ICH S5(R3)
Detection of toxicity to reproduction for human pharmaceuticals

Explanatory slides agreed by EWG members

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Explanatory Note

- This presentation is published with the draft Guideline to explain the proposals made by the ICH S5(R3) EWG.
- The explanatory slides should facilitate understanding, promote essential input for guidance revision, and inform on solicited data necessary to finalize the guideline after the regional consultation period.

Outline

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Background

Experience with standard and novel testing paradigms as well as scientific, technological and regulatory knowledge has significantly evolved since the S5 guidance was first adopted over 20 years ago, which offers numerous opportunities to:

- enhance human risk assessment
- reduce animal use when executing developmental and reproductive toxicity testing

Guideline Objectives

- Re-focusing the guidance on human risk assessment strategies, while acknowledging the value of the study design recommendations in ICH S5(R2)
- Aligning with recommendations in the ICH M3(R2), S6(R1), and S9 guidances and expansion on the principles
- The revised ICH S5 Guideline is intended to provide human safety assurance at least equivalent to that provided by current testing paradigms.

Scope of the Guideline

Pharmaceuticals, including biotechnology-derived products

Vaccines (and their novel constitutive ingredients) 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 is determined by ICH M3(R2), ICH S6(R1), and ICH S9.

Introduction & Proposed General Principles

- Identify hazard and characterize reproductive risk for humans
- Flexibility in testing strategy is proposed, including potential use of alternative assays (*in-vitro*, *ex-vivo* or non-mammalian *in-vivo* assay(s) intended to evaluate a developmental endpoint)
- Proposed considerations for an overall integrated testing strategy (ITS):
  - the target population (reproductive potential and severity of disease)
  - the formulation and route(s) of administration
  - the use of any existing data on toxicity, PD, PK, and similarity to other compounds in structure or activity
  - selection of specific studies, test species/test system and dose levels

Proposed Strategies for Reproductive Toxicity Assessment

Evaluate the need for reproductive toxicity testing.

Proposed considerations:

a) the target patient population and duration of dosing,

b) the known pharmacology of the compound,

c) the known toxicity of the compound,

d) any existing knowledge of the impact of the target(s) on reproductive risk,

e) data from alternative assays that could be relied upon to identify hazard and/or risk

Proposed Strategies for Reproductive Toxicity Assessment

<u>Strategy to address Fertility and Early Embryonic Development:</u>

To examine stages A and B, generally only in rodents or rabbits;

Acknowledges limited feasibility of mating studies in dogs, non-human primates (NHPs)

Outlines the value of repeat dose toxicity studies

- for histopathological evaluation of reproductive organs, and potential inclusion of additional examinations;
- to obviate the need for dose ranging studies
- to decide on the value of routine fertility studies

Addresses importance to evaluate reversibility of effects for risk assessment

Proposed Strategies for Reproductive Toxicity Assessment

Strategies to address Embryo-Fetal Development (EFD)

- Routine Approach (stages C to D)

Expands on the number of species to be tested for on- and off-target effects, depending on PD activity in test species and therapeutic modality (Type of pharmaceutical such as small chemical entity, monoclonal antibody, oligonucleotide, nanobody, peptide, protein, vaccine)

Considers the use of non-routine models, surrogates and transgenic models, also in place of NHPs.

Proposed Strategies for Reproductive Toxicity Assessment

- Optional Approaches for Addressing EFD

Proposes qualification strategies for and use of alternative assays (*In-vitro*, *ex-vivo* or non-mammalian *in-vivo* assay(s) intended to evaluate a developmental endpoint; i.e., teratogenicity or embryo/fetal lethality (TEFL))

Qualified alternative assays in combination with one or more in vivo mammalian EFD studies.

- Justified as part of an ITS (i.e. severity of the disease, patient characteristics, (pharmaceutical target) limitations of some traditional test systems, pharmacological or biological plausibility for developmental toxicity)
- No specific assays recommended

Proposed Strategies for Reproductive Toxicity Assessment

Alternative assays should be GLP compliant and qualified for their intended context of use (e.g.):

- As part of an ITS for assessing EFD endpoints (Scenarios)
- Deferral of definitive studies
- Complete replacement of one species when used in conjunction with an EFD study in limited circumstances
- Contributing to the weight of evidence in case of equivocal animal data
- Toxicity precludes attaining a relevant exposure
- Low systemic exposure in humans (ophthalmics)

- Examples of EFD Testing Strategies using alternative assays:
  - Scenario 1: late-life onset diseases
  - Scenario 2: severely debilitating or life-threatening disease(s)

Proposed Strategies for Reproductive Toxicity Assessment

- Approaches for Deferral of Definitive EFD Studies in 2 Species

applies to circumstances where 2 definitive EFD studies are warranted to allow inclusion of Women Of Child-Bearing Potential (WOCBP) in absence of definitive studies

☞Introduces an addition to ICH M3(R2) preliminary EFD (enhanced pEFD) study: A study that is

- GLP compliant,
- increases the number of pregnant animals to ≥ 8 per group, and
- includes fetal skeletal examinations.

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Proposed Additional Approaches to ICH M3(R2) Allowing Deferral of Definitive EFD Studies

Approach	Stage of Development			
	Limited inclusion of WOCBP[a]	Unlimited inclusion of WOCBP up to start of Phase 3 (supports Phase 2a/b)[b]	Unlimited inclusion of WOCBP up to marketing (supports Phase 3)	To support marketing[c]
A	1st species EFD (enhanced pEFD or definitive) + Qualified alternative assay		2nd species definitive EFD	1st species definitive EFD if not conducted earlier
B	1st species pEFD + 2nd species EFD (enhanced pEFD or definitive)		1st species definitive EFD	2nd species definitive EFD if not conducted earlier
C[d]	2 species pEFD	2 species definitive EFD		

[a] Up to 150 WOCBP receiving investigational treatment for a relatively short duration (up to 3 months).
[b] All approaches include "where precautions to prevent pregnancy in clinical trials (see above) are used."
[c] For monoclonal antibodies, the ePPND is generally conducted before marketing approval (see ICH S6(R1)).
[d] See ICH M3(R2) for regional differences.

