S9 Implementation Working Group

ICH S9 Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals

Questions and Answers

Current version

dated 8 June 2016

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

ICH Secretariat, Chemin des Mines 9, P.O. Box 195, 1211 Geneva 20, Switzerland

Telephone: +41 (22) 338 32 06 - admin@ich.org, http://www.ich.org

In order to facilitate the implementation of the ICH S9 Guideline, the ICH Experts have developed a series of Q&As:

S9 Q&As
Document History

Code	History	Date
S9 Q&As	Endorsement by the ICH Assembly under *Step 2a*. Endorsement by the ICH Regulatory members of the Assembly under *Step 2b*. Release for public consultation.	15 June 2016

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PREFACE

The ICH S9 Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals reached *Step 4* in November 2009 and the guideline was a significant advance in promoting anticancer drug development. Since reaching *Step 4*, all the parties using the guideline have experienced some challenges around implementation. Implementation of the guideline has revealed areas that are open to broad and divergent interpretation by both regulatory authorities and industry. For this reason, an Implementation Working Group (IWG) was formed in October, 2014, by the International Council for Harmonization, formerly the International Conference on Harmonisation (ICH), to develop Questions and Answers to provide additional clarity around anticancer pharmaceutical development. The Questions and Answers developed by the IWG are intended to facilitate the implementation of the S9 Guideline and, of additional benefit, to continue progress in the 3Rs of Reduction, Refinement, and Replacement in use of animals.

S9 Questions and Answers

1. INTRODUCTION - SCOPE

#	Questions	Answers
1.1	The ICH S9 Guideline provides information for pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies. Are all initial development plans for anticancer pharmaceuticals covered under S9?	Most initial development programs are performed in patients (adult and pediatric) whose disease is resistant and refractory to available therapy, the nonclinical program described in ICH S9 is applicable. See also the answer to Q1.2. For other initial development programs in cancer, ICH S9 should be used as a starting point, and other studies added as appropriate with reference to ICH M3 and S6. For initial development programs for pharmaceuticals to treat patients with early stage disease where there is no prior clinical experience, the nonclinical studies described in ICH M3 may be appropriate. In some situations where the development pathway is not clear, regulatory agencies should be consulted.
1.2	If the First in Human (FIH) study is conducted in a patient population with resistant and refractory disease, will subsequent Phase I studies in a different cancer, but still a resistant and refractory population, still be covered under S9?	Yes.
1.3	In general, the guidance has been interpreted as applying when life expectancy is approximately 3 years. It would be useful to provide further clarity about the intended population.	The S9 Guideline does not make a reference to years of life expectancy and the application of the guideline should not be based on an expectation of survival as measured in years. The intent of the Scope is clarified in questions 1.1 and 1.2.
1.4	Can the principles of ICH S9 be applied to non-oncology therapeutics where the disease is life-threatening with limited therapeutic options?	These indications are outside of the scope of ICH S9. See ICH M3(R2) for guidance on when particular studies can be abbreviated, deferred, omitted or added on a case-by-case approach to optimize drug development for life-threatening or serious diseases other than cancer.

1.5	Are clinical trials in the adjuvant setting covered under ICH S9?	Yes. ICH S9 should be used as the starting point for drugs used in adjuvant setting even when there is a lack of detectable residual disease if the disease has a high rate of recurrence. In other situations with high cure rates, additional nonclinical studies may be needed. In all cases, it is important to consider the natural course of the disease. See also the response to Question 1.1 and 1.6.
1.6	In the case where a therapeutic increases survival – what further toxicology work is recommended, if any, and the appropriate timing of any studies?	When the anticancer pharmaceutical is shown to extend survival of patients, no additional general toxicology studies are usually warranted. The clinical safety data in the intended population is more relevant to assess human risks than those generated in additional animal studies. Toxicology studies other than general toxicology may be needed on a case-by-case basis. If additional studies are important, such studies could be available post-approval.
1.7	The Scope indicates that in patients with long expected survival, the recommendations for additional nonclinical general toxicology studies depend on the available nonclinical and clinical data and the nature of toxicities observed. Are additional nonclinical safety tests needed, when an anti-cancer pharmaceutical, in clinical development or approved for a particular malignant tumor according to the S9 Guideline, is to be applied to another indication that is not immediately life-threatening, but is serious?	When moving therapeutic development from an approved indication in oncology or from an unapproved indication with a sufficient nonclinical and clinical safety dataset, to an unapproved oncology indication that is not immediately life-threatening but is serious, additional general toxicology studies e.g., chronic studies (6 or 9 month-studies) are generally not warranted unless there is a specific cause for concern. Similar to the response under Question 1.6 the clinical safety data generated in the patient population for the approved indication is most meaningful and relevant to inform the safety plan for the patient population in the unapproved indication. Toxicology studies other than general toxicology may be needed on a case-by-case basis.

