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Exploring the relevance and considerations of implementing alternative approaches to the assessment of reproductive and developmental toxicity of pharmaceuticals under ICH S5(R3)

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The 3Rs principle (Replace, Reduce and Refine) and the ICH S5 (R3) guideline have globally advanced alternative methods for reproductive and developmental toxicity assessment. These developments bring about stringent requirements and challenges. Reproductive and developmental toxicity assessment is complex, and current alternatives don't fully replicate *in vivo* drug actions, impacting sexual maturation, fertilization, gametogenesis, syncytial development, postnatal maturation and sexual functionality.

ICH S5 (R3) promotes reducing animal use without compromising risk assessment quality, emphasizing justification for including alternative tests in the strategy, adherence to Good Laboratory Practice (GLP), and evaluation of drug metabolite effects following ICH M3 guidelines. The guideline doesn't prescribe specific methods but demands rigorous method validation and lists 29 reference compounds causing maternal embryofetal lethality (MEFL) in non-clinical or human studies with minimal maternal toxicity. Test endpoints should align with objectives and predictive capabilities.

The guideline marks a significant step forward in alternative methods for reproductive and developmental toxicity evaluation. However, practical implementation must consider the test substance's characteristics, distribution, usage, application, and align with regulatory standards. Ongoing exploration and validation are essential.

Comprehensive and successful approaches for *in vitro* drug reproductive toxicity assessment using an integrated testing strategy (ITS) are still evolving. Global institutions should actively develop, validate, and apply these methodologies, collaborating with regulators to elevate alternative methods from a supportive to a leading role. Our institution has devised comprehensive combinations of *in vitro* developmental toxicity and toxicokinetic studies in rodents and non-rodents to advance alternative methods in evaluating reproductive and developmental toxicity.

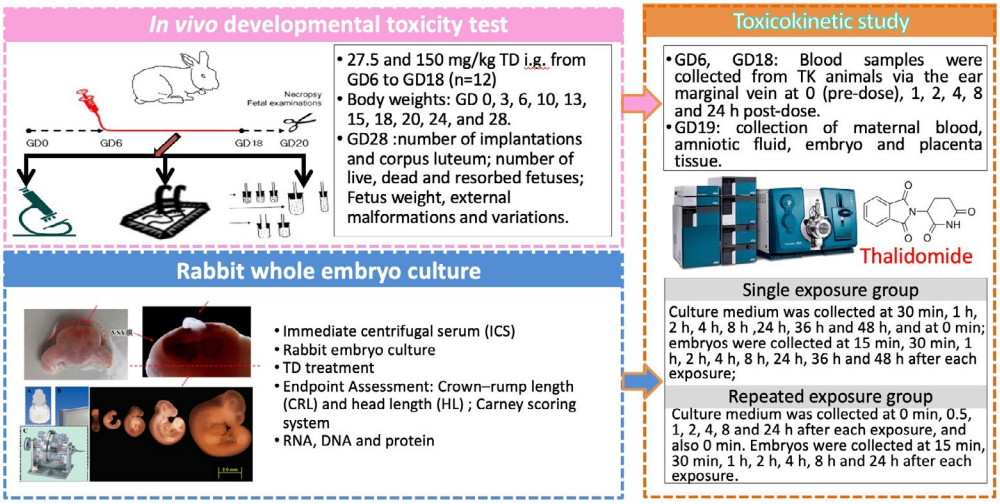

Figure 1: Establishment of an *in vitro* method of rabbit embryo toxicity with toxicokinetics study.

Biography

Jun Guo, MD, PhD is Director and FM of the National Evaluation Centre for Toxicology of Fertility Regulating Drug at the Shanghai Institute for Biomedical and Pharmaceutical Technologies. Her extensive expertise focuses on pharmacological and toxicological research as well as non-clinical safety evaluation of drugs. Present she is working as a Council Member of the Chinese Society of Toxicology (CSOT). She is also the Executive Member and Secretary General of the Special Committee on Reproductive Toxicology within the CSOT. With over a decade of leadership experience, she has led and contributed to numerous national, provincial and ministerial research initiatives. Her contributions extend to more than 30 published papers and 5 books, either as sole editor or co-editor, reinforcing his prominent position in the field.

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