Non-clinical testing of human medicinal products and 3Rs

Non-clinical Working Party activities

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Non-Clinical Working Party (NcWP)

- Preparing and updating guidelines
- European and international co-operation
- Liaising with stakeholders
- Training for assessors
- Product-related support a.o. to EMA committees

Non-Clinical Working Party

- Meetings once a month
  Annual stakeholder meeting, usually in October
- Chair: Susanne Brendler-Schwaab (BfArM)
  Vice-Chair: Karen Van Malderen (FAMHP)
- Supported by expert groups
- Close collaboration NcWP – 3RsWP
- Workplan & priorities published:

https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/non-clinical-working-party

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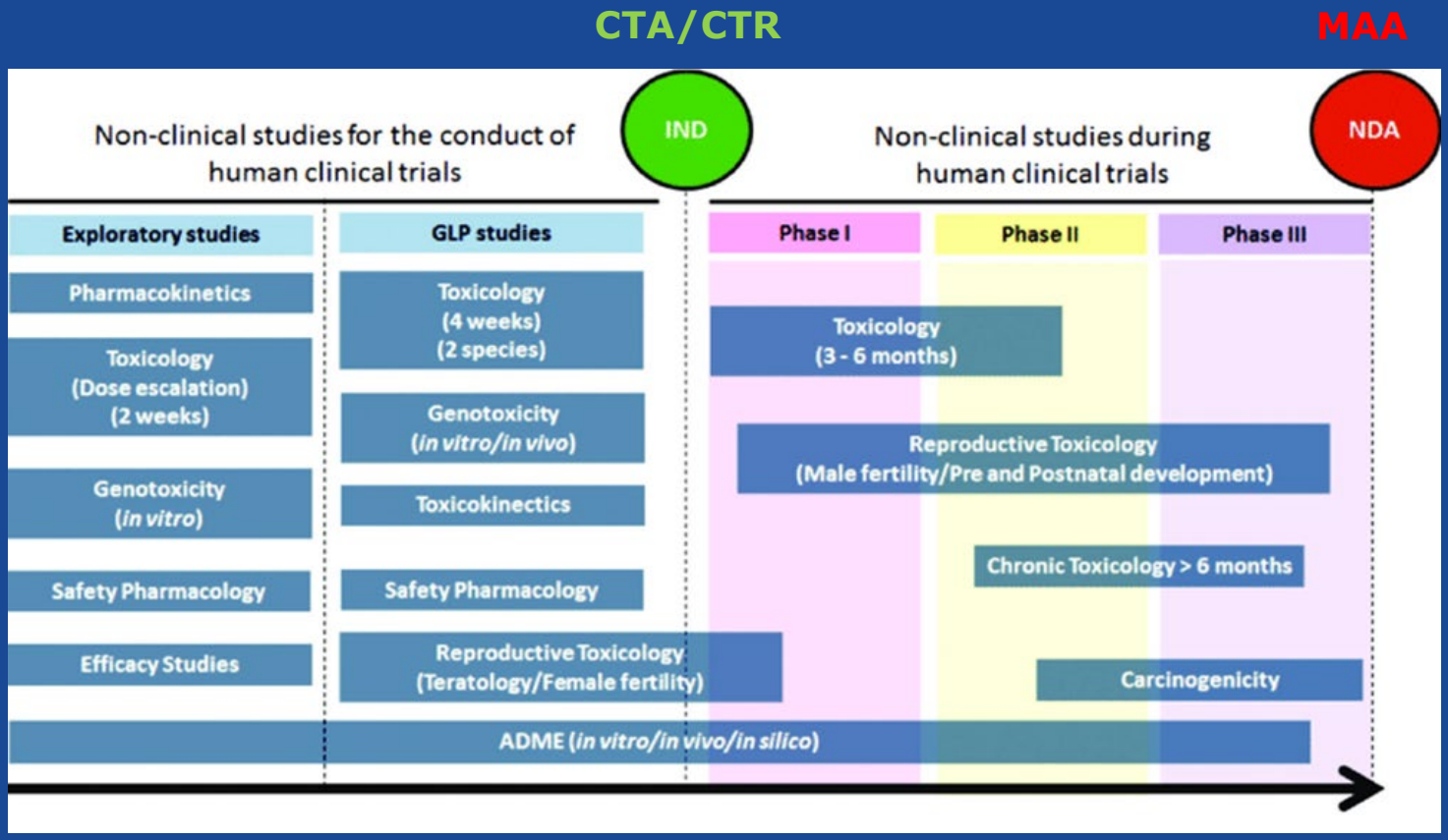
Non-Clinical Testing Requirements & opportunities for 3Rs implementation

