# The Revision leading to ICH S5(R3)

Reproductive Toxicity Testing – NAM-based Approaches

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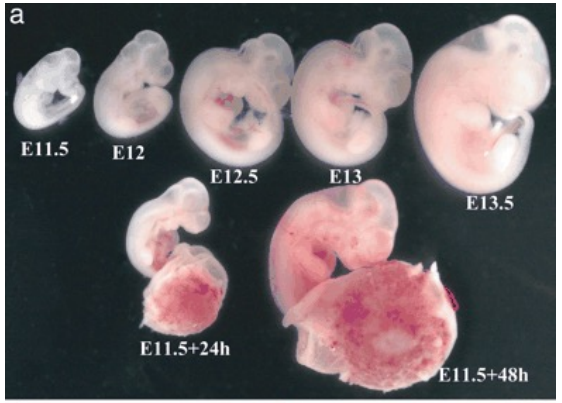
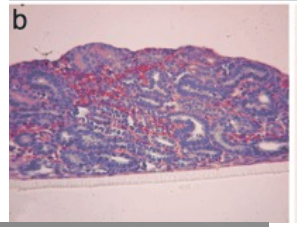
***The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the Belgian Federal Agency for Medicines and Health Products or the European Medicines Agency***

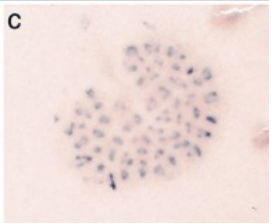
# Reality check: revising an ICH guideline

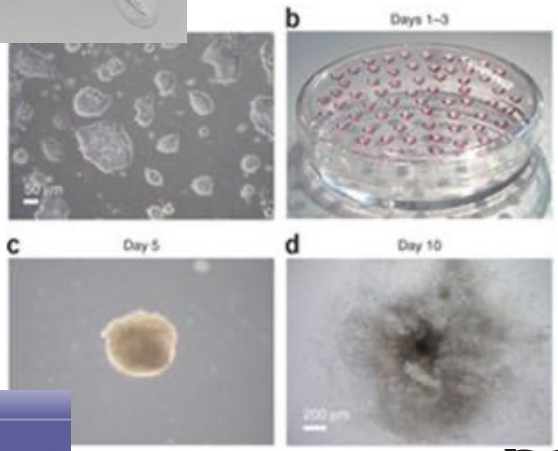
# What preceded regulatory discussions:

| Assay | Developmental period | Test accuracy % | Animal use | Limitations | ECVAM validation | Lit. |
|---|---|---|---|---|---|---|
| Rat/rabbit whole embryo culture | Early to mid organogenesis (ltd period of embryogenesis) | 80% for 20 tested cmpds | Yes | No metab., (experimental *ex vivo* approaches) -interlab variation(subjectivity), -costly, time consuming | Yes (Rat) | Piersma et al. 2004 |
| Zebrafish | cleavage, segmentation, majority of organogenesis to skeletogenesis | 31 test compounds; 87%, 75-92% | Yes (non-mammalian) | Nonmammalian metabolisation, Chorion may hamper compound uptake (DMSO) | No (Zebrafish embryo acute toxicity test for acute aquatic toxicity testing, 2014) | Brannen 2010<br>Van den Bulck 2011 |
| Embryonic stem cell test „Hanging drop" | Cardiomyocyte differentiation | 78%<br>81% | No | Metab., less predictive for drugs (ReProTect) | Yes | Genschow 2002<br>Whitlow 2007<br>Genschow 2004<br>Marx-Stölting 2009 |
| Micromass assay (limb bud) | Chondrocyte differentiation | 70% | Yes | No metabolic competence | Yes | Genschow 2002<br>Spielmann 2004 |



# ICH Workshop, Tallinn, June 2010

## *In Vitro* Models for Reproduction Toxicity Workshop – Use?

Workshop held as part of an assessment of whether the S5(R2) Guideline on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility needed to be revised.

