REGULATORY UPDATES IN DEVELOPMENT AND REPRODUCTIVE TOXICOLOGY FOR HUMAN PHARMACEUTICALS

SFT, 5 November 2019

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ICH
harmonisation for better health

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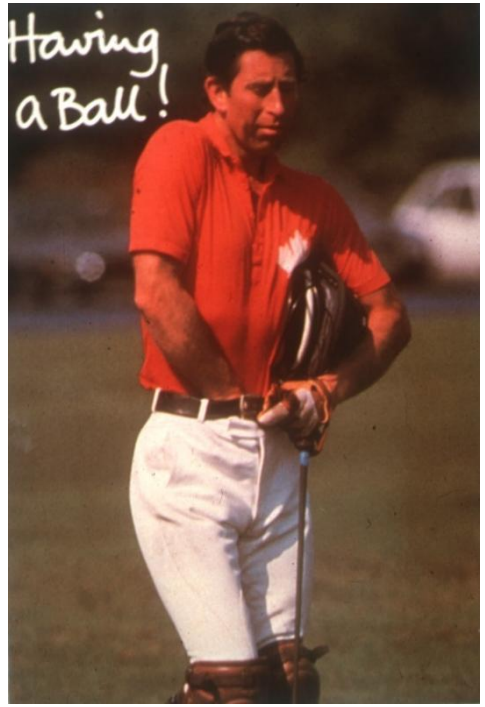
Disclaimer

Some of the views expressed in this talk are those of the presenter (me alone)

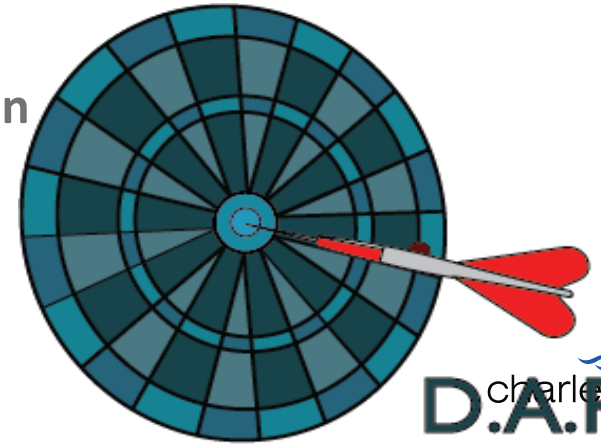
In the beginning, 1960s: Thalidomide tragedy

Catholic University of America

Niños con focomelia, consecuencia de la exposición a la talidomida



- 1966: FDA, Guidelines for Reproduction studies for safety evaluation of drugs for human use
  - ➢ **A three-segment design**
- 1993: ICH S5, originally issued, **Detection of Toxicity to Reproduction** for Medical Products
- Updates 1995, 2000 (R2): Detection of Toxicity to Reproduction for Medical Products **& Toxicity to Male Fertility**
- R3: Detection of **Reproductive And Developmental Toxicity** for Human Pharmaceuticals → 2019, 2020 ?



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General Principles

- Expands scope to include vaccines* and Biopharmaceuticals

  *Vaccines (and their novel constitutive ingredients) for infectious diseases

- Aligns with more recent ICH guidelines: e.g. M3, S6, S9

- Elaborates on use of exposure margins in dose selection

- Includes a section on risk assessment

- Gives recommendations on the use of alternative methods to replace or defer animal tests (3Rs)

ABBREVIATIONS AND ACRONYMS

DART	Developmental And Reproductive Toxicology
EFD, pEFD	Embryo-Fetal Development, preliminary EFD
FEED	Fertility and Early Embryonic Development
MEFL	Malformation or Embryo-Fetal Lethality
PPND, ePPND	Pre- and Post-Natal Development, enhanced PPND
TK	Toxicokinetics
MOA	Mode Of Action
WOE	Weight Of Evidence
MRHD	Maximum Recommended Human Dose
JAS	Juvenile Animal Study

DESIGN OF IN-VIVO MAMMALIAN STUDIES

- No significant changes from ICH S5(R2)
  - « Routine Species »: Rat, Rabbit, Mouse
  - « Non-routine Species »: Cynomolgus monkey (NHP), minipig (new)

    NHP only used as last resort: Use of surrogate molecules or GM animals encouraged (but still rare)

- 3-study design is usually appropriate

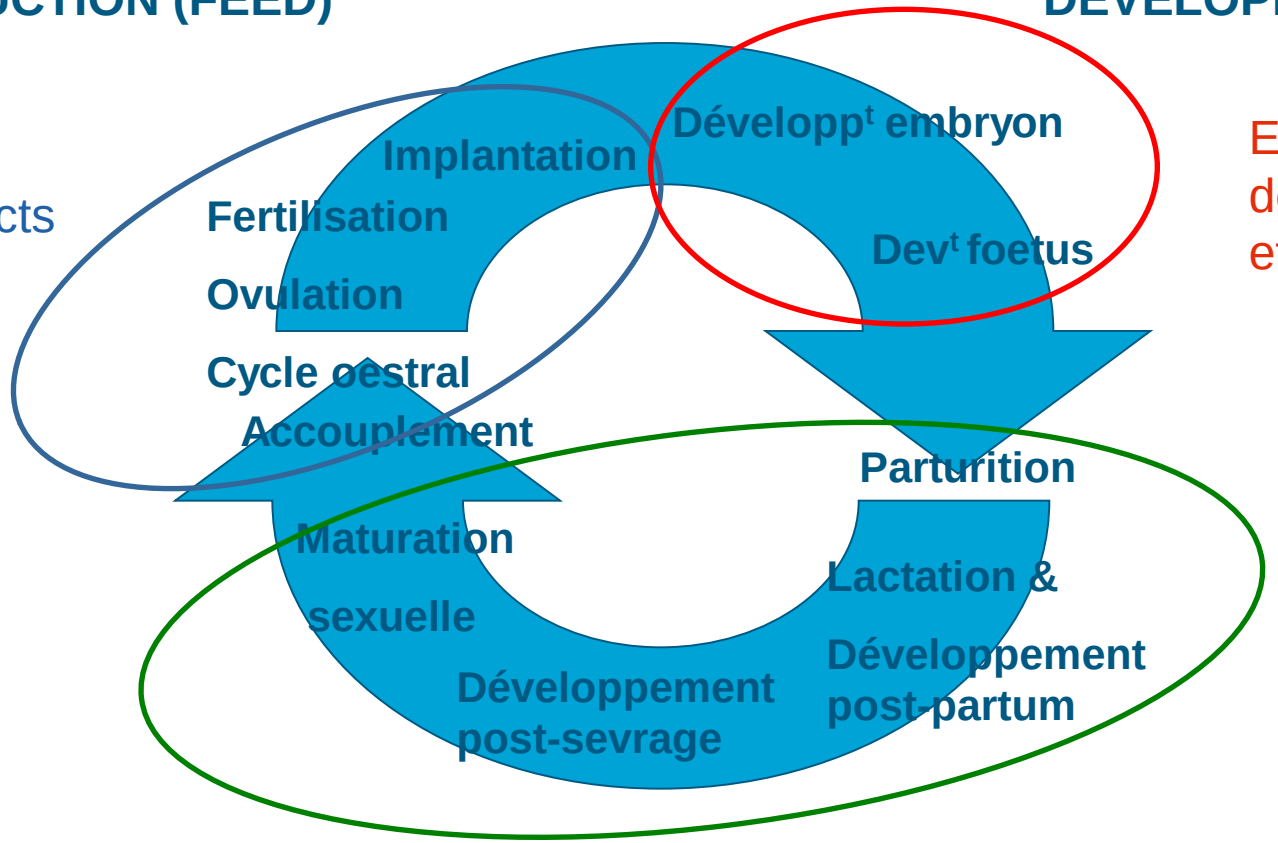
- Combinations are possible:
  - FEED + EFD most common
  - ePPND in NHP

