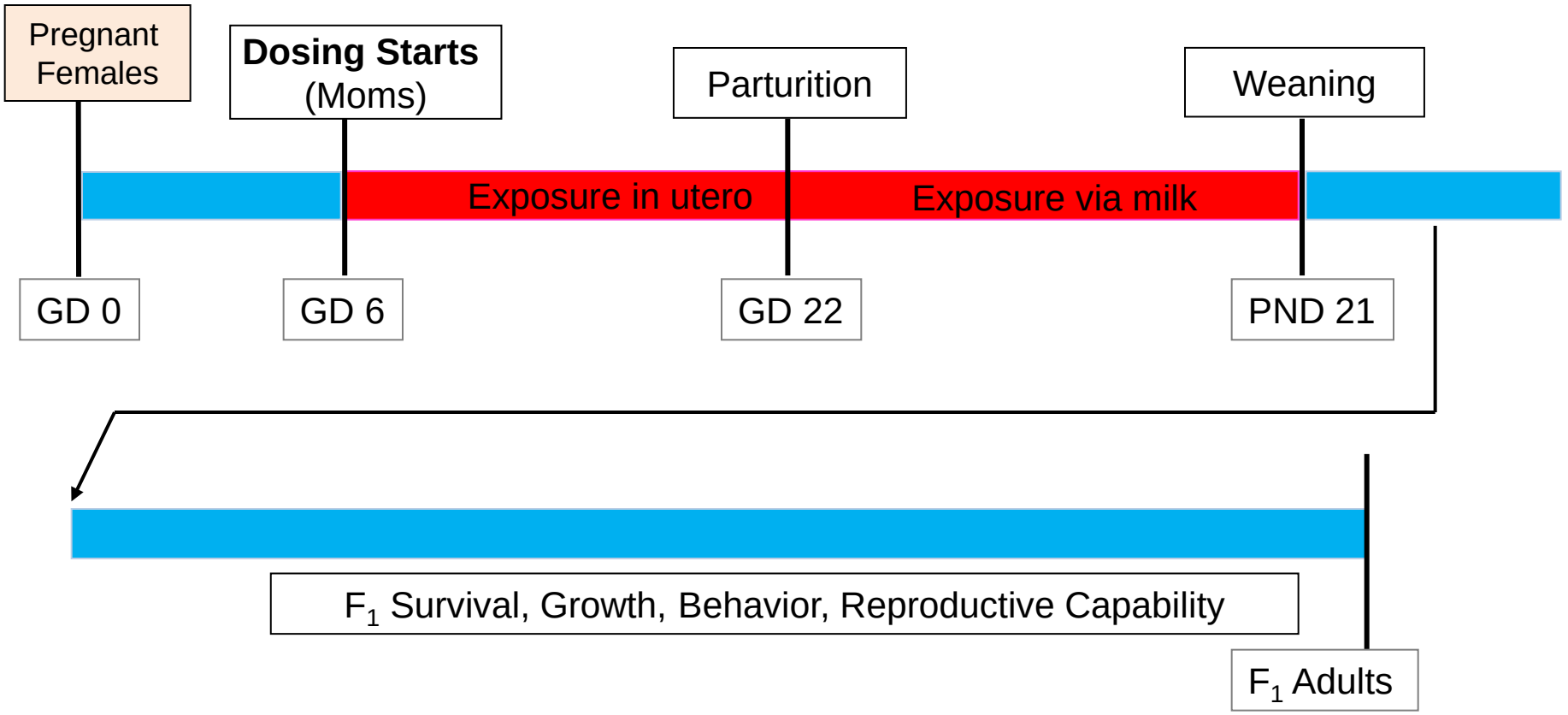
F. **Weaning to sexual maturity** - postweaning development & growth, adaptation to independent life, attainment of full sexual function

Standard Study Designs ICH S5(R2)



