Reproductive Toxicity

An introduction to regulatory aspects on detection of toxicity to reproduction for medicinal products

Günter Waxenecker

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Unique aspects of reproductive toxicity

- any substance can be teratogenic if given to the right species, at the right stage in development (Karnofsky's Law) also organ- and dose-specific, and exposure-dependent
- we know a lot more about animal reprotoxicity (animal to human and animal to animal concordance)
- Animal testing is required for predicting human toxicity

  Relevance of findings for humans needs to be assessed

  Mechanistic studies required to demonstrate irrelevance of findings
- Significance of findings

  Background incidence, categorization and hierarchy of findings, terminology

Clinical relevance of reprotoxicity

- 10–14% of all clinically recognized pregnancies result in spontaneous abortion
  - the actual rate of pregnancy loss, as shown with the use of biochemical assays, is actually two to five times higher.
- the mean age of women at childbirth is 30 or above (and increases)
  - older maternal age is one consistent risk factor causing early pregnancy loss
  - Strong age profile of people using medicines
- France: more than 1/3 pregnancies are **unintended**, although the rate of contraceptive use is high.

OECD Family database
Chan et al 2010
Diamond-Smith et al 2014

General principles of teratology

1. The final manifestations of abnormal development are **death, malformation, growth retardation and functional disorder**.
2. Susceptibility of the conceptus to teratogenic agents varies with the developmental stage at the time of exposure (**Critical periods of development**)
3. Teratogenic agents act via **specific pathways**
4. Manifestations of abnormal development increase in degree from the no-effect to the totally lethal level as dosage increases. (**Dose-related effect – Threshold**)
5. The access of adverse environmental influences to developing tissues depends on the **nature of the agent**.
6. Susceptibility to a teratogen depends on the **genotype** and on the **interaction** with the environment (mother/embryo - metabolism/PK)

Wilson (1973)

Re(volution)

*Reproductive toxicity testing is the only area in experimental toxicity test settings, where there is a strict **before** and **after** – the difference being **thalidomide**: revolution without evolution*

Rat & rabbit testing became gold standard for EFD studies

→ Initial ICH activities on S5 were driven by a strong need for harmonization

Bass R. et al in Global Approach in Safety Testing, 2013

ICH HARMONISED TRIPARTITE GUIDELINE

DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY S5(R2)

→ chemicals

Aim of reproduction toxicity studies....

... is to reveal any effect of one or more active substance(s) on mammalian reproduction:

- effects on the reproductive competence of adult animals (parents)
- effects induced or manifested in the embryonic or fetal period and those induced or manifested postnatally (e.g. behaviour, lactation - Development of its offspring, developmental toxicity)

The combination of studies selected should allow exposure of mature adults and at all stages of development from conception to sexual maturity.

- To allow detection of immediate and latent effects of exposure, observations should be continued through one complete life cycle, i.e. from conception in one generation through conception in the following generation.

ICH S5(R2)

Stages of a reproductive life cycle

A. Premating to conception (adult male and female reproductive functions, development and maturation of gametes, mating behavior, fertilisation).

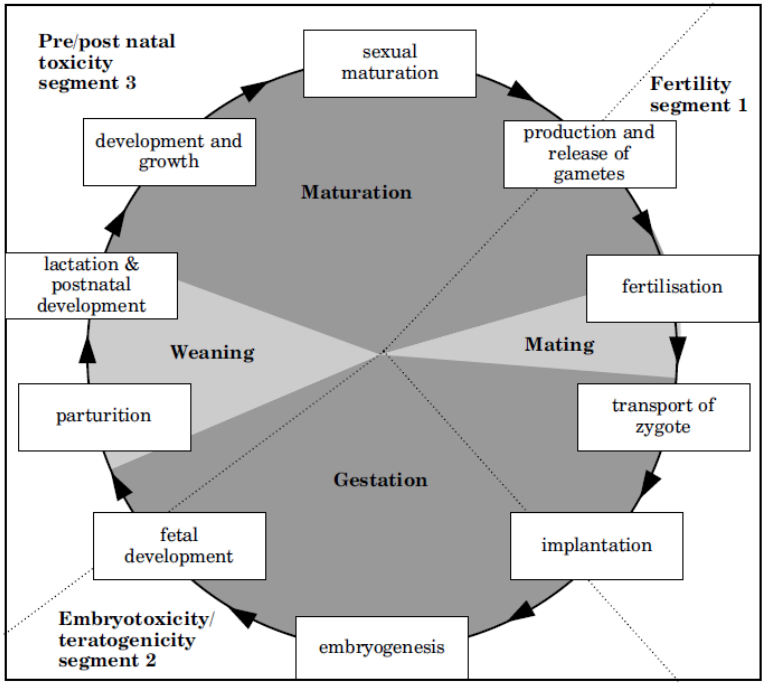
B. Conception to implantation (adult female reproductive functions, preimplantation development, implantation).