3 study design

REPRODUCTION (FEED)

DEVELOPMENT (EFD)

Fertility and early embryofetal development effects

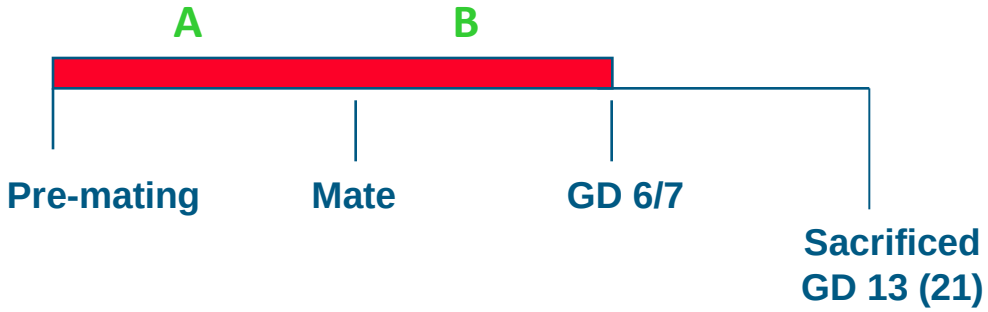


Embryofetal development effects

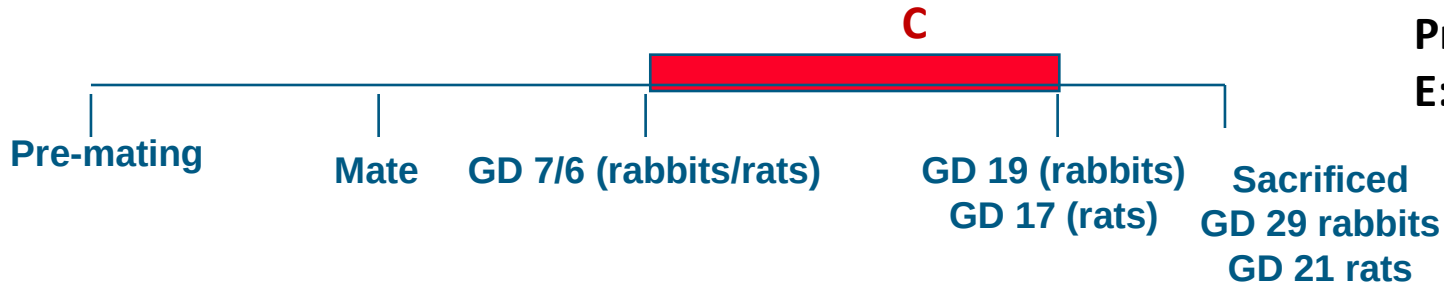
Pre- and Post-Natal Development Effects (PPND)

3-in vivo mammalian study design usually appropriate cf. ICH S5(R2)

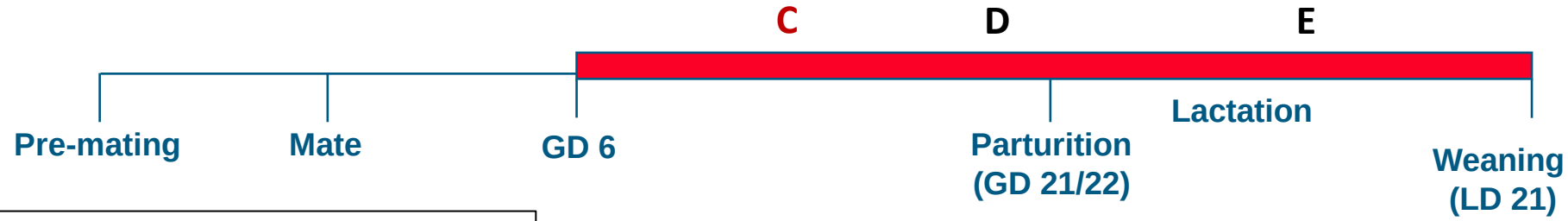
1. FEED: Fertility and early embryonic toxicity study (R)



2. EFD: Embryo-fetal development toxicity study (R + NR)



3. PPND: Pre-and postnatal developmental toxicity study (R)



A: PreMating to Conception
B: Conception to Implantation

C: Implantation to closure of Hard Palate (main organogenesis)

D: Hard closure Palate to end of Pregnancy
E: Birth to Weaning

= 4 or 5 studies for small molecules (see next slide)

FERTILITY AND EARLY EMBRYONIC DEVELOPMENT (FEED)

16 M & F / group

At least 2 weeks of dosing of males before mating, longer if effects expected on testis

May dose Males and Females in same study, or separate studies (arms)

Histopathology and sperm analysis optional

Males may be evaluated by mating in 13-week general tox study

- Separate female study

Mating not feasible in NHPs for biopharmaceuticals

- Fertility evaluation based on histopathology in repeated-dose studies (ICH S6)
- Repeated-dose studies should include mature animals
  - Not necessary for drugs to treat advanced cancer (ICH S9)

EMBRYO-FETAL DEVELOPMENT (EFD) STUDIES

2 species still required (unless NHP is only responsive species)