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Proposed Strategies for Reproductive Toxicity Assessment

Strategy to Address Effects on Pre- and PostNatal Development (PPND)

- Aim is to detect adverse effects following maternal exposure (implantation through weaning; stages C through F) to monitor potentially delayed effects
- Usually in rats, but other species possible

Toxicokinetics

- Proposed considerations on the importance of exposure information (also applies to alternative assays) and fetal exposure of interest to facilitate data interpretation
- Acknowledges limited ability to translate placental and lactational excretion data from animals to human fetal exposure

Proposed Test System Selection

Routine test species:

Provides considerations on how to choose the primary species when a study is warranted

- Rats are the most often used primary species for all stages of reproductive testing
- Describes species selection for preventative vaccines for infectious diseases

Proposed Test System Selection

Second test species for EFD studies:

- Points to consider for the selection of a second species

Non-routine test species:

- Can be appropriate to evaluate the effects on the various reproductive stages.
- The suitability depends on the reproductive endpoints
  - Table of species advantages/disadvantages (Annex)
  - Discusses use of NHPs, surrogate molecules, genetically modified models in case of limitations in pharmacological relevance, also for biotechnology-derived products (ICH S6(R1))

Proposed Test System Selection

Other Test Systems

Disease Models

- Not routinely used, but can be informative in some cases

Genetically Modified Models and Surrogate Molecules:

- To investigate effect of the intended pharmacology on reproduction
- Clarifies that the model should generally be evaluated with the clinical candidate to assess both on- and off-target effects
  - In absence of adequate activity against the target receptor, surrogate molecules can be used.

Proposes More Dose Level Selection Options

Dose Selection Common to all Pharmaceuticals, Including Biotechnology-derived Pharmaceuticals

- Toxicity-based Endpoints
- Absorption, Distribution, Metabolism and Excretion-based Saturation of Systemic Exposure Endpoint Endpoint
- Exposure-based Endpoint (new)
  - Potential use of > 25 fold exposure at maximum recommended human dose can be adequate in absence of toxicity-based endpoints
- Maximum Feasible Dose Endpoint (new)
- Limit Dose Endpoint
- Selection of Lower Dose Levels (new)

Dose Selection and Study Designs for Vaccines

Considerations for dose, route of administration, and dosing schedule for prophylactic and therapeutic vaccines (adjuvanted or not) against infectious diseases

- Recommends testing full human dose, a single dose level can be sufficient
- Recommends episodic dosing, and at least one dose during pregnancy
- For novel, active constituent ingredient (including novel adjuvants), consideration of additional testing strategies similar to those for non-vaccine products can be appropriate

Proposed Designs and Evaluations of In Vivo Mammalian Studies

Includes designs of possible combinations of studies:

- Three separate studies to assess all stages: FEED, EFD, PPND
- Single study design (stages A→F)
- Two study design (fertility/EFD + PPND, A→F + EFD)
- Combination design of repeated dose and fertility studies
  - ☞ Study details can be found in Annex.
- Evaluation of Data
  - ☞Outlines Data Handling, Data Presentation and Statistics for in vivo Studies

Proposed Principles of Risk Assessment

Factors to estimate the likelihood of increased reproductive or developmental risk for humans to determine the level of concern:

- animal-human exposure ratio, level of maternal toxicity, dose-response relationship, type of observed effect(s), cross-species concordance, or similarity of pharm / tox mechanisms.

Comparison of exposure at the NOAEL is a critical determination

- Proposal for decreasing concern over an exposure range of 10 to 25 x (animal NOAEL to human MRHD)

Proposed Principles of Risk Assessment

Risk Assessment for Reproductive and Developmental Toxicities

In this guideline, the term teratogenicity is in reference to malformations.

In general, teratogenicity and embryo-fetal lethality (TEFL) are the critical endpoints in assessing developmental toxicity

Reversible or minor manifestations (eg, changes in fetal weight, skeletal variations) by themselves are of lesser concern, although their presence can influence the risk perspective.

Proposed Qualification of Alternative Test Systems for Regulatory Acceptance

- Provides a framework to facilitate the qualification of alternative assays.
- Assays qualified based on performance (reliability and predictivity) with known developmental toxicants
  - Some compounds have been identified for inclusion on the ICH Reference Compound List (see next slide)
  - Selection factors for the ICH Reference Compound List
- Performance Factors

Proposed Qualification of Alternative Test Systems for Regulatory Acceptance ctd.

- The ICH Reference Compound List **is not complete**.
  - We are soliciting data for additional reference compounds for potential inclusion into the list, including relevant information.
  - A template is provided.
- Assay Qualification Information to be Provided to Health Authorities
  - No centralized approval process for regulatory acceptance of qualified alternative assays is proposed – remains agency specific.

Summary of Proposed Guidance Revision

- Focus on application to human risk assessment
- Additional dose selection endpoints
- Emphasizes the use of existing data
- Integrated testing strategies for assessing reproductive toxicity, including for biologics
- Guidance on alternative assays: requirement of use & possible integration in risk assessment
- Focus of EFD risk assessment on teratogenicity or embryo/fetal lethality