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 and growth, adaptation to independent life, attainment of full sexual function).



ICH S5(R2) and Spielmann 2009

Selection and number of species

- ...use mammalian species.
  - desirable to use the same species and strain as in other toxicological studies.
  - Rats predominant: practicality, background knowledge.
- In embryotoxicity studies only, a second mammalian species traditionally has been required, the rabbit being the preferred choice as a "non-rodent“...background knowledge, availability and practicality.
- *Note 5 (2.1) Selection of species and strains*
  - *All species have their disadvantages, for example...*
  - *... If it can be shown - by means of kinetic, pharmacological and toxicological data - that the species selected is a relevant model for the human, a single species can be sufficient.*

ICH S5(R2) Section 2

Other test systems

- In short, there are no alternative test systems to whole animals currently available for reproduction toxicity testing with the aims set out in the introduction (Note 6).

- *Uses of other test systems than whole animals*
  - *Other test systems have been developed and used in preliminary investigations ("pre-screening" or priority selection) and secondary testing.*

ICH S5(R2) Section 2

➢ Many alternative systems show high sensitivity (true positive rate)

Barrow P. 2016

Dosing and maternal toxicity

- Dosages:
  - Choice of the high dose... based on data from all available studies
  - Some minimal toxicity (reduced bw gain...) is expected in the high dose dams
  - *1 g/kg/day should be an adequate limit dose (Note 7)*
  - *But: Dose-response relationship: wide dose intervals would be inadvisable (Note 8)*
  - ➢ results should be direct effects of the compound (not due to maternal toxicity!)

ICH S5(R2) Section 3.1

- Maternal toxicity:
  - Potential significant confounding factor in data interpretation.
  - Also distinguish ‘‘true’’ maternal toxicity from exaggerated pharmacology.

Beyer et al. 2011: ILSI/HESI Maternal toxicity workshop

Kinetics

The exposure in pregnant animals of the compound and/or metabolites should be assessed

measure systemic exposure for verification purposes and to **relate to human exposure**

- Plateau in plasma concentration?
- Frq differences bw pregnant and non-pregnant
- consider preliminary studies!

EMEA/CHMP/203927/2005 Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling
ICH S5(R2) Section 3
ICH S3A

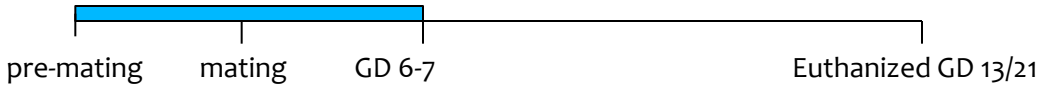
Proposed study designs

- Decision on the most appropriate strategy and choice of study design:
  - use ALL available data:
    - pharmacological
    - toxicological
    - kinetic data of the compound
    - class effects

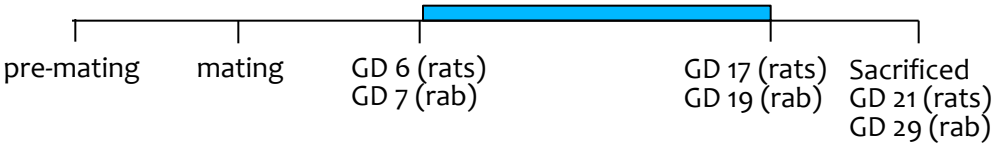
- Group sizes:
  - should allow meaningful interpretation of data, educated guess – bw 16 to 20 litters for rodents and rabbits should be evaluable (Note 13)