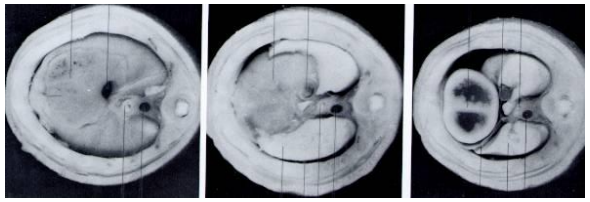
- 16 to 20 litters for rodents & rabbits
- Approximately 16 pregnant females / group (NHP)

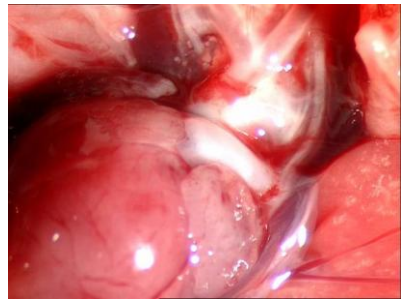
If drug is not active in any species, EFD studies in 2 species still required (off-target)

→ MEFL in one species at therapeutically-relevant exposures can be sufficient

« Although it is preferable to examine all rodent fetuses for both soft tissue and skeletal alterations (if methods allow), it is acceptable to submit 50% of fetuses in each litter to separate examinations »

- Soft tissues: fixed → fresh examinations





IRFM* Accreditation

***IRFM: International Register of Fetal Morphologists**

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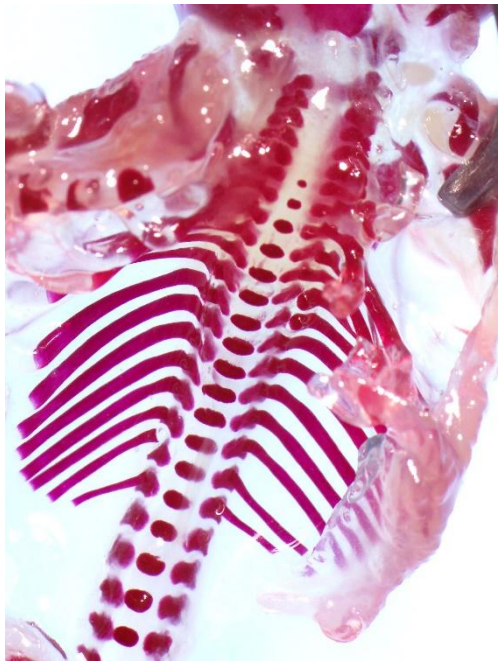
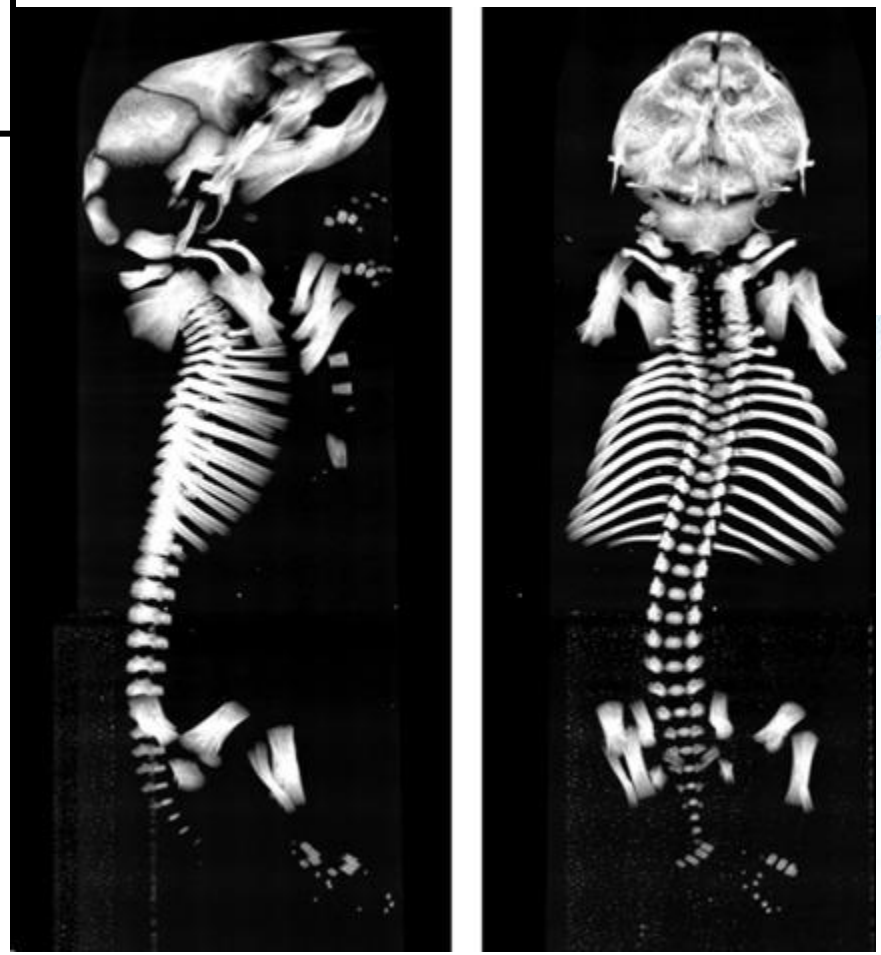
SKELETAL EXAMINATION

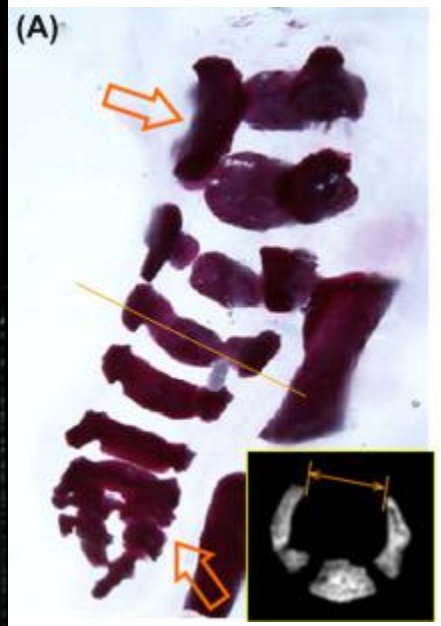
Alizarin red staining (or double staining)

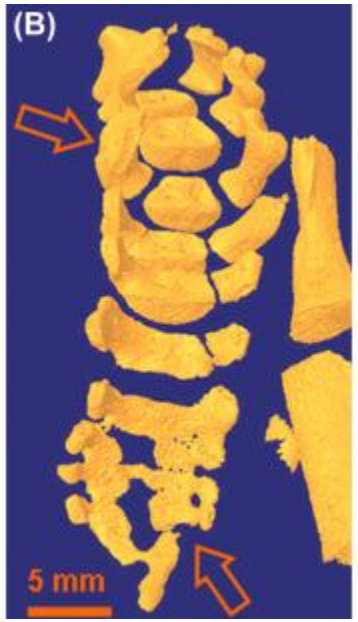
versus micro-CT

Regulatory acceptance
Not used in routine
Transient skeletal findings









Micro-CT: Micro-Computer Tomography (scan)