2. STUDIES TO SUPPORT NONCLINICAL EVALUATION

#	Questions	Answers
2.1	In Section 2.1 "Pharmacology", the guidance states that studies should characterise "anti-tumor activity" of the pharmaceutical. The inference is that these are *in vivo* studies. The typical animal models (e.g., xenografts) are not generally predictive of human response. Is *in vivo* characterisation necessary to address pharmacology?	If *in vitro* systems used for pharmacology studies of anti-tumor activity are demonstrated to generate relevant data, then they should be considered sufficient.
2.2	Is there the need for nonclinical lactation and placental transfer studies?	There is no specific need for lactation or placental transfer studies.
2.3	Should recovery groups be included in toxicology studies supporting FIH toxicology studies?	A scientific assessment of the potential to recover should be provided in all general toxicology studies used to support clinical development although recovery groups should not automatically be included in all general toxicology studies. This information can be obtained by an understanding that the particular effect observed is generally reversible/non-reversible or by including a recovery period in at least one study and one dose level, to be justified by the sponsor.
2.4	Should recovery groups be included on 3-month toxicology studies to support Phase III?	Recovery in 3-month studies is not specifically warranted unless there is a compelling concern from clinical studies that recovery animals could address. A scientific assessment of the potential to recover from toxicity should be provided for general toxicology studies used to support clinical development, although recovery groups should not automatically be included in all general toxicology studies. A more directed approach using appropriate models can be appropriate to address a specific safety question.
2.5	Patients with cancer are often given supportive care drugs (e.g. antibiotics). Is there a situation where adding supportive care drugs to toxicology studies are appropriate?	Treating affected animals with supportive care during toxicology studies can be appropriate in some cases, e.g., when secondary infection due to immunosuppression is observed on the study. Giving supportive care prophylactically to all animals is generally not recommended.

2.6	Is there any guidance on the need for abuse liability studies for drugs developed under ICH S9?	Nonclinical studies for abuse liability are generally not warranted to support clinical trials or marketing of pharmaceuticals for the treatment of patients with advanced cancer.
2.7	What is the utility of tissue cross reactivity studies for biopharmaceuticals containing a Complementary Determining Region (CDR) (i.e., mAbs, Antibody Drug Conjugates (ADCs)) that fall under ICH S9 and do these studies need to be conducted?	Tissues cross reactivity studies are not needed with the initial Investigational New Drug (IND) or later in development, unless there is a specific cause for concern. In cases where there are no pharmacologically relevant species, human tissue cross reactivity should be considered.
2.8	The guidance allows for testing in only one species if there is a positive signal for embryofetal lethality or teratogenicity. If clear evidence of embryofetal lethality or teratogenicity is observed in a dose-range finding study in one species, is a definitive study in that species recommended?	If a study shows clear signs of embryolethality or teratogenicity in one species, then that study may be sufficient to support marketing even if it is a pilot/dose range finding study.
2.9	In cases where the mechanism of action is expected to yield a reproductive toxicity risk and/or knock out animals or use of surrogate biologics in rodents have demonstrated a reproductive risk, should these approaches be considered sufficient for hazard identification, or should a study in pregnant Non-Human Primates (NHPs) be conducted?	A weight-of-evidence assessment of reproductive risk should be provided. An NHP study to assess EFD hazard should not be considered a default approach. Development toxicity studies in NHP can only provide hazard identification according to ICH S6 (R1). The expected reproductive hazard should be appropriately indicated in the label.
2.10	Section "2.6 Genotoxicity". Which and how many *in vitro* studies would have to be positive in order to make the *in vivo* assays unwarranted?	If both *in vitro* (mutagenesis and clastogenicity) assays are positive, then the *in vivo* assay is generally not warranted.