ICH S5(R2) Section 4

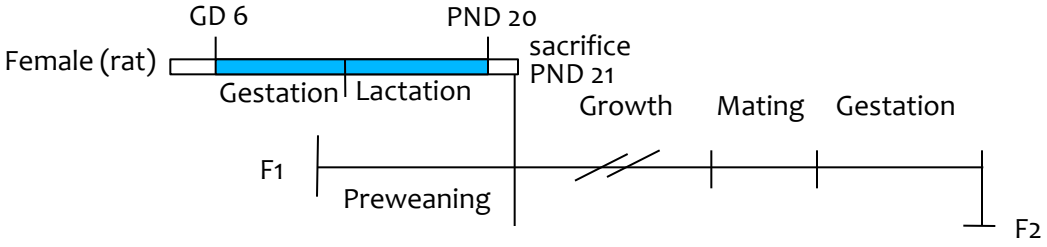
Consider a 3-study design ("The most probable option")



- 4.1.1. Fertility + EED (Stage A-B (pre-mating, conception, implantation) Segment I)



- 4.1.3. EFD Toxicity study (Stage C-D; implantation, closure of hard palate, Seg II, Teratology study)



- 4.1.2. Peri/postnatal study (Stage C-F, Seg III)

- But **other strategies** could be **as valid** (2- and 1-study design)
- leave no gaps between stages
- In case of signals, information on the mechanism is desirable.

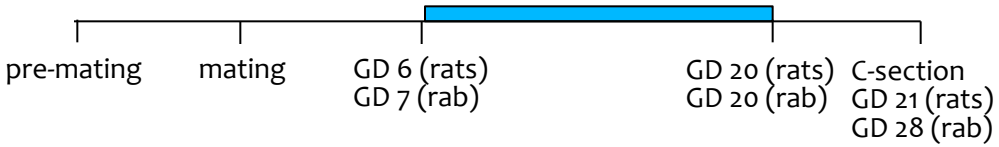
ICH S5(R2) Section 4
EMEA/CHMP/203927/2005

Fertility and Early Embryonic Development

- Stage A-B (or pre-mating, conception and implantation); Segment I
- Design guided by results of RDTSs: separate or combined male and female study
- Administration period:
  - Provided no effects have been found in RDTSs of at least one month duration that preclude this, a premating treatment interval of 2 weeks for females and 4 weeks for males can be used (Note 12).
    ☞ addendum allows for 2 weeks prior to mating
- Evaluation of
  - maturation of gametes,
  - mating behavior,
  - fertility,
  - preimplantation stages of the embryo,
  - Implantation of the embryo into the uterus.
- At least **one** species, preferably rats.

ICH S5(R2) Section 4

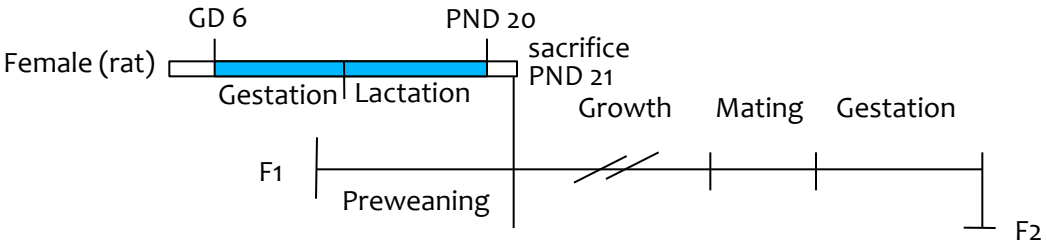
Embryo-fetal development toxicity study



- Stages C-D; Seg II, Teratology study
- Aim:
  - To detect adverse effects on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation to closure of the hard palate
- Administration period
  - The treatment period extends from implantation to the closure of the hard palate
- Evaluation of
  - enhanced toxicity relative to that in non-pregnant females,
  - embryofetal death,
  - altered growth
  - structural changes.
- **Two** species (preferably rat) and one non-rodent (preferably rabbit)