Pre-/Postnatal Development Study in the Rat

Group size = 24 females



PPN Endpoints

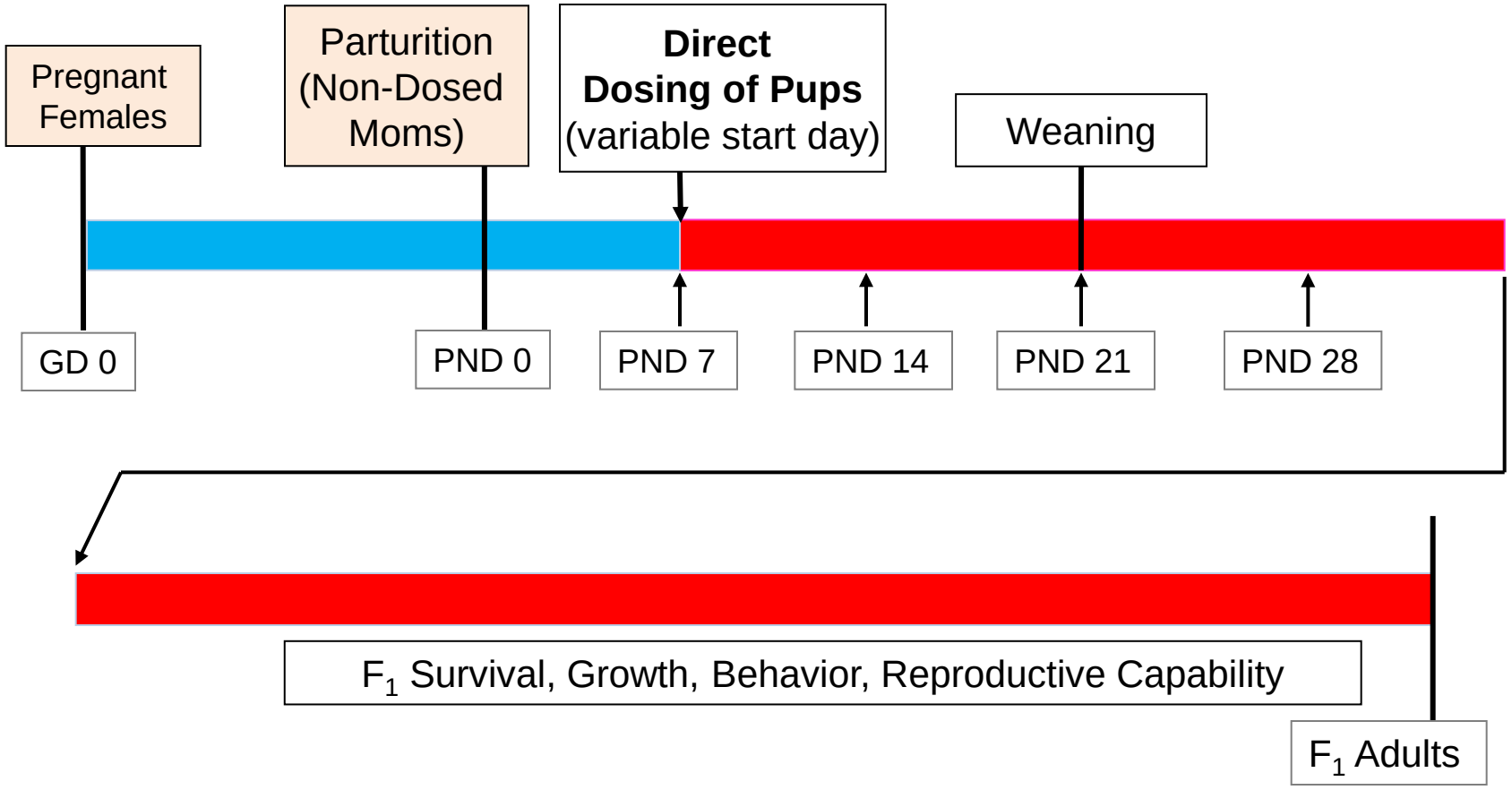
F_0 Mothers	F_1 Offspring
Adult Toxicity	Survival
Gestation, Parturition	Growth
Lactation Process	Behavior • motor activity • learning and memory • Reflex development
	Reproduction
(*Drug in Milk*)	Systemic Exposure

- Drug in milk not typically measured
- Systemic exposure in nursing pups measured more often, but not universally
- Data in offspring confounded by pre- and postnatal exposure

Juvenile Toxicity Study

- Conducted to support pediatric clinical trials
- Direct dosing to juvenile animals
- Dosing can start as early as newborn
  - But – age of dosing will be determined by age of youngest children in clinical trials
- Toxicity and systemic exposure data collected

Juvenile Toxicity Study in the Rat
Direct Dosing of Pups



Juvenile Toxicity Endpoints

Juvenile Animals
Survival
Growth
Behavior • motor activity • learning and memory • Reflex development
Reproduction
Systemic Exposure

Mothers not dosed – no ability to evaluated drug in milk

Available Nonclinical Data

Pre-Postnatal Study	Juvenile Toxicity Study
Drug in milk not typically measured **- but** it could be	Drug levels in milk not available
Offspring exposures are available	Offspring exposures are available
Juvenile toxicity data exists, **but** confounded by exposure period	Juvenile toxicity data exists, not confounded by in utero exposure
	But - age varies at start of dosing, not always applicable to breastfed baby

No one perfect study to address lactation/ breastfed baby

But – data are available!