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PRE- AND POST-NATAL DEVELOPMENT (PPND) STUDY

For biopharmaceuticals with no pharmaceutical activity in other species:

ePPND in NHP replaces EFD and PPND studies (cf. ICH S6)

- At least 2 dose groups + control
- Approximately 16 pregnant females / group (ICH S6(R1) states 6-8 infants / group at PND 7)
- Infant exposure determination and JAS endpoints potentially useful

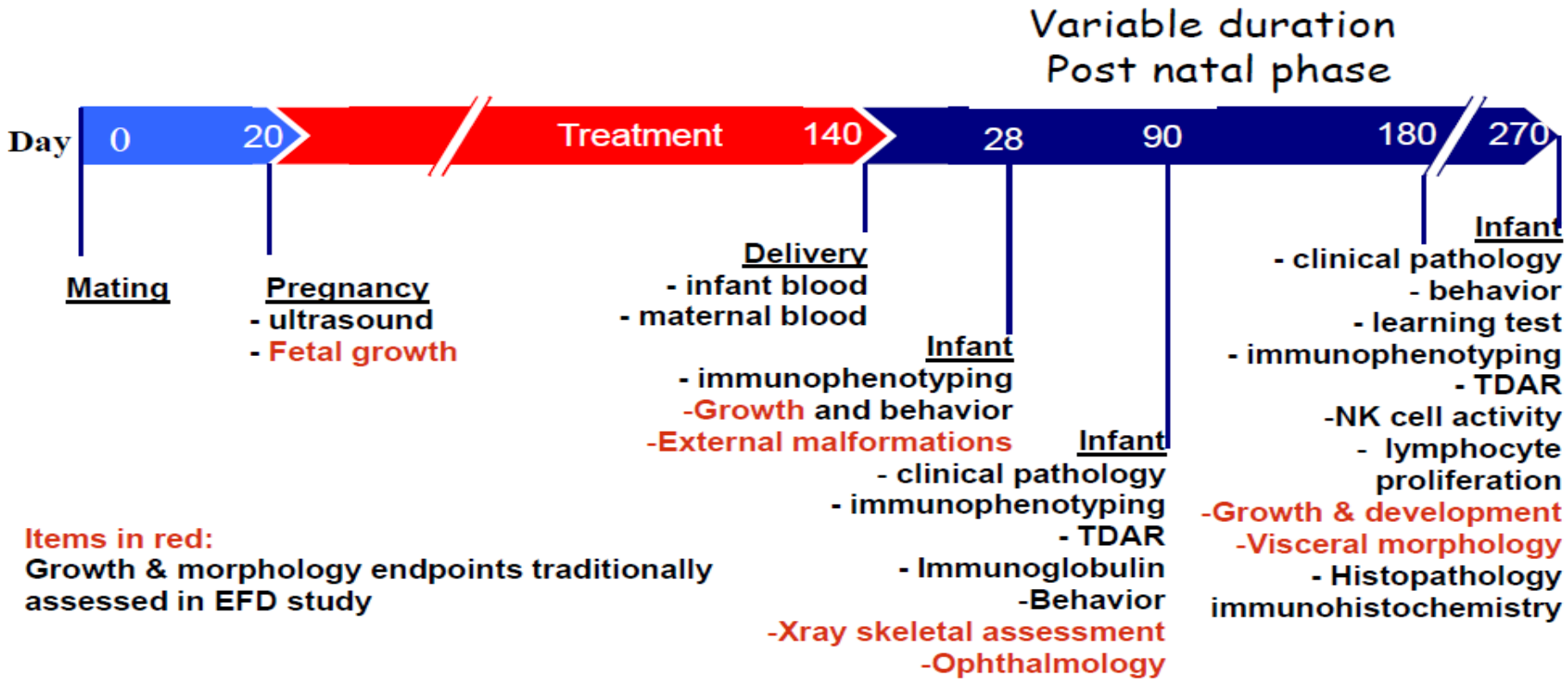
Juvenile study endpoints can be included to avoid separate JAS

- Rarely (never) useful for small molecules since pediatric plan (PIP) is required long before PPND

Pup exposure assessment (and/or milk analysis) remains optional (3Rs?)

From J. Stewart, 2009

Enhanced PPND



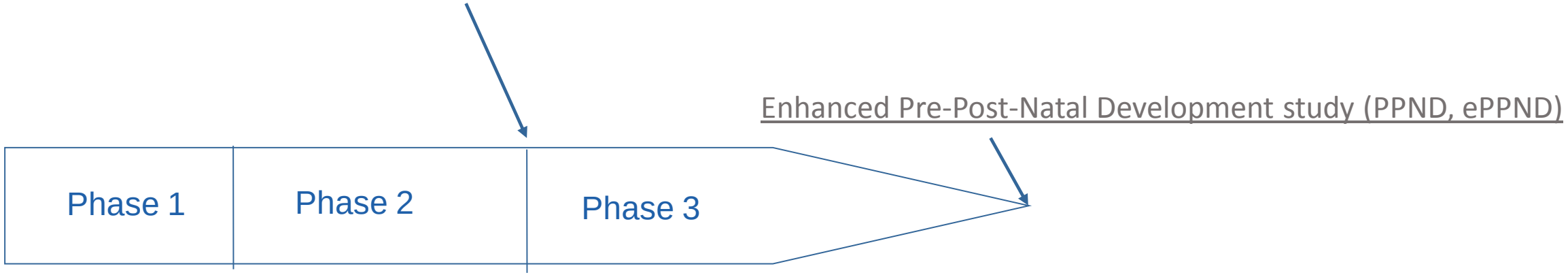
Post natal phase duration & endpoints designed to address specific mAb concerns eg ontogeny of immune system, CNS development etc

mAb	Outcome
Rituximab	Expected B-cell depletion in neonates shown to be transient
Adalimumab	No effects in infants in ePPND; TNF KO mice had shown immune impairment

ICH-M3: timing des études en fonction des essais cliniques

Biopharmaceuticals (only active in NHP):

If no sufficient preventive precautions, EFD completed or an interim report of the ePPND (after delivery)