ICH S5(R2) Section 4

Pre- and postnatal development, including maternal function



- Stage C-F, Seg III
- Aim:
  - To detect adverse effects on the pregnant/lactating female and on development of the conceptus and the offspring following exposure of the female from implantation through weaning.
  - observations should be continued through sexual maturity
- Administration period:
  - Females exposed to the test substance from implantation to the end of lactation (i.e. stages C to E)
- Evaluation of
  - enhanced toxicity relative to that in non-pregnant females,
  - pre- and postnatal death of offspring,
  - altered growth and development,
  - functional deficits in offspring, including behavior, maturation (puberty) and reproduction (F1).
- At least **one** species, preferably rats;

ICH S5(R2) Section 4

Statistics and Data presentations

- Statistics:
  - the basic unit of comparison is the mating pair or litter, not the foetus or neonate
  - interpretation based on biological plausibility

- Data presentations
  - should be able to follow the history of any individual animal
  - Group summary values should be presented in a form that is biologically plausible

ICH S5(R2)

Reprotox testing with Biologicals

For biotechnology-derived pharmaceuticals

- *the evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species*.
- *Developmental toxicity studies in NHPs can only provide hazard identification.*
- *If relevant only in NHPs, there is still a preference to test the clinical candidate.*
- *When the weight of evidence suggests that there will be an AE on fertility or pregnancy outcome …additional nonclinical studies might not be warranted*.

➢More flexible, but science-based approach

ICH S6(R1)

Patients with advanced cancer

- *EFD Toxicity study for MAA,*
  - *Not for CTs*
  - *Not if compound is genotoxic and targets rapidly dividing cells or belong to a class known to cause developmental toxicity*
  - *For small molecules, if EF lethality or teratogenicity is shown, second species testing is not warranted*
  - *For biopharmaceuticals one relevant species is usually sufficient*
- *A study of fertility and early embryonic development and a PPND study is generally not warranted to support CTs or for MAA of pharmaceuticals intended for the treatment of patients with advanced cancer.*