PLLR Requirements

- Risk Summary – Lactation
  - Effects on milk production
  - Presence of drug in human milk
  - Effects on the breastfed child
  - Animal data not included if human data exist
  - Animal data, when included, should only state presence or absence of drug in milk
  - "*Due to species-specific differences in lactation physiology, animal lactation data typically do not reliably predict levels in human milk; however, animal lactation data can be helpful in predicting whether a drug and/or its active metabolite(s) will be present in human milk.*"

Drug Secretion into Milk[1]

Mechanisms of Drug Secretion	
Simple diffusion	Carrier-mediated diffusion
Pinocytosis	Reverse pinocytosis
Active transport	

Drug Characteristic	Milk/Plasma (M/P) Ratio
Highly lipid-soluble	**~1**
Small, water soluble drugs (MW<200)	**~1**
Weak acids and bases	**~1**
Highly protein-bound in maternal serum	**<1**
Actively transported drugs	**>1 or <1** (depends on direction)

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[1]From: *Drugs During Pregnancy and Lactation, Treatment Options and Risk Assessment*, 3rd Edition, Schaefer, Peters, Miller, eds.

Species Comparison for Lactation

- Lack of good information in the literature on species differences, in general
- Similarities in hormonal control of milk production
- Species differences:
  - Mammary gland anatomy
  - Storage and release of milk into ducts
  - Protein and fat composition of milk
- Not clear how these factor into drug levels in milk
- Drug concentration cross-species comparisons lacking

Ito et al., 2013 Study

Pharm Res, 30:2410-2422

Purpose: Analyze concentrations of 27 drugs in mouse milk and compare to human milk concentrations

Methods:

- Dose mice with implanted micro-osmotic pumps
- Measure M/P ratio, and compare to human M/P ratio
- Compare actual concentrations with those predicted by **models using physicochemical parameters of drug**[1]
- Measure lipid and protein-unbound fractions in mouse and human plasma and milk

[1] Koshimichi (2011) Drug Met Distr, 39:2370–2380

Ito et al., 2013, cont.

Results:

1. M/P ratio generally 2-fold higher in mice than humans
   - *Unbound* M/P ratio similar between mice and humans
   - Difference predictable based on differences in protein and lipid content in mouse vs. human milk

2. 18 of 27 drugs – concentrations close to values predicted by pH-partition model, when corrected for protein and lipid differences
   - **Suggests drug secretion mediated by diffusion**

3. 9 of 27 drugs – concentrations were not close to predicted values
   - **Suggests drug secretion mediated by active transport**

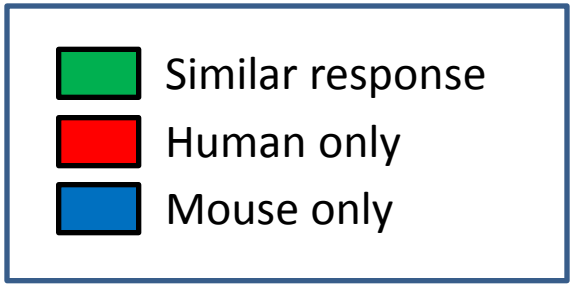
Ito et al., 2013, cont.

- Higher M/P than predicted:
  - Cimetidine, clindamycin, aclycovir, terbutaline
  - Suggests active transport – BCRP (ABC) or other
- Lower M/P than predicted:
  - Cefotaxime, trazodone, metformin, tripolidine, verapamil
  - Suggests absorptive reuptake transport

Ito et al., 2013, cont.

- Higher M/P than predicted:
  - **Cimetidine**[1], **clindamycin**, **aclycovir**, **terbutaline**
  - Suggests active transport – BCRP or other
- Lower M/P than predicted:
  - **Cefotaxime**, **trazodone**, **metformin**, **tripolidine**, **verapamil**
  - Suggests absorptive reuptake transport
- **Considerable species differences**

[1]Dostal 1990, McNamara 1992, Oo 1995



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Conclusions – Animal to Human Extrapolation

- Animal studies can generate data on lactation, drugs in milk, and health of newborn
- Lactation – cross-species extrapolation possible
- Health of breast-fed child
  - Data can be generated on exposures and toxicity in offspring
  - Risk assessment based on animal data is possible
  - Human studies would be best, but could be difficult
  - Animal data might be useful in absence of clinical data

Conclusions, conc.

- Drug concentrations in milk
  - Gaps exist in our knowledge of cross-species concordance
  - Species differences exist in composition of milk, secretory processes, etc.
  - Drugs that diffuse – extrapolation possible (M/P ratio)
  - Drugs secreted by active transport – need more data
  - Biggest gap – how to tell which category the drug falls into
  - **Increased urgency for human lactation studies**
  - **Closing data gaps could facilitate extrapolation in future**
- PLLR – clarity needed around expectations for generating and using animal data in Lactation Section