

**Final Concept Paper**  
**S5(R3): Detection of Toxicity to Reproduction for Human Pharmaceuticals**  
**dated 9 February 2015**  
*Endorsed by the ICH Steering Committee on 27 March 2015*

### **Type of Harmonisation Action Proposed**

Revision of the ICH S5 (R2) Guideline as defined in the “Revised ICH Procedures” (2011), section “3. Revision Procedure”<sup>1</sup>.

### **Statement of the Perceived Problem and Background**

The S5(R2) Guideline on Reproductive Toxicity was written over 20 years ago. Since its implementation, not only has experience been gained with the testing of pharmaceuticals using the current and novel testing paradigms; but scientific, technological and regulatory knowledge has also significantly evolved. Consequently there are now opportunities for modernising testing paradigms to enhance human risk assessment, while also potentially reducing animal use. In addition, there may be areas in which the guideline could be revised or amended for greater clarity or usefulness as well as to align more fully with other guidelines, e.g. ICH M3(R2), ICH S6(R1) as well as ICH S9.

ICH S5(R3) should provide human safety assurance at least equivalent to that provided by current testing paradigms.

ICH S5(R3) Guideline should therefore address the following topics:

- Alignment of the existing ICH S5(R2) Guideline with the revised ICH S6(R1) and ICH M3(R2) and the ICH S9 Guidelines. Several different ICH guidances make specific recommendations on the conduct of Embryo Fetal Development (EFD) assessments. These are not currently represented in the ICH S5(R2) guidance. Furthermore, some of the approaches recommended could be adapted in principle to circumstances beyond those discussed in these other guidelines. For example, ICH S9 states that “*in cases where an embryofetal developmental toxicity study is positive for embryofetal lethality or teratogenicity, a confirmatory study in a second species is usually not warranted.*” ICH S5(R3) could identify other serious and life-threatening diseases where a single positive study could suffice, particularly if the mode of action is thought to convey a reproductive risk. Likewise, ICH M3(R2) allows for a specific study design (ie, a preliminary EFD study), which could be elaborated upon in ICH S5(R3) *along with a strategy for inclusion of such data in an integrated EFD risk assessment.*
- Elaborate on how human exposure data could be used to determine appropriate dose levels for mammalian reproductive toxicity studies, to optimise testing strategies for

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#### <sup>1</sup> **3) Revision Procedure (Category 3)**

If an adopted guideline needs to be revised, then the formal ICH *Step* procedure should take place rather than the Q&A process. Any revision or modification to an existing ICH guideline should fall into the “Revision Procedure” category\*.

There are two approaches for revision of an existing ICH guideline under this category. The first approach involves amendments being made directly to the content of the existing guideline e.g., in cases where the scientific/technical content is no longer up-to-date or valid. The second approach is where the existing guideline is not modified, but instead an Addendum or Annex to that guideline is developed. The latter approach is normally used where no amendments to the content of the existing guideline are necessary but there is a need to provide further complementary guidance.

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human risk assessment, and to provide more clarity to section 3.1 of the current guideline. Opportunities for improvement might include providing guidance on appropriate exposure multiples or other endpoints for high dose setting in reproductive toxicity studies, as do other ICH guidelines (e.g. ICH M3(R2)). In addition, as the current ICH S5(R2) suggests providing dose response data and establishing a no observed adverse effect level (NOAEL), ICH S5(R3) could clarify expectations when such a dose response and NOAEL would be in the anticipated sub-therapeutic exposure range.

- Expand the options of combining reproductive toxicity studies and their designs as appropriate for specific purposes. Examples might include combination of rat fertility and EFD studies in females; the conduct of a single study in female rats addressing fertility, EFD and pre and post-natal development PPND; incorporation of rat male functional fertility evaluations into repeat dose toxicity studies; and combination of peri-postnatal and juvenile rat studies. The delineation of these options could enhance human risk assessment (e.g. for compounds with long half-lives) whilst contributing substantially to reduction in animal usage.
- Clarification on several of the technical recommendations present in the current guideline based on the evolved science (e.g. toxicokinetics, refinement of behavioural and functional tests). The current wording in ICH S5(R2) indicates that data on comparative kinetics may be useful to extrapolate the results to humans (assess the relevance). In the light of the current knowledge, however, it is now considered that information on systemic exposure of pregnant animals is essential for the interpretation of study results, and thus to assess human safety.
- ICH S5(R2) already highlights the value of “*other test systems*” (section 2.2). However, the guideline also states that “*other test systems cannot provide assurance of the absence of effect nor provide perspective in respect of risk/exposure*” in the context of the entire reproductive cycle. Nonetheless, after two decades of scientific progress, a number of *in vitro*, *ex vivo* and non-mammalian *in vivo* assays are being used as discovery screens for EFD. In addition, some of these assays are being examined for use for regulatory purposes under defined scenarios. ICH S5(R3) will note that *in vitro*, *ex vivo* and non-mammalian *in vivo* assays are not to be considered the default approach but might be considered for regulatory purposes under limited circumstances, yet to be defined. Specific *in vitro*, *ex vivo* and non-mammalian *in vivo* assays will not be recommended in the guideline. The guideline may include basic principles, possibly as appended information, that would assist in the development and potential regulatory use of *in vitro*, *ex vivo* and non-mammalian assays.
- Describe the circumstances under which the outcome of “*preliminary EFD studies*” (as described in ICH M3(R2)) could determine the ultimate risk assessment for EFD, thereby providing more clarity on the application of section 11.3 and Note 4 of ICH M3(R2). This could, for example, involve elaboration on the circumstances under which a clearly positive (e.g. foetal malformation and death) preliminary EFD study might obviate the need for more comprehensive evaluation in a definitive EFD study.

### Issues to be Resolved

The following major issues have been identified:

- Agreement on appropriate multiples above human exposure and other endpoints that could be used for dose selection in reproductive toxicity studies;
- Agreement on criteria for species selection taking into account relevance to humans;

- Development of basic principles for possible regulatory acceptance of *in vitro*, *ex vivo*, and non-mammalian *in vivo* EFD assays;
- Design of optional integrated testing strategies involving an *in vivo* mammalian EFD assessment and *in vitro*, *ex vivo* and non-mammalian *in vivo* EFD assays, and the limited circumstances under which such a testing strategy would be considered.

### **Type of Expert Working Group and Resources**

In order to have the appropriate expertise and to keep the size of the EWG manageable, it is suggested that each ICH party have the flexibility to nominate up to three experts to allow for a broad range of subject expertise to be adequately represented. The EWG will be comprised of two to three members nominated by EU, EFPIA, FDA, PhRMA, MHLW, JMPA, Health Canada and Swissmedic. One member can also be nominated by WHO Observer, biotech industry, and as well as RHIs/DRAs/DoH (if requested).

This Expert Working Group for ICH S5(R3) will revise the guideline and conduct the necessary data analysis in line with the identified topics.

### **Timing**

Taking into account that complex issues mentioned above need to be addressed and taking into account that data analysis will be required a time frame for revision to a *Step 2* by the EWG of approximately 2.5 years from the establishment of the EWG is foreseen.

A period of 2 years is foreseen for *Step 4*.