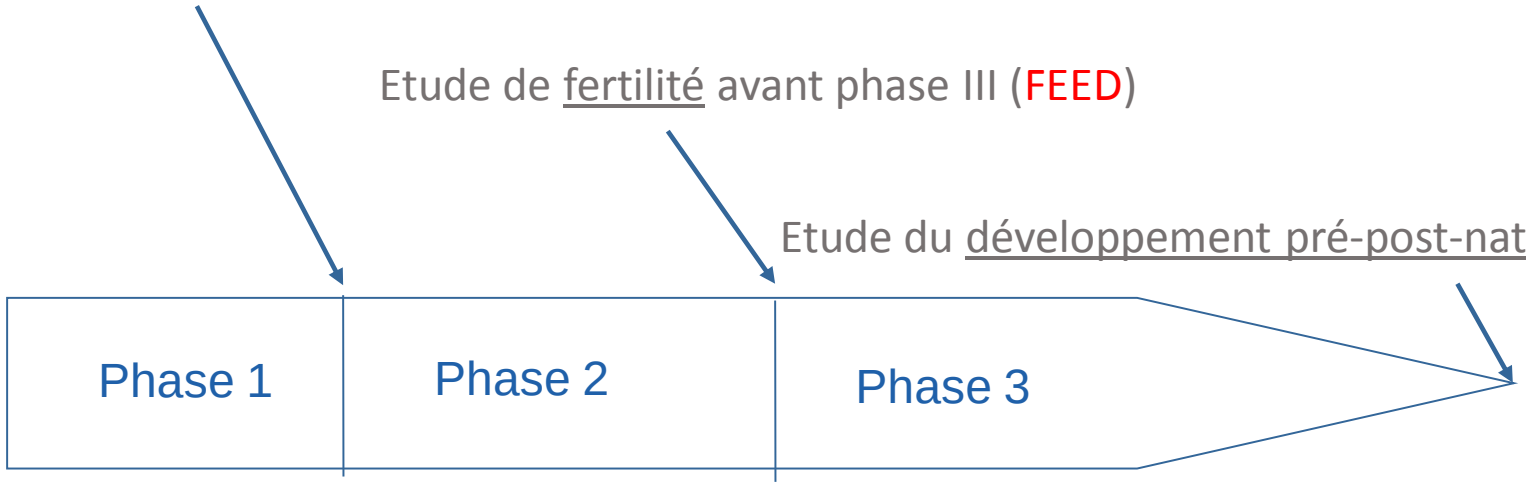
Fertility evaluation based on histopathology in repeated-dose studies (cf. ICH S6: at least 3 months + sexually matures).

ICH-M3: timing des études en fonction des essais cliniques

Étude du développement embryofœtal (EFD) inclusion de femmes en âge de procréer (généralement en phase II), sauf si absence de risque de grossesse et durée courte (USA) → possibilité de résultats préliminaires (pEFD) pour petits effectifs/durée limitée de phase II (≤ 150 WOCBP*, ≤ 3 months)

Etude de fertilité avant phase III (FEED)

Etude du développement pré-post-natal avant mise sur le marché (PPND, ePPND)



*WOCBP: Women Of Child Bearing Potential

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ICH-S5(R3): timing des études en fonction des essais cliniques

(pEFD) inclusion de femmes en âge de procréer (sans restriction de l'effectif)

Etude de fertilité avant phase III (FEED)

Étude du développement embryofœtal (EFD)

Etude du développement pré-post-natal avant mise sur le marché (PPND, ePPND)

pEFD (requirements of ICH M3)

- At least 6 litters per group
- External & internal soft tissue exams of fetuses required
- TK & skeletal examinations optional

Additional endpoints in at least one GLP pEFD study in a pharmacologically relevant species

- Increased group size (n not specified)
- Skeletal examinations
- TK

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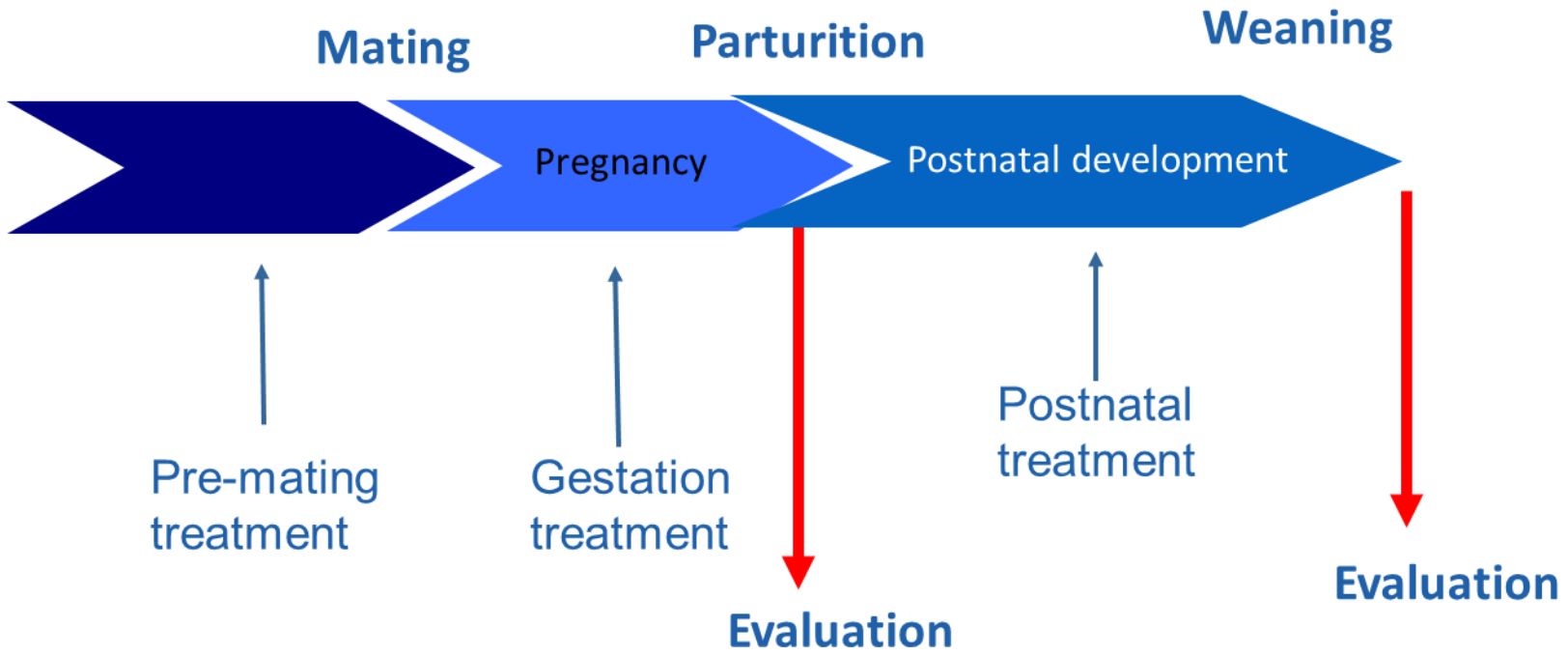
Vaccines: In traditional species (ex. Rabbit)

There are no requirements to assess effects on male fertility.