It was agreed that no further work needed to be undertaken on the topic at the current time at the ICH level

More work needed on:

- Enhancing applicability of mEST for risk assessment
- rat vs rabbit comparison
- Establish robustness of *in vitro* approaches with more pharmaceuticals in different labs

# Follow-up on reproductive toxicity testing


discussion on:

- Value of rodent versus non-rodent species (rat or rabbit) in the evaluation human pharmaceuticals for their effects on embryo-foetal developmental: what data are needed?
- Value of 3R methods to detect crucial developmental effects? What type of data is available? Can recommendations be given for further evaluation of these in vitro methods?
- mEST: various endpoints, various protocols!
- Other 3R models used: zebrafish, whole rat embryo culture


Objectives:

- to bring scientific information about new in vitro technologies for reproductive and developmental toxicology testing to FDA
- to provide a forum for scientists from FDA, academia, and industry to discuss how these new technologies could eventually be integrated into FDA's regulatory paradigm.

# Unique aspects of reproductive toxicity testing

- **EFDT studies in rat/rabbit have added value over single studies**

***see Theunissen et al. 2016***

**Comparing rat and rabbit embryo-fetal developmental toxicity data for 379 pharmaceuticals: on systemic dose and developmental effects**

Critical Reviews in Toxicology , 2016

**Comparison of rat and rabbit embryo–fetal developmental toxicity data for 379 pharmaceuticals: on the nature and severity of developmental effects**

Critical Reviews in Toxicology , 2016

HESI

  - ☞ Even the design of alternative tests need to cover this aspect
  - ☞ Maternal toxicity/exaggerated pharmacology complicate data interpretation of *in vivo* studies

- **Data on human teratogenicity are scarce**
  - ☞ If the aim is to replace rat/rabbit EFD testing the alternative assays need to predict rat/rabbit teratogenicity/fetal lethality

- **3R considerations:**
  - ☞ Segment I-III studies, incl DRF studies: 6792 total animal use

*Chapman et al. 2013*

# 3rd Revision of ICH S5

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS**

**S5(R3)**

Final version
Adopted on 18 February 2020

**This document was developed based on a concept paper data March 27th 2015!**

# 3rd Revision of ICH S5: The Basics


**Aim of developmental and reproductive toxicity (DART) studies:**
**to reveal any effect of the pharmaceutical on mammalian reproduction and development relevant for human risk assessment**

**The risks to all stages of reproduction and development should be assessed, unless the stage is not relevant to the intended population.**

**Guideline is structured as core text plus annexes:**

- Annex 1: in vivo study designs
- Annex 2: alternative assays

# 3rd Revision of ICH S5: AIM

- **Alignement with existing regulatory guidelines under ICH:**
  ICH M3(R2), ICH S6 (R1), ICH S9
- **Scope expanded to include vaccines and biopharmaceuticals**
- **Definition of appropriate exposure margins to guide dose selection, i.e. high dose setting**
- **Incorporation of a new section dedicated to Risk Assessment**
- **Basic principles for possible regulatory acceptance of alternative assays and the conditions of use thereof**

# ICH S5(R3): SCOPE

**Guideline applies to:**

- pharmaceuticals, incl. biotechnology-derived products
- vaccines for infectious diseases
- novel excipients

**Does not apply to:**

- cellular therapies, gene therapies and tissue-engineered products

**Whether and when non-clinical studies are warranted:**

Please see ICH M3(R2), ICH S6(R1), and ICH S9

# ICH S5(R3): General Considerations for Reproductive Toxicity Assessment

**Stages of Reproduction**

A) Premating to conception
B) Conception to implantation
C) Implantation to closure of the hard palate
D) Closure of the hard palate to the end of pregnancy
E) Birth to weaning
F) Weaning to sexual maturity

**Non-clinical Studies**

1) a fertility and early embryonic development study (FEED stages A and B),
2) embryo-fetal development studies in two species (EFD -stages C and D),
3) a pre-and a postnatal development study (PPND –stages C through F).