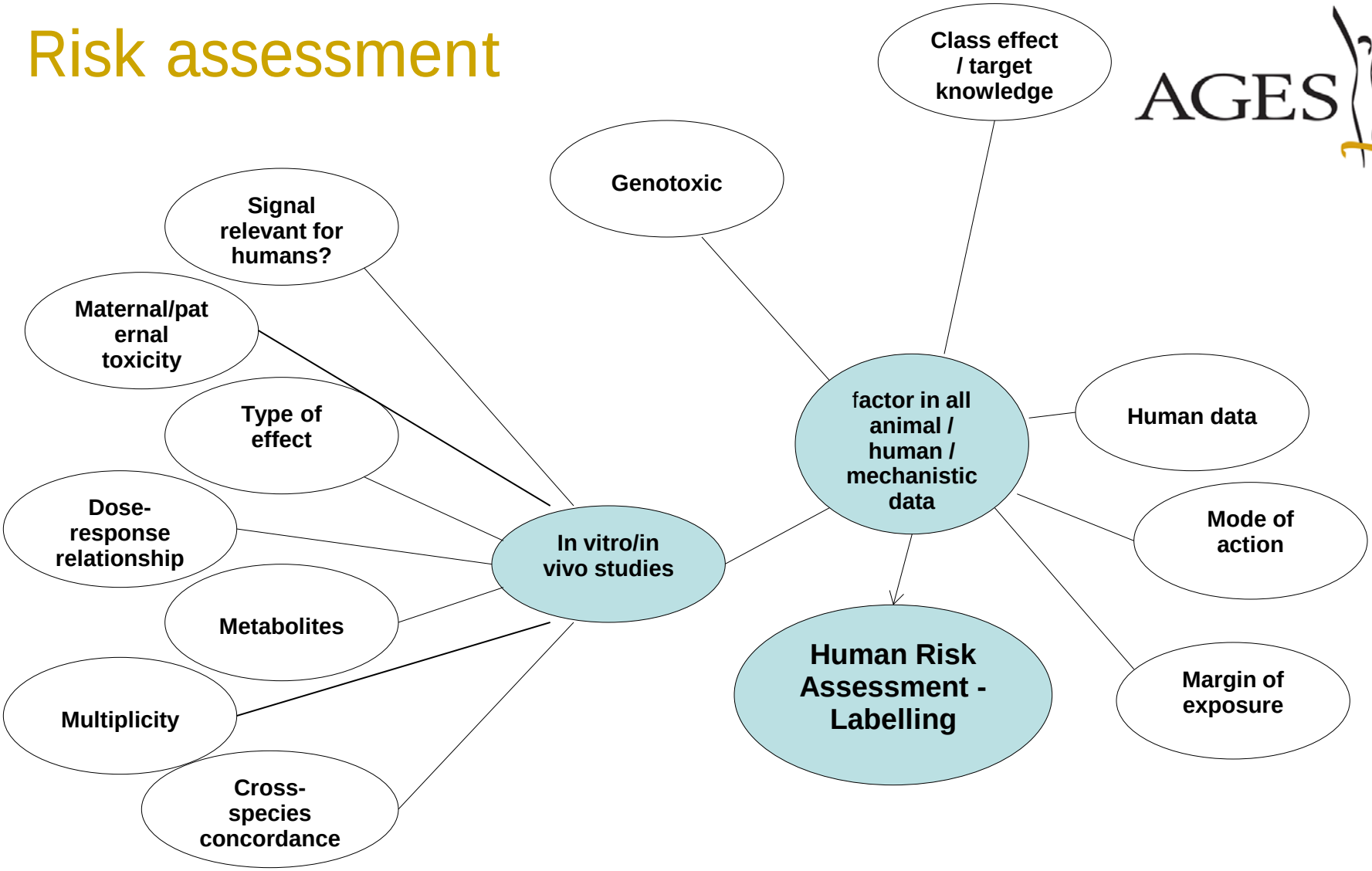
ICH S9
ICH S9 Q&A (draft)

Timing of studies

- Based on evaluation of reproductive organs in the RDTSs
  - Male fertility studies not needed for Ph I and II trials
  - Women not of childbearing potential can be included in clinical trials
- For WOCBP not using highly effective birth control or whose pregnancy status is unknown all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed before inclusion in any clinical trial.
- Inclusion of <150 WOCBP, treatment for a relatively short duration: preliminary EFD studies from two mammalian species required
- Inclusion of >150 WOCBP: definitive EFD studies, 2 species
- Submit PPND data for Marketing authorisation