Combined Developmental toxicity study before MAA

Design:



DOSE SELECTION (ANNEX 1)

High dose

Based on 1 to 5 endpoints: Toxicity (maternal/parental), saturation of exposure, max feasible dose (limit dose 1 mg/kg), exposure margin (new)

➢ For small molecules:

- Exposure in pregnant animals **> 25-fold** (AUC or Cmax) than the MRHD can be used for the high dose
- GLP-compliant TK data in pregnant animals are required
  - May be generated in pEFD or in Definitive study

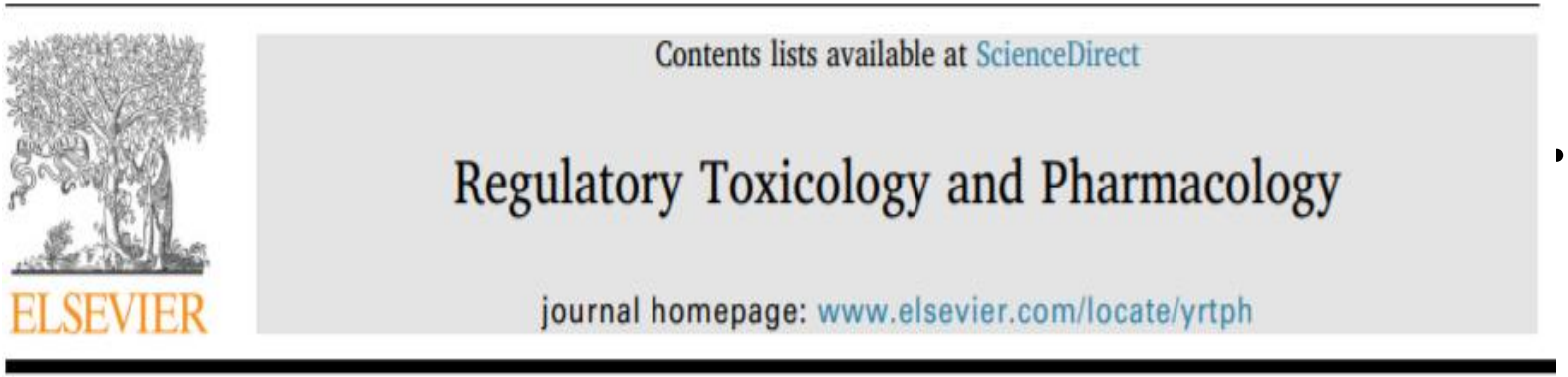
➢ For biopharmaceuticals (as specified in ICH S6)

- The maximum intended pharmacological effect in the preclinical species or a 10-fold exposure multiple over that to be achieved in the clinic, whichever is higher.

Lower dose levels

- generally to establish a NOAEL for DART and dose-response relationship, when possible
- Low dose generally provide a 1 to 5-fold margin over human exposure at MRHD
- Doses resulting in sub-therapeutic exposure not usually useful

https://doi.org/10.1016/j.yrtph.2019.04.005, available on line 11 April 2019


Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Analysis of exposure margins in developmental toxicity studies for detection of human teratogens

Paul A. Andrews[a,*], Diann Blanset[b], Priscila Lemos Costa[c], Martin Green[d], Maia L. Green[e,1], Abigail Jacobs[d], Rajkumar Kadaba[f], Jose A. Lebron[e], Britta Mattson[e], Mary Ellen McNerney[g], Daniel Minck[d], Luana de Castro Oliveira[c], Peter T. Theunissen[h], Joseph J. DeGeorge[e,2]

- **6-fold exposure margin** in DART studies sufficed to detect teratogenic hazards for 22 human teratogens
- **These data support the principles of risk assessment**:

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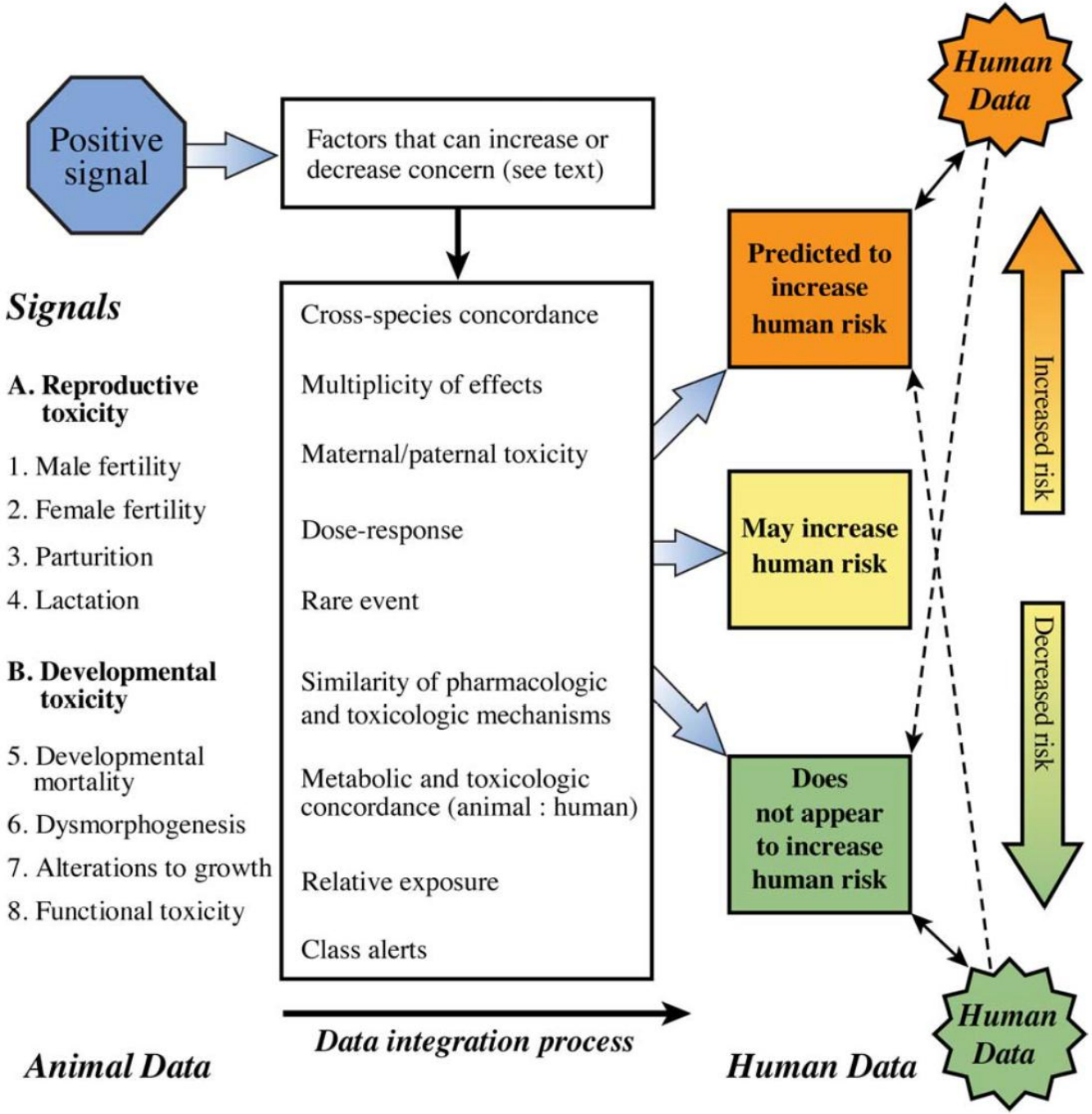
https://www.fda.gov/media/72231/download



