EL3

Issues and challenges in reproductive toxicity testing, including juvenile animal studies

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ICH M3(R2) Guidance has helped clarify the timing of reproductive toxicology studies in drug development. However, the guidance remains general and may not apply to all drug candidates for all circumstances. Therefore, in addition to the guidance document, other factors such as pharmacological, pharmacokinetic (PK), and toxicological characteristics of the drug candidate, and clinical trial design should be considered when planning the timing of these studies. In embryo-fetal development studies, exposure to drug could be indicated by the presence of maternal toxicity, and ICH did not require collection of toxicokinetic (TK) data in these studies. This results in the absence of TK data in some studies, and assessment of risk to pregnant mothers is done using the conversion of animal dose to human equivalent dose based on body surface area. This approach is less precise and occasionally not accepted by regulatory agencies. In rabbit embryo-fetal development study, the absence of PK/ADME data, coupled with the occasional absence of TK data, has led many to question the relevance of this species in risk assessment. A survey has been conducted to address this question. Under the EMA regulation, planning for the juvenile animal study should be submitted early in development. Two approaches are generally considered when designing the juvenile animal study. In the targeted design approach, the study will evaluate target organs of concern in the target population. In the absence of target organs, the modified general toxicity screening approach may be used to identify hazards in the young and developing animals.