Pharmacology
Pharmacokinetics
Toxicology

- Repeat-Dose Toxicity
- Genotoxicity
- Reproductive / Developmental and JuvenileToxicity
- Carcinogenicity
- Local Tolerance
- Other Toxicity Studies



Andrade et al. Brazilian Journal of Medical and Biological Research (2016) 49(12)

Carcinogenicity

ICH S1A Need for carcinogenicity studies of pharmaceuticals
ICH S1B Carcinogenicity: testing for carcinogenicity of pharmaceuticals
ICH S1C(R2) Dose selection for carcinogenicity studies of pharmaceuticals

Basic Testing Scheme

Long-term rodent carcinogenicity study

+

Long-term carcinogenicity study in a 2nd rodent species

OR

Short or medium-term in vivo rodent test system

[1]Long-term studies
rat (24 months), mouse (18 months)
min. 50/sex/group + satellite TK groups

[2]Transgenic and knockout animal models
e.g. TgrasH2, P53
Or Initiation/Promotion models in rodents
20-25 animals/sex/group (max 6-9 months)

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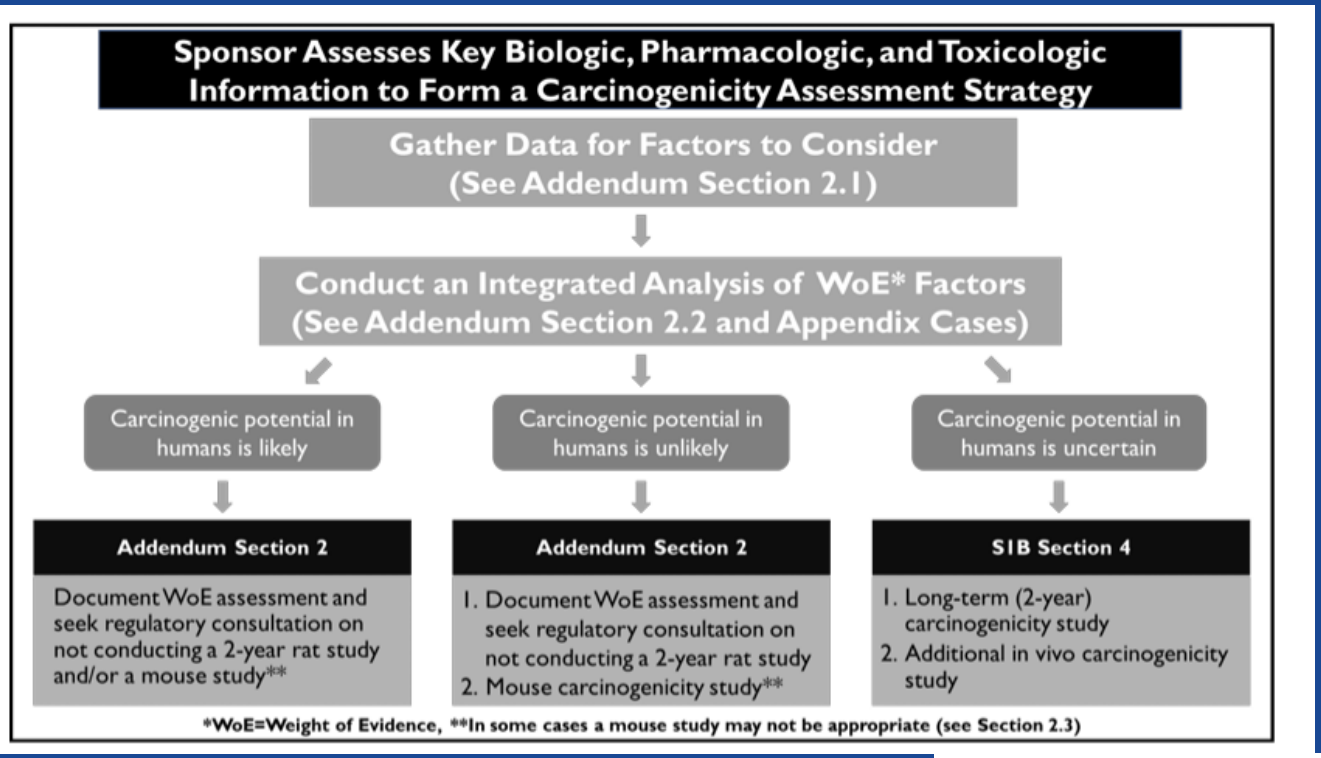
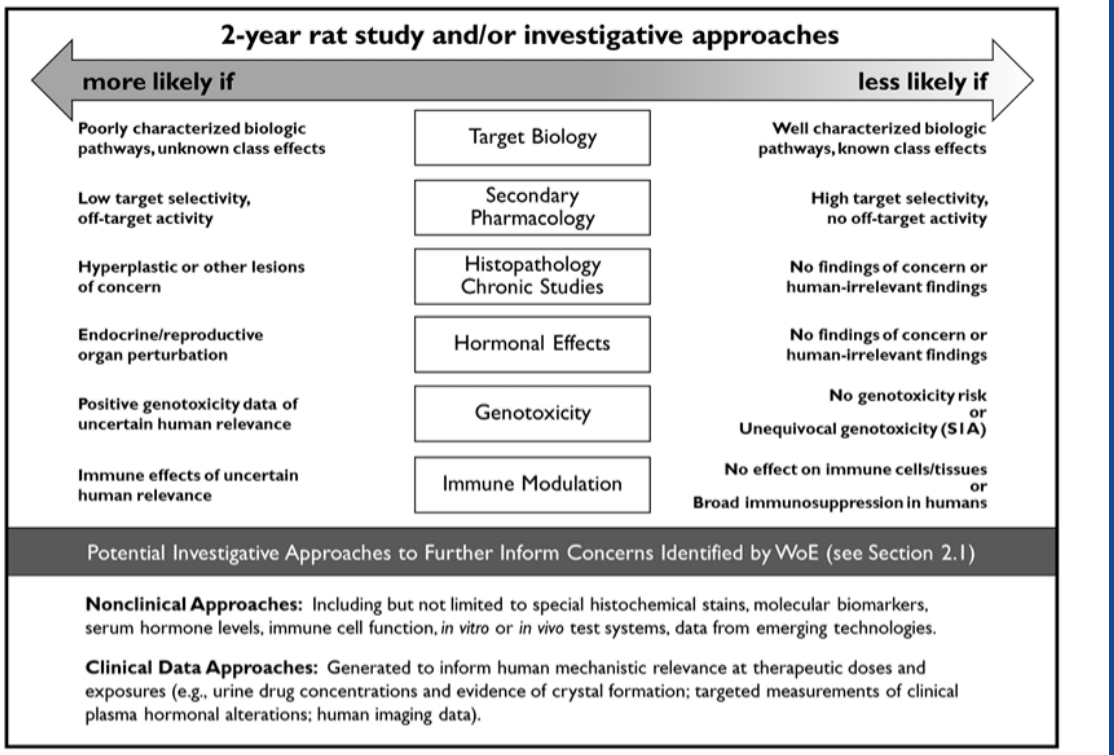


ICH S1B(R1)

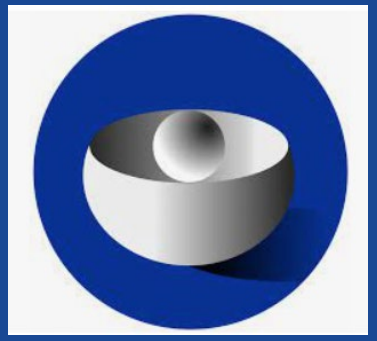
Legal effective date: March 2023

- Weight-of-evidence (WoE) approach to determine if a 2-year rat study adds value
- Plasma exposure ratio endpoint (50X human exposure) for high-dose selection in rasH2-Tg mouse model



