Final Concept Paper
S9: Q&As on Nonclinical Evaluation for anticancer pharmaceuticals
dated 22 October 2014
Endorsed by the ICH Steering Committee on 23 October 2014

Type of Harmonisation Action Proposed

Maintenance of ICH S9 by Q&As.

Statement of the Perceived Problem

The ICH S9 Guideline reached *Step 4* in November 2009 and the guideline is a significant advance in promoting anticancer drug development; however, it is vague in some places and open to broad and divergent interpretation by both regulatory authorities and industry. For example, the scope of the guideline indicates that the document is intended to cover treatment of patients with serious and life threatening malignancies. This has been interpreted various ways by ICH Members and Observers. Other areas that could be clarified center around interpretation and implementation of provisions of the guideline. These topics are discussed in detail below with specific reference to the relevant section of the guideline. To promote consistent interpretation and implementation of the guideline by ICH member regions and Observers and, of additional benefit, to continue progress in the 3Rs of reduction, refinement, and replacement, harmonised clarification is needed which may be readily addressed by Q&As and case examples.

Preliminary Identification of Topics to be Resolved

Topics Related to the Scope

1. The Scope of ICH S9 states that the guideline applies to cancer in patients with severe and life-threatening malignancies. This has been interpreted in varying ways by ICH Members and Observers. Programs for pharmaceuticals for treatment of a cancer that has no or poor therapeutic options, and is invariably fatal, yet patients may have an extended survival period, have been interpreted as either in or out of Scope. For example, some sponsors conduct studies such as fertility and pre-and postnatal studies, regardless of whether the pharmaceutical would fall within the intended Scope of ICH S9, to avoid potential delays in a development program. Thus, a full battery of nonclinical studies as described by ICH M3, compared to the more abbreviated pathway described by ICH S9, is the preferred development pathway due to varying interpretations of the scope of ICH S9, possibly due to the lack of clarity in the wording of the scope.

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2. There is a disconnect between ICH S1A and ICH S9 as to when carcinogenicity studies are needed, and some clarification would be useful. Carcinogenicity studies are not considered necessary, according to ICH S9, for patients with severe or life-threatening malignancies, and refers to ICH S1A regarding the appropriateness of a carcinogenicity assessment. As described by ICH S1A, carcinogenicity studies are generally expected when the duration of the pharmaceutical use is at least 6 months continuous use, or repeated intermittent use. Where the life-expectancy is short (i.e., less than 2 - 3 years) no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When pharmaceuticals are intended for adjuvant therapy in tumor free patients or for prolonged use, carcinogenicity studies are usually needed. The intent of ICH S9 with regard to carcinogenicity testing is not clear. This disconnect between ICH S1A and ICH S9 may be leading to additional carcinogenicity studies that do not add to the safety assessment of a pharmaceutical.
3. Section 3.4 of ICH S9 discusses the duration of toxicology studies to support moving to Phase II and into second or first line therapy in patients with severe and life threatening malignancy. For treatment of these patients, studies of 3 months duration are sufficient to support marketing. The question often arises as to the duration of nonclinical studies needed when the disease is not *immediately* life-threatening, even though it is serious, i.e., patients with no or poor therapeutic options. The S9 Guideline has been interpreted to mean either that nonclinical studies of 6 and 9 months duration are needed, or that the available clinical and nonclinical data may be sufficient to warrant continued clinical investigation to the treatment of patients with cancer without the need for additional nonclinical studies. Some clarity around what constitutes a sufficient nonclinical dataset for this patient population would be useful.

Topics related to the guideline Interpretation and Implementation

1. The S9 Guideline states that an assessment of the potential to recover from toxicity should be provided but provides few other details, and sponsors and regulators have interpreted this language in different ways. What constitutes an adequate assessment is not described, such as whether recovery groups are needed in both first-in-human and the chronic studies, one species or all species, etc., leading to use of recovery groups by default in all pivotal nonclinical studies to avoid delays in development.
2. A toxicology study in only one species may be sufficient for a cytotoxic drug, determined on a case-by-case basis, as described in section 2.4. The foundation of this recommendation was consistency with an EMA guideline in effect at the time ICH S9 was written, in which rodents only were sufficient to initiate a clinical investigation. Elsewhere in the guideline (section 3.4), it states that studies (plural) of 3 months duration are sufficient for marketing. The S9 Guideline is not clear whether or not general toxicology studies in 2 species are recommended for continued clinical development for this class of compounds.

3. Section 4.1 of the guideline states that the safety of the conjugated material is the primary concern, and the safety of the unconjugated material can have a more limited evaluation. There is no discussion of what constitutes a "more limited evaluation", leaving sponsors and regulators to guess the intent. Some clarity would lead to more consistent interpretation. For Antibody Drug Conjugates (ADC), this uncertainty has led to additional arms in animal studies with the small molecule and the unconjugated antibody, or separate, complete toxicological evaluation of each separate constituent of the ADC. As this class of compounds is of growing importance, clarity about the need for the toxicological evaluation of the various components is essential.
4. For evaluation of impurities, section 4.4 of ICH S9 discusses the attributes of a qualification assessment to justify impurity levels for both non-genotoxic and genotoxic impurities. For genotoxic impurities, S9 states that "justifications described above should be considered to set higher limits" than approaches discussed elsewhere, a vague reference to ICH M7, currently under development. The "justifications described above" include reference to the limits specified in Q3A and Q3B. If the limits specified by ICH Q3A and Q3B are acceptable for genotoxic impurities, as some interpret this section, this should be clearly stated in ICH S9.
5. The guideline provides minimal detail around some aspects of drug development, including ADME (absorption, distribution, metabolism, and excretion), drug-drug interactions, and in vitro pharmacology screens. Some additional detail around these topics would add clarity.

Additional topics for clarification around interpretation of wording and implementation of the guideline as identified by the IWG should be addressed in the Q&A. Identification of specific areas for clarification will also be requested of Observer representatives as Observers did not participate in the initial development of the guideline and thus clarity around specific topics or wording would be helpful.

Type of Implementation Working Group

We recommend setting up an Implementation Working Group (IWG). The IWG will be comprised of two members nominated by EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada and Swissmedic. One member can also be nominated by WHO Observer, biotech industry as well as RHIs, DRAs/DoH (if requested).

Timetable

Basically, the work should be conducted primarily by email and teleconferences. Questions outlined in the Concept Paper will be submitted to the IWG for discussion and additional questions will be solicited from all members of the IWG. Prior to and during the initial telecom (expected in January 2015), additional questions will be solicited. Early discussions will focus on assessing which questions are easily answered by simple clarification in the wording and which may necessitate more extensive explanations. The former would be posted as *Step 4* and the later would likely necessitate consultation at *Step 2*.

Composition of the IWG determined	4Q 2014
Initial teleconference to determine ground rules and solicit additional questions	1Q 2015
Publication of answers at *Step 4*	2Q 2015
Address any questions that may need consultation	4Q 2015
Face-to-face meeting (if necessary) to address difficult questions	2Q 2016
Finish work of IWG	4Q 2016