Handout

ESTP International Expert Workshop

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Communication of Adversity for the Female Reproductive System at the Program Level

The toxicological assessment of a compound usually includes multiple in-vitro and in-vivo studies aiming to define conditions of safe use for production workers and end users.

The iterative process of identifying a possible hazard due to the compound, defining the relevant exposure scenario and developing a risk assessment can be highlighted by considering the development of a "standard" pharmaceutical molecule: To enter the **first human trials** (Phase 1) in healthy volunteers normally repeated dose toxicity testing in two species is available. At this stage no dedicated reproductive toxicity testing is done, and effects on female reproductive organs might not be in focus as the studies are usually conducted in male humans. If the compound still shows promise the **efficacy of the compound** will be tested in humans, but only after additional general toxicity studies covering the duration of the treatment in the human study and at least embryo-fetal developmental (EFD) studies are completed to allow for the inclusion of women of childbearing potential (WOCBP). After demonstrating the safety and efficacy in these studies, and before **entry in the larger clinical studies**, long term toxicity studies and the fertility and early embryonic developmental (FEED) studies have to be completed. The carcinogenicity studies and the Pre-and Postnatal developmental (PPND) studies are only needed for **marketing of the compound**.

This means the risk assessment for effects on the reproductive capacity of women included in a Phase 2 study usually is based on the results of repeat dose studies and only if these studies show possible effects e.g. additional nonclinical studies might be included to better characterize this potential hazard or include special monitoring of early safety biomarkers might be included in the human studies. **The Guidance for Industry – "Reproductive and Developmental Toxicities – Integrating study results to assess concerns"** (FDA guidance, 2011) provides decision trees for the assessments of Reproductive/Developmental Toxicity, including female fertility.

The following gives some definitions of concepts and common acronyms and provides references to relevant regulatory guidelines and publications.

General Definitions and Abbreviations:

Hazard:	The intrinsic property of a substance that has the potential to cause harm.
Risk:	The likelihood that a hazard will cause harm under defined conditions of exposure.
Adverse effect:	Change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences. Decisions on whether or not any effect is adverse require expert judgement. (according to IPCS/WHO 1994)
BMD:	Benchmark Dose: Statistically derived dose/exposure level corresponding to a defined response rate, like increased incidence of an adverse effect.
NOEL:	No observed effect level: The highest dose at which no biological response could be detected.
LOEL:	Lowest observed effect level: The lowest dose at which some biological response could be detected.
NOAEL:	No observed adverse effect level: The highest dose at which no adverse response could be detected.
LOAEL:	Lowest observed adverse effect level: The lowest dose at which an adverse response could be detected.
MTD:	Maximum tolerated dose: The highest dose that not causing unacceptable effects.
WOCBP:	Woman of Childbearing Potential (see ICH M3)
DART:	Developmental and Reproductive Toxicity (see ICH S5)
EFD	Embryo-Fetal Development (see ICH S5)
FEED	Fertility and Early Embryofetal Development (see ICH S5)
PPND	Pre- and Postnatal Development (see ICH S5)

Guidelines for pharmaceuticals:

The guidelines of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (**ICH**) provide the concepts and studies necessary to develop new pharmaceuticals and are widely accepted. The good starting point to understand the principle of nonclinical safety assessment for pharmaceuticals is the multidisciplinary guideline **M3(R2) – Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization**, which defines the type and timing of nonclinical safety studies needed to support human clinical trials and marketing authorization.

More detailed information on different aspects for the safety assessment is given in the dedicated safety guidelines listed below. ICH S5(R3) is dedicated to DART testing.

No.	*Title*	Scope
S1A	*Need for Carcinogenicity Studies of Pharmaceuticals*	Defines when carcinogenicity studies are necessary for new drugs.
S1B	*Testing for Carcinogenicity of Pharmaceuticals*	Provides principles for conducting long-term carcinogenicity studies.
S1C(R2)	*Dose Selection for Carcinogenicity Studies of Pharmaceuticals*	Offers guidance on selecting appropriate doses for carcinogenicity testing.
S2(R1)	*Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*	Describes standard in vitro and in vivo tests to detect genotoxic potential.
S3A	*Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*	Guides the integration of pharmacokinetics into toxicity studies.
S3B	*Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies*	Provides recommendations for tissue distribution studies in repeated-dose toxicity.
S4	*Duration of Chronic Toxicity Testing in Animals (Rodents and Non-Rodents)*	Specifies durations for chronic toxicity studies to support long-term human use.