2.11	Section "2.9 Photosafety Testing" states that if initial assessment of phototoxic potential based on physico-chemical properties indicates a phototoxic risk, when is it recommended to conduct nonclinical photosafety studies?	ICH S10 should be consulted for assessment of photosafety risk, if the approaches outlined in ICH S9 and ICH M3 (R2) are not adequate.

3. NONCLINICAL DATA TO SUPPORT CLINICAL TRIAL DESIGN AND MARKETING

#	Date of Approval	Questions	Answers
3.1	**3.1**	In Section 3.1 "Start Dose of First Administration in Humans" reference is made to immune agonist biopharmaceuticals. Small molecule drugs can also be immune agonists. Can a Minimally Anticipated Biological effect level (MABEL) approach also be used for small molecules?	If appropriate, a MABEL could be used for small molecules. A MABEL approach should be considered if risk factors are derived from knowledge regarding (1) the mode of action, (2) the nature of the target, and/or (3) the relevance of animal models.
3.2	**3.1, Note 2**	Can it be clarified that Note 2 on Highest Non-Severely Toxic Dose (HNSTD) can be used for biopharmaceuticals as well?	The HNSTD may be appropriate in determining a starting dose (e.g., when drug is not an immune agonist) taking into consideration differences in binding affinity and pharmacological properties of the biopharmaceutical (including ADCs).
3.3	**3.3, 3.4**	ICH S9 states that in cases where the available toxicology information does not support a change in clinical schedules, an additional toxicology study in a single species is usually sufficient. What additional toxicology studies should be conducted, one month or 3-month toxicology study, if the 3-month studies with the original	If needed, a short term study up to 1-month duration should generally be sufficient to support a change in schedule (See ICH S9, Table 1 for additional guidance).

		schedule have already been conducted?	
3.4	**3.4, 2.4**	What general toxicology studies are recommended for continued clinical development, including marketing, for genotoxic drugs targeting rapidly dividing cells?	For genotoxic drugs targeting rapidly dividing cells (e.g., nucleoside analogs, alkylating agents, microtubule inhibitors) that have anti-proliferative effects (evident in rapidly growing tissues) expected to be consistent across different species, toxicity studies in one rodent species of 3-month duration is considered sufficient for continued clinical development and registration.
3.5	**3.5**	Section 3.5 of ICH S9 states that pharmaceuticals planned for use in combination should be well studied individually in toxicology evaluations. How are these nonclinical data considered "well studied individually in toxicology evaluations" to support a combination studies?	"Well-studied individually" means a toxicological evaluation sufficient to support clinical studies of the individual pharmaceutical alone. If sufficient clinical data e.g., a completed Phase I or a monotherapy phase within Phase I) are available to support a combination study, additional nonclinical data may not be warranted. A rational to support the combination should be provided, which can include *in vitro* or *in vivo* data or a literature assessment. If there is no or very limited human safety data for one of the combination components, a nonclinical pharmacology study of the combination should be considered, in addition to the toxicology studies with the single agent. For drugs that are pharmacologically inactive as a single agent, see the response to Question 3.7.
3.6	**3.5**	The guideline states that data to support a rationale for the combination should be provided prior to starting the clinical study. What is "data to support a rationale for the combination study"?	A scientific rationale should be provided to justify a combination clinical study. Data demonstrating increased anti-tumor activity by combined pharmaceuticals in pharmacology studies (e.g., animal tumor models, *in vitro* or *in vivo* studies based on mechanistic understanding of target biology) should be provided to support rationale for the combination, if feasible. This data could be from in-house studies or the scientific literature.
3.7	**3.5**	Section "3.5 Combination of Pharmaceuticals" states that cancer drugs are often studied against the background of standard of care and/or in many combination studies. The guidance suggests that if at least one drug is in early stage development "i.e. the human toxicity profile has not been characterised", then a	a. If pharmacology investigations indicate the potential for synergistic toxicity of unpredictable magnitude which precludes predictable clinical dose adjustment and suggests that clinical monitoring may be insufficient to mitigate the risk on its own, then a dedicated *in vitro* or *in vivo* combination study should be considered. b. For compounds with no relevant models and safety risk for combination is of concern, assessment of combination can be based on relevant in vitro tests, and/or *in vivo* studies based on mechanistic understanding of target biology.