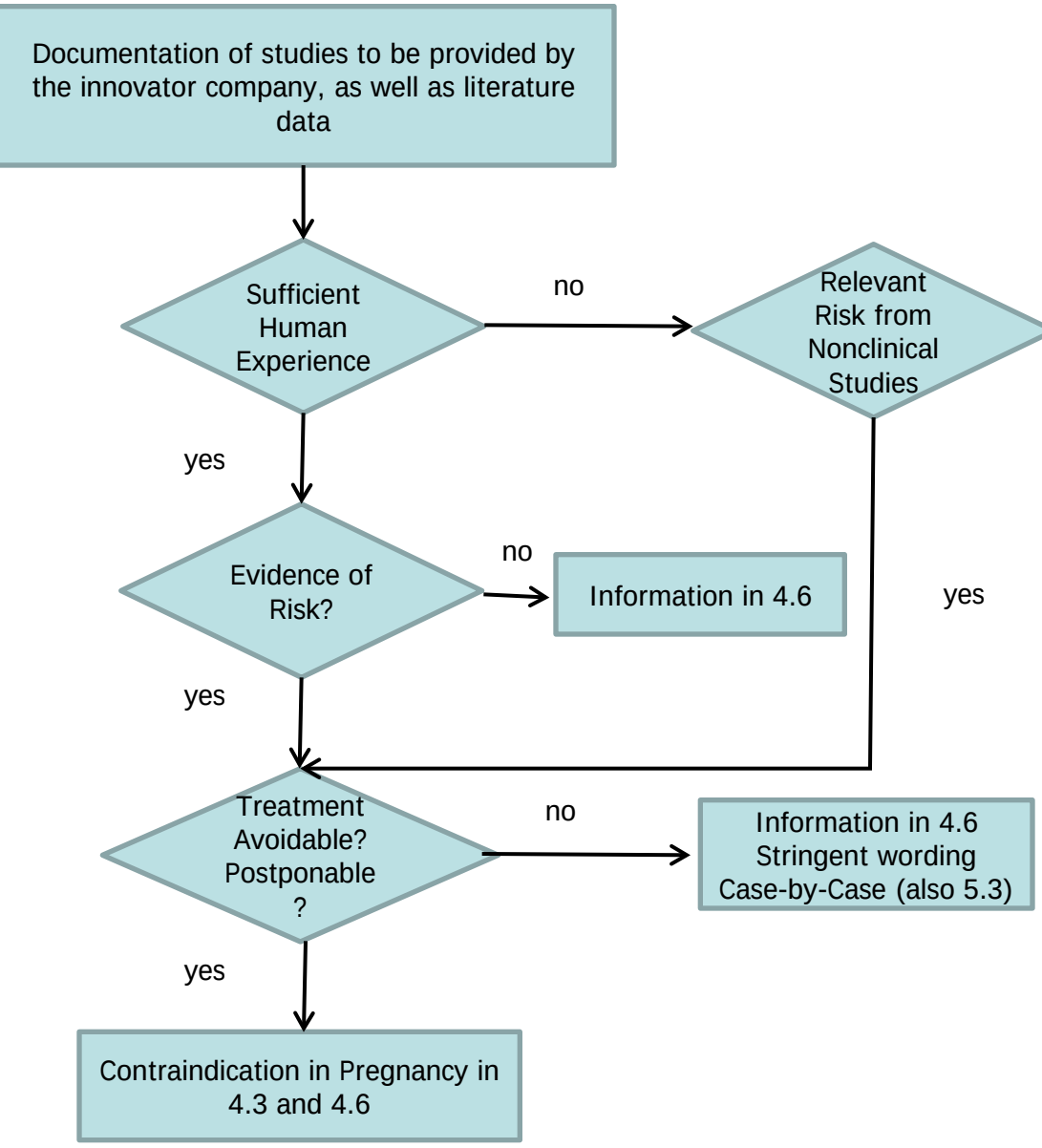
ICH M3(R2)

Risk assessment



- significance (biological/statistical)
- strength of signal

EMEA/CHMP/203927/05 Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling



Decision scheme Contra-indication in Pregnancy

See also

Integration table for risk assessment and recommendation for use

EMEA/CHMP/203927/05 Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling

ICH S5: From R2 to R3
Revision ongoing

Current *Step 4* version
Parent Guideline dated 24 June 1993
(Addendum dated 9 November 2000 incorporated in November 2005)

Excellent safety track record developmental toxicity, but

- The S5(R2) Guideline on Reproductive Toxicity was written **over 20 years ago**.
- Scientific, technological and regulatory knowledge has significantly evolved
- Opportunities exist to reduce animal use

Guidelines

- ICH S5(R2) Reproductive toxicology: detection of toxicity to reproduction for medicinal products including toxicity to male fertility (CPMP/ICH/386/95)
- ICH M3(R2) (CPMP/ICH/286/95): non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals – Questions & Answers!
- EMEA/CHMP/203927/05 Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling
- ICH S3A (CPMP/ICH/384/95) Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies
- ICH S6(R1) (EMA/CHMP/ICH/731268/1998): Preclinical safety evaluation of biotechnology - derived pharmaceuticals
- Recommendations related to contraception and pregnancy testing in clinical trials, September 2014; CTFG
- CPMP/SWP/2600/01 PtC on the Need for assessment of reproduction toxicity of human insulin analogues
- Q&A on the withdrawal of the CPMP Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465)
- Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines, WHO 2013
- EMEA/CHMP/313666/2005 Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data
- CHMP/SWP/169215/05 Need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications

Thanks!