No.	*Title*	Scope
S5(R3)	*Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility*	Covers testing strategies for reproductive and developmental toxicity.
S6(R1)	*Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*	Addresses safety testing for biologics including monoclonal antibodies and recombinant proteins.
S7A	*Safety Pharmacology Studies for Human Pharmaceuticals*	Defines core safety pharmacology studies for CNS, cardiovascular, and respiratory systems.
S7B	*Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation)*	Focuses on assessing proarrhythmic risk, especially QT prolongation.
S8	*Immunotoxicity Studies for Human Pharmaceuticals*	Provides guidance on evaluating immunotoxic potential of drugs.
S9	*Nonclinical Evaluation for Anticancer Pharmaceuticals*	Tailors nonclinical safety requirements for oncology drugs.
S10	*Photosafety Evaluation of Pharmaceuticals*	Offers a framework for assessing phototoxicity risk.
S11	*Nonclinical Safety Testing in Support of Development of Paediatric Medicines*	Addresses juvenile animal studies and pediatric-specific safety considerations.
S12	*Nonclinical Biodistribution Considerations for Gene Therapy Products*	Guides biodistribution studies for gene therapy products to assess tissue targeting and off-target effects.

Guidelines for Chemicals

The recent discussions on adversity assignment in toxicologic pathology showed some bias towards pharmaceuticals and did not mention other chemical use cases in much detail.

There exists a multitude of national and international regulations for chemicals for different use, like biocides, cosmetics, food additives or industrial chemicals. A comprehensive summary of all the relevant differences is not possible here, but at least the different, general assessment for chemicals between the European and US-American regulatory agencies might be mentioned. In Europe the assessment is basically hazard-driven, meaning if a relevant DART effect is identified (this includes female fertility) the compound might end on the high concern list, even if exposure of consumers to the compound might not be demonstrated. In the US the process is more risk-based and allows for an easier waiving of possible concerns based on an assessment that the observed hazard will not cause a relevant risk. This difference in hazard and risk assessment between pharmaceuticals and chemicals, and the name of the regulatory body involved in the decision-making process have no impact on the basic toxicological assessment either on study level or general assessments of substances.

OECD Guidance Document 43 "On mammalian reproductive toxicity testing and assessment" (OECD, 2008) gives a comprehensive overview on the general process and provides some insights how risk assessment of female reproductive organ effects can be supported. The topic of "Endodrine Disruption" is not yet included in this guidance document but has gained high relevance in the last years for risk assessment of chemicals. For general information on this fast developing topic see OECD Endocrine Disrupters.

The following table lists several OECD guideline studies with relevant endpoints for female reproductive organs and reproductive toxicity. The list is limited to mammals.

No.	*Title*	Scope
407	*Repeated Dose 28-day Oral Toxicity Study in Rodents*	Assesses effects of repeated oral exposure over 28 days in rodents, including clinical, hematological, and histopathological parameters.
408	*Repeated Dose 90-Day Oral Toxicity Study in Rodents*	Evaluates systemic toxicity from daily oral dosing over 90 days in rodents, supporting subchronic safety assessment.
409	*Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents*	Evaluates systemic toxicity from daily oral dosing over 90 days in non-rodent species supporting subchronic safety assessment.

No.	*Title*	Scope
414	*Prenatal Developmental Toxicity Study*	Investigates potential effects of substances on embryo-fetal development following maternal exposure during pregnancy.
415	*One-Generation Reproduction Toxicity Study*	Evaluates effects on fertility and reproductive performance in one generation of animals.
416	*Two-Generation Reproduction Toxicity Study*	Assesses reproductive toxicity across two generations, including fertility, gestation, and offspring development.
421	*Reproduction/Developmental Toxicity Screening Test*	Provides initial data on reproductive and developmental toxicity, useful for early hazard identification.
422	*Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*	Combines repeated-dose toxicity and reproductive/developmental screening in a single study design.
440	*Uterotrophic Bioassay in Rodents: A Short-Term Screening Test for Oestrogenic Properties*	Detects estrogenic activity of chemicals based on uterine response in ovariectomized female rodents.
443	*Extended One-Generation Reproductive Toxicity Study*	Comprehensive study of reproductive and developmental effects, including endocrine-sensitive endpoints and optional second generation.
451	*Carcinogenicity Studies*	Long-term studies to identify potential carcinogenic effects of chemicals in rodents.