# General Considerations for Reproductive Toxicity Assessment

**Think about:**

- Target population and conditions of use
- Clinical Formulation and Route of administration
- Existing data: toxicity, pharmacology, pharmacokinetics, other compounds
- Biology of the target, role of target in reproduction or development

**These factors will impact the <u>extent</u> of the reproductive toxicity testing and the <u>design</u> of the studies**

# General Considerations for Reproductive Toxicity Assessment

**Toxicokinetics (ICH S3A):**

- Critical to facilitate data interpretation
- Can be generated in reproductive toxicity studies or in repeat dose toxicity studies
- Effect of pregnancy on exposure
- Excretion in breast milk: samling milk or exposure of offspring pre-weaning
- GLP compliance

**Combination of studies possible to address specific product needs and in line with 3Rs!**

e.g. EFD/FEED and RDT/FEED
See Annex 1.

# Fertility and early embryonic development - FEED

**Only in rodents**

**DRF can be replaced by 2-week RDTS**

**For biopharmaceuticals (ICH S6):**

- No stand-alone fertility studies in NHP
- Use of surrogate product/transgenic model to avoid use of NHP if justified
- Rodents or rabbits can be used if pharmacologically relevant
- Replacement possible by histopathology of reproductive tissues in RDTS of at least 3 months
- Animal should be sexually mature at study initiation

**For Anticancer pharmaceuticals (ICH S9):**

- data from repeat dose toxicity study sufficient

# Embryo-foetal development - EFD

**Small molecules: rodent and non-rodent species**

- At least one of the test species should exhibit the desired PD. If not, consider non-routine species, genetically modified animals, or surrogates.
- Genetically modified animals/surrogate most useful for hazard identification.
- In absence of relevant models → 2-species testing to detect adversity of off-target effects or secondary pharmacology.
- Avoid EFD Studies in multiple species if:
  - Clearly positive results in a single species at exposures similar to that at the projected clinical exposure at the MRHD
  - Evidence suggesting an adverse effect of the intended pharmacological mechanism on EFD (e.g. MoA)
  - Under limited circumstances, alternative assays can be used

# Embryo-foetal development - EFD

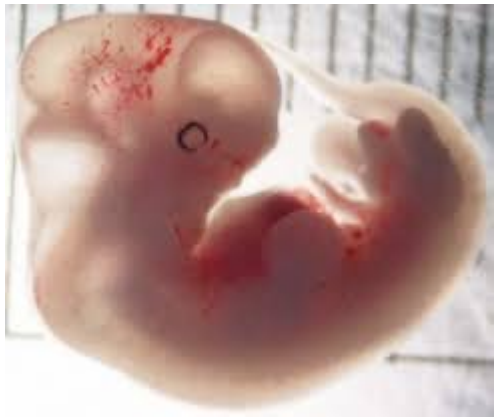
**Biopharmaceuticals (ICH S6):**

- If rodent not pharmacologically relevant → single species EFD in pharmacologically relevant non-rodent species
- Use of surrogate product/transgenic model to avoid use of NHP
- If NHP only relevant species → ePPND reduces need for 2 separate studies
- If no relevant species, no genetically modified animals or surrogates available → in vivo reproductive toxicity testing not meaningful. The approach used for risk assessment should be justified.

**Anticancer pharmaceuticals (ICH S9):**

- One relevant species sufficient if
  - clearly positive results in single species @ exposures similar to that at MRHD
  - evidence suggests adverse effect of intended pharmacological mechanism on EFD (e.g., MoA)
  - Under limited circumstances, alternative assays can be used