Irreversible development endpoints, i.e. embryo-fetal death or malformation, are of high concern

High concern when NOAEL <10-fold exposure (above 10-fold margin concern reduced)

Effects >25-fold exposure-based endpoint of minor concern

Generally, transient findings (e.g. structural variations, such as wavy ribs in rodents) of less concern when isolated

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ALTERNATIVE ASSAYS

Potential uses (to date):

- Confirmation of a suspected adverse effect on EFD based on MoA (fig 1)
- When toxicity in animal species precludes human-relevant systemic exposures
- Support for a WOE assessment when animal studies show equivocal findings
- As partial support for inclusion of WOCBP in clinical trials of phase 2 (up to 150 WOCBP for up to 3 months): « Qualified alternative assays which predict the outcome in 1 species »
- Pharmaceuticals for severely debilitating, life-threatening or late-life onset diseases (fig 2)
- Can be used to elucidate mechanisms of toxicity & assist translation of non-clinical findings to human risk (already used in drug discovery)
- Qualification defined by the characterization of biological mechanisms covered & chemical applicability domain

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HESI-SPONSORED EVALUATION OF ZEBRAFISH ASSAY

https://doi.org/10.1016/j.reprotox.2019.02.004, available online on March 2019

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

A multi-institutional study benchmarking the zebrafish developmental assay for prediction of embryotoxic plasma concentrations from rat embryo–fetal development studies

Steven Cassar[a,*], Manon Beekhuijzen[b], Bruce Beyer[c], Robert Chapin[d], Martina Dorau[e], Alan Hoberman[f], Eckart Krupp[e], Isabelle Leconte[g,1], Don Stedman[d], Christine Stethem[h], Daphne van den Oetelaar[b], Belen Tornesi[i]

- The ZF development assay predicted (within 1-log) the rat maternal exposure levels associated with embryotoxicity 75% of the time
  - Actually comparable with rat-rabbit concordance for embryotoxic plasma levels (80%)
- Used « Daston list »*

*A current list of compounds in training and test sets, including 39 +ve teratogens (shown to induce MEFL in animals (in the absence of overt maternal toxicity) and/or in humans to qualify Alternative Assays (problems to list negative compounds)

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SUMMARY OF MAJOR CHANGES

Extended scope: biologics, vaccines,..

Addition of exposure margin based limit dose

Guidance on qualification and use of alternative methods

An expanded pEFD in at least 1 species, plus a routine pEFD in other species can allow inclusion of unlimited number of WOCBP up to Phase 3

Addition of sections on data interpretation and risk assessment

- Actually unify principles already applied by various agencies today (FDA at least from 2011)

Contributes to reduce the number of animals used for the DART evaluation

MERCI !

References:

https://database.ich.org/sites/default/files/S5-R3_EWG_Draft_Guideline.pdf

https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

https://database.ich.org/sites/default/files/S9_Guideline.pdf

https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf

https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Guidance-for-Industry--Considerations-for-Developmental-Toxicity-Studies-for-Preventive-and-Therapeutic-Vaccines-for-Infectious-Disease-Indications.pdf

https://onlinelibrary.wiley.com/doi/epdf/10.1002/bdr2.1350

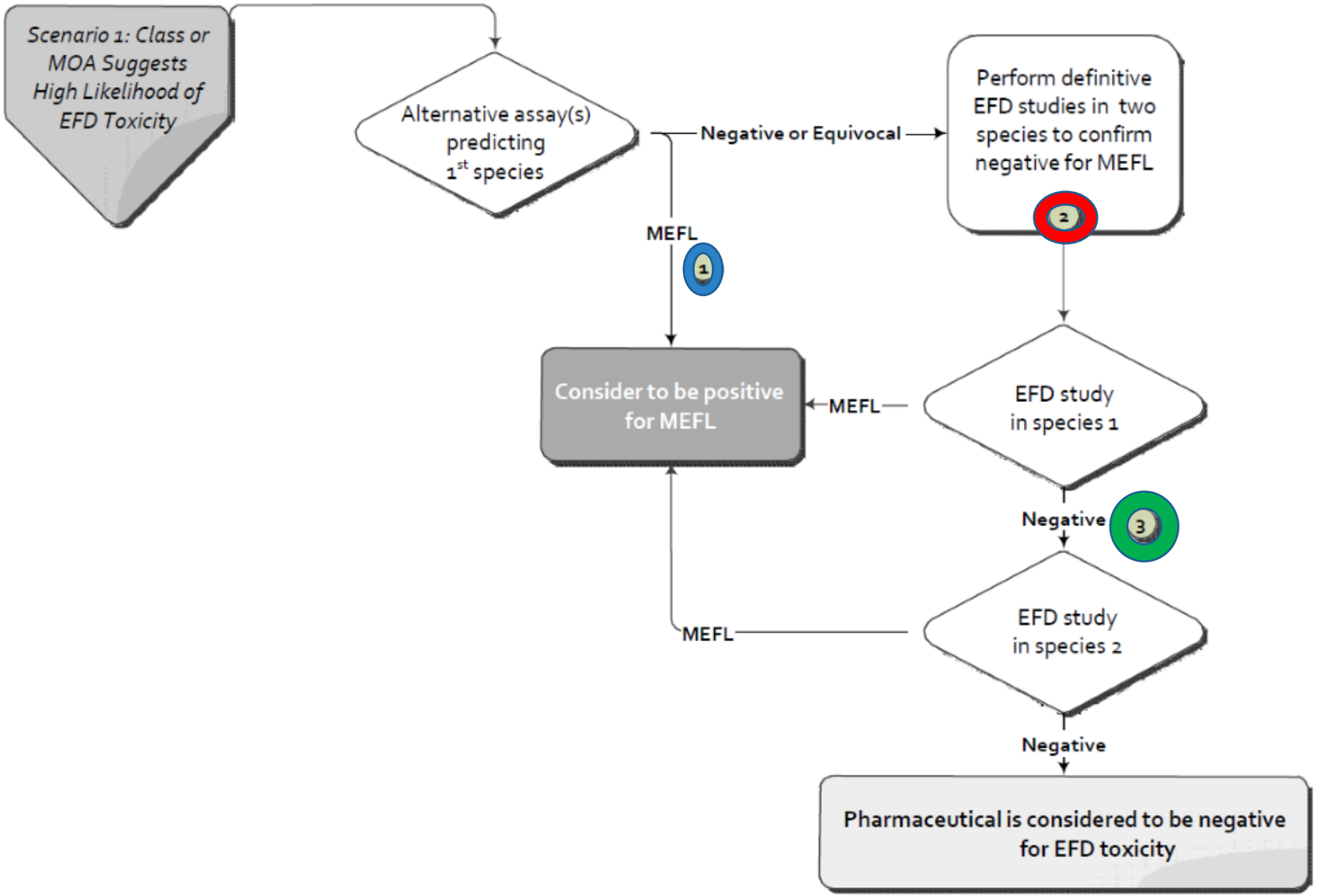
https://www.fda.gov/media/72231/download (US Guidance for Industry (FDA, CDER): Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns, Sept 2011)