ICH S1B(R1) implemenation – Role of NcWP

- NcWP Operational expert group
  - Review WoE evaluation and provide advice on the need to perform carcinogenicity studies to Scientific Advice Working Party (SAWP)
  - 2023: 15 cases reviewed & agreed that 2y rat study is not expected to add value



- ICH Implementation Working Group
  - Monitoring of implementation of the WoE approach to identify any areas of inconsistency and discuss how they can be addressed

Juvenile toxicology

ICH S11 Guideline on Nonclinical safety testing in support of development of paediatric pharmaceuticals

Objectives ICH S11:

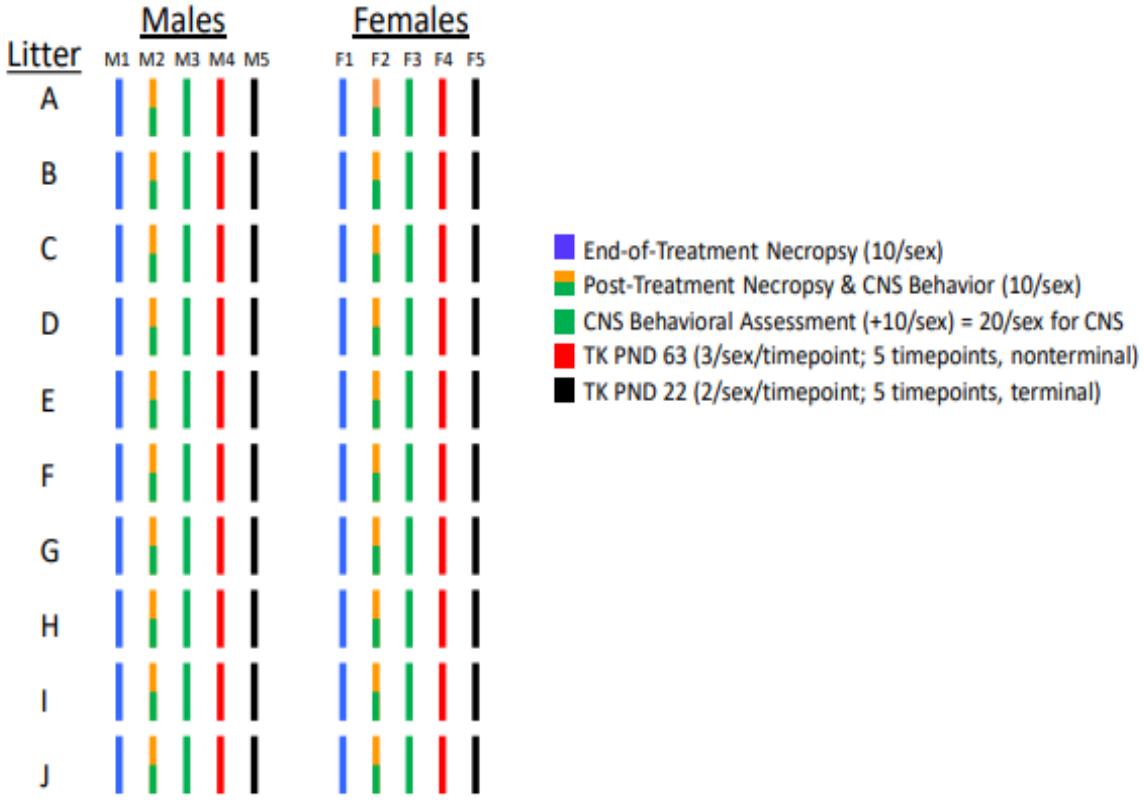
Harmonisation among regions

Timely conduct of paediatric clinical trials

Reduce the use of animals (3Rs)

- Weight of evidence (**WoE**) approach
- **Early** consideration of NC strategy
- **Customised** Juvenile Animal Studies (JAS)