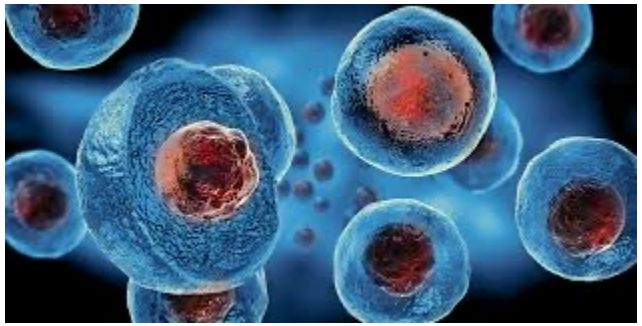
# Embryo-foetal development - EFD

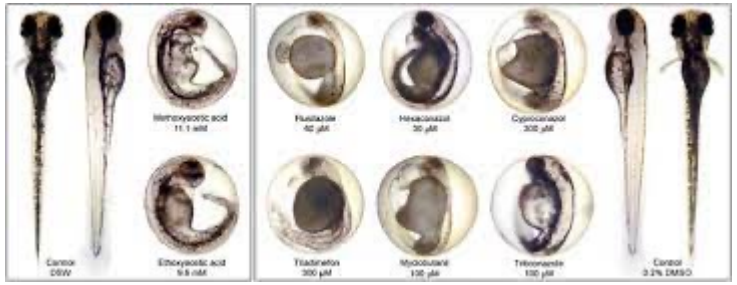


## Alternative Approaches

- Encouraged
- Potential to defer or replace conventional in vivo studies
- Should provide a level of confidence of human safety assurance at least equivalent to that provided by the current teting paradigms

→ *see presentation by Peter Theunissen for details*





# Embryo-foetal development - EFD

**Data generated from qualified alternative assays conducted alone or in conjunction with one or more in vivo studies can be used to support hazard identification and risk assessment under limited circumstances.**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/544278/1998
Committee for Medicinal Products for Human Use

ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals
Step 5

| | |
|---|---|
| Transmission to CHMP | 10 July 2017 |
| Adoption by CHMP for release for consultation | 20 July 2017 |
| Start of consultation | 31 August 2017 |
| End of consultation (deadline for comments) | 28 February 2018 |
| Final adoption by CHMP | 30 January 2020 |
| Date for coming into effect | 30 July 2020 |

- in accordance with **GLP** & **qualified for context of use**
- GL annex provides basic scientific principles to assist in assay qualification for regulatory use
- If used for MOA exploration or not intended to substitute for in vivo endpoint : no such rigorous qualification is required.

***Context of use: applicability domain and regulatory conditions under which assay results are reliable***

# Pre- and Postnatal Development - PPND

**Rodent studies**

**Prior studies inform on study design and dose levels**

**Modified designs to include additional parameters (see ICH S11)**

**Biologicals (ICH S6(R1)):**

- Enhanced PPND reduces need for 2 separate studies

**Anticancer pharmaceuticals (ICH S9):**

- No PPND studies

# Test species

**Routine and non-routine species** listed with advantages and disadvantages (see annex 1)

**Preventative and Therapeutic Vaccines against Infectious Diseases**

- Should demonstrate an immune response
- Typically single species (rabbits, rats, or mice) with use of full human, single dose level
- When there is a lack of an appropriate animal model (including NHP), an EFD toxicity study in rabbits, rats, or mice can still provide important information

**Disease Models, Genetically Modified Models, & Surrogate Molecules**
Can be valuable for investigating pharmacological effects on development and reproduction