https://database.ich.org/sites/default/files/S11_EWG_Draft_Guideline.pdf (NCS for Pediatric Medecines, under public consultation)

Back up slides

FIGURE 1: USE OF ALTERNATIVE ASSAYS FOR PHARMACEUTICALS

Expected to be EFD toxicants



- No additional assessment warranted
- Alternatively, pEFD studies can be used; however negative results should be confirmed by a definitive study in the relevant species
- …2nd in vivo assay not warranted if the 1st study is positive

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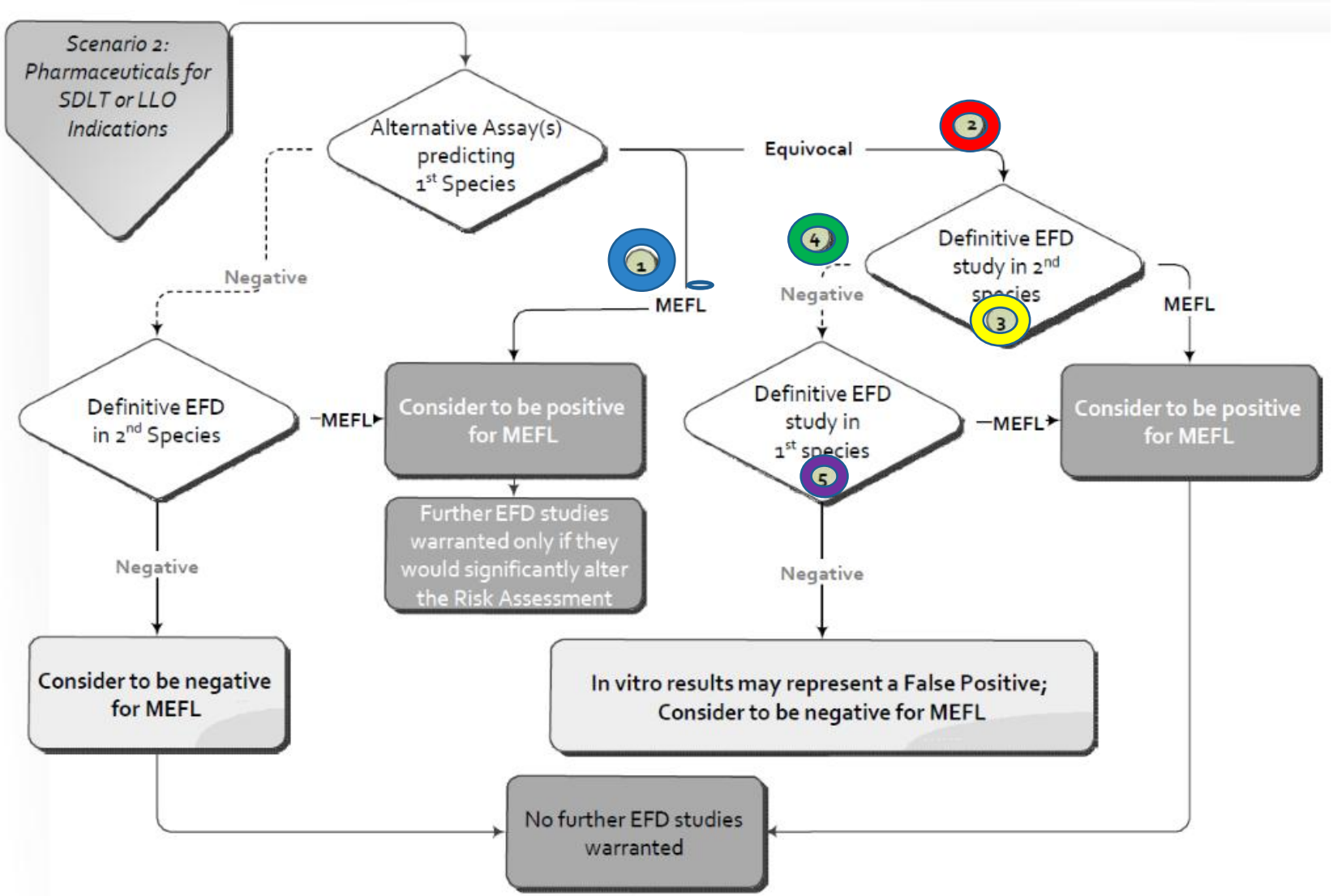
FIG 2: USE OF ALTERNATIVE ASSAYS

for Severely Debilitating or Life-threatening or Late Life Onset Diseases



1. MEFL signal at clinicall relevant extrapolated exposures can be sufficient without further assessment
2. Negative results from definitive EFD studies in two species needed to establish false positive alternative assay results represent
3. Given low likelihood of pregnancy in patient population a pEFD study in the 2nd species is generally sufficient.
4. 2nd in vivo assay not conducted if first is positive.
5. Same species as the alternative assay is intended to predict.

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