Figure Represents One Dose Group of 10 litters with 5 pups/sex



ICH S11 implementation – Role of NcWP

- Review paediatric investigation plans (PIPs) and scientific advices for EMA Paediatric Committee (PDCO) & SAWP

- 2023: 125 PIPs reviewed

- Current approach
  - ✓ Push back JAS proposals if it is unclear which concerns are driving the study (WoE) or unlikely to result in clinically meaningful data
  - ✓ Challenge endpoints if lack of rationale (neurobehavioral, mating assessments)
  - ✓ Recommendation to avoid (too) immature age at study start

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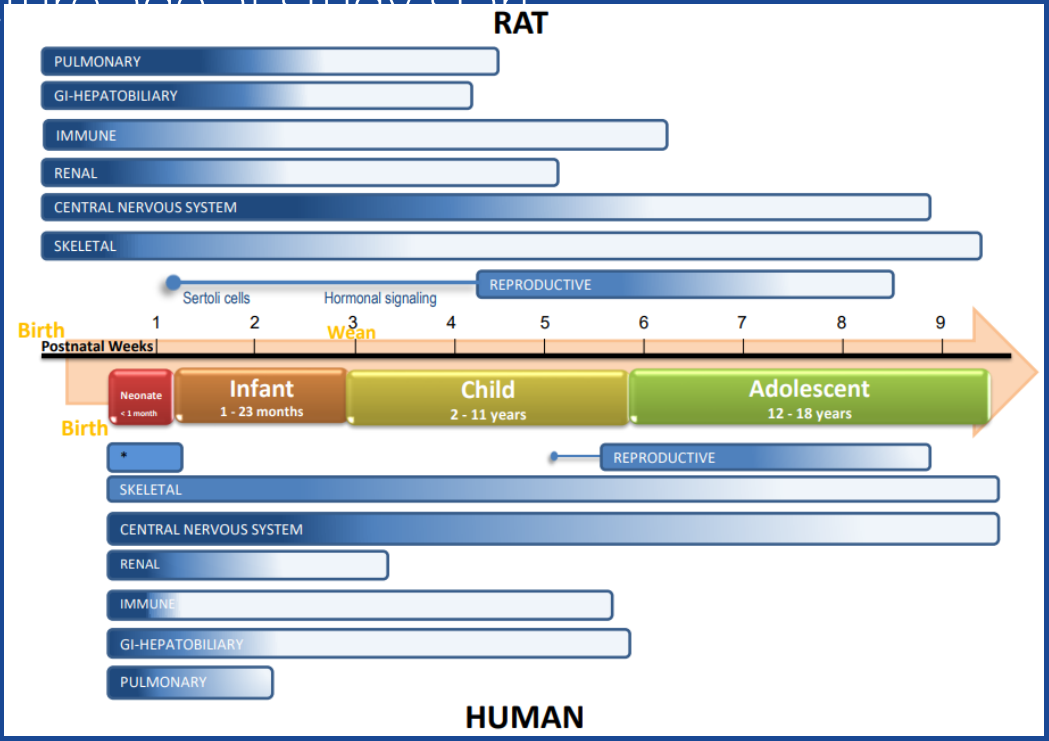

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ICH S11 implementation – Role of NcWP

- Interactions with FDA & Swissmedic
- Updated training material for EU assessors
- Revision of PIP template for sponsors
- Retrospective review (ongoing):
  - ✓ To improve regulatory alignment and expectations between applicants and EMA.
  - ✓ To consider 3Rs considerations and to identify opportunities for the reduction or optimisation of JAS designs
  - ✓ To optimise guidance

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Review of Local Tolerance Guideline

2024

- EMA/CHMP/SWP/2145/2000 rev.1

- "Stand-alone" studies on local tolerance are generally not required
- In vitro local tolerance testing and /or integration of appropriate endpoints into general toxicity studies highly recommended

Joint NcWP 3RsWP activities

Use of Non-Human Primates (NHPs)

- EFPIA survey in collaboration with NcWP/3RsWP
- Interested party meeting
- Reflection paper on the alternatives to the use of NHPs

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THANK YOU FOR YOUR ATTENTION

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