# Dose selection – NEW: Exposure Margin Based Endpoint

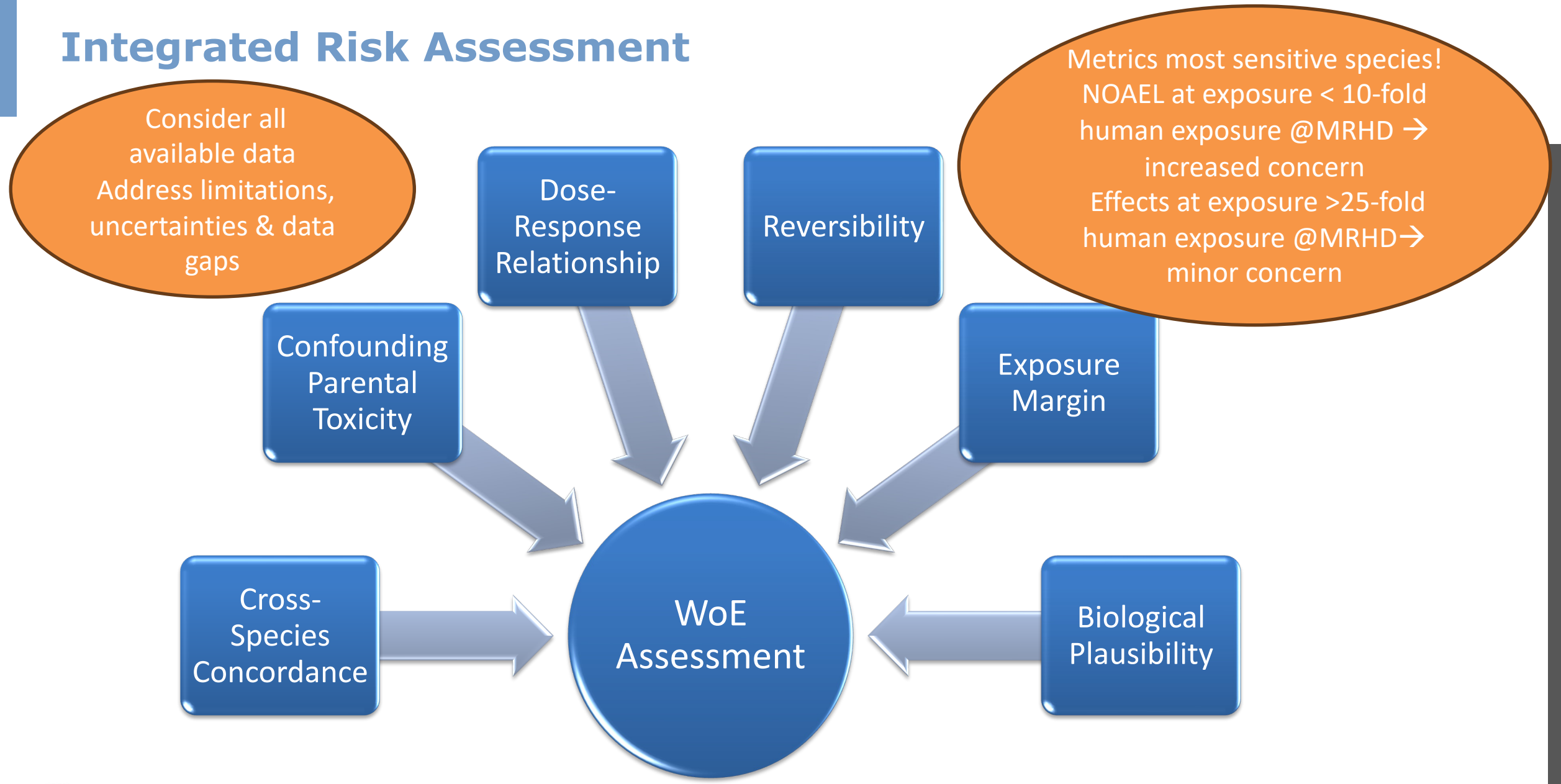
- **25-fold exposure in pregnant animals at the MRHD (GLP DRF or pEFD)**
  →generally considered appropriate as the maximum dose

- **Usually parent drug levels** (metabolites see ICH M3 & ICH M3 Q&A)
- **Special considerations for prodrugs**

- **Higher doses if PD activity in test species is limited at 25-fold**

- **Total vs. fraction unbound pharmaceutical exposures (ICH S3A)**
- **Biopharmaceuticals:**
  - Maximum intended pharmacological effect in preclinical species or approximately 10-fold exposure multiple over the maximum clinical exposure, whichever is higher
  - Dose adjustment for differences in target binding affinity and other relevant factors (ICH S6)

# Integrated Risk Assessment



# In summary


**Revision :**

- focus on application to human risk assessment
- offers additional dose selection endpoints
- emphasizes the use of existing data
- describes integrated testing strategies for assessing DART, incl. for biologics.
- outlines guidance on qualification of alternative assays for use in risk assessment for regulatory purposes
  → see presentation by Peter Theunissen

**Consideration of the 3Rs in the design of the experimental strategy**
→ minimize animal use, while not diminishing overall human risk assessment

**Always read the revised guideline in conjunction with ICH M3, ICH M3 Q&A, ICH S6 & ICH S9**


תודה
Dankie
Gracias
Спасибо
شكراً
Merci
Takk
Köszönjük
Terima kasih
Grazie
Dziękujemy
Dėkojame
Ďakujeme
Vielen Dank
Paldies
Kiitos
Täname teid
谢谢
Thank You
Tak
感謝您
Obrigado
Teşekkür Ederiz
감사합니다
Σας ευχαριστούμε
ขอบคุณ
Bedankt
Děkujeme vám
ありがとうございます
Tack

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