		pharmacology study with limited safety endpoints should be conducted. a. Under what circumstances would a dedicated toxicology study be recommended? For compounds with no appropriate rodent tumor model, what is the guidance regarding assessment of combination products?	
3.8	**3.5**	Does the ICH S9 Guideline apply to the drug itself having no or less anti-tumor efficacy, such as an enhancer, that is intended to be developed as the drug combined only with the certain anti-tumor drug for the treatment of patients with advanced disease in late stage development? If S9 does apply, which nonclinical studies are recommended for an Investigational New Drug (IND) or New Drug Application (NDA) / Biological License Application (BLA)?	Yes, a drug such as an enhancer used in combination with another drug is within the Scope of S9 if it is intended to treat cancer. Data to show that the drug is non active should be provided. A toxicological evaluation of the individual drugs alone may be limited to short term studies. The full battery of toxicology studies should be done for the combination.
3.9	**3.6**	The guideline states that juvenile animal studies should be considered only when human safety data and previous animal data are insufficient. Under what situations would a juvenile animal study be warranted? What should be the goal of a juvenile animal study to support development in paediatric patients with cancer?	Juvenile toxicity studies should only be performed when available animal models are believed to generate data relevant for paediatric safety, and there is a clear value for such data for supporting clinical paediatric development. This is normally not the case for paediatric clinical trials in children with limited available therapeutic options and short life expectancy. Clinical data from adults is typically available prior to initiation of these paediatric trials; this data is used to set a starting dose and inform monitoring plans. In addition, these trials are usually done in a controlled setting with substantial safety monitoring. Pharmacology data and toxicology data from adult animals can also inform on safety.

			When clinical development is pursued in children with longer life expectancy, the need for juvenile toxicity testing should be a case by case decision based on the available knowledge on pharmacology, nonclinical and clinical safety and the presence of safety concerns where a juvenile toxicity study could add important information. When studies are needed, ICH S11 should be consulted to address the design of the juvenile animal study. A dialogue with the regulatory agency is also encouraged. To support the clinical development in a paediatric-only indication, the age of animals in the repeat-dose toxicity studies should be chosen to cover the age of the patient population in the initial clinical trials.

4. OTHER CONSIDERATIONS

#	Questions	Answers
4.1	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. For an ADC, what does a more limited evaluation mean?	The whole ADC molecule should be tested in at least one species. See Question 4.3 for a discussion of the payload/linker.
4.2	If the antibody has not been separately characterised, should an arm of the antibody only be included in a toxicology study?	In general, studies of the mAb alone are not warranted.
4.3	Are studies with the payload and/or linker only recommended?	The pilot studies and the nature of the payload will determine what additional studies, if any, are appropriate with the payload or payload with linker. Evaluation of the linker alone is not usually warranted. If the toxicity of the payload or payload with linker has been characterized (e.g., through pilot studies), a Good Laboratory Practice (GLP) study of the payload/linker may not be warranted or could be further abbreviated. If the toxicity of the payload/linker has not been characterized, the payload/linker could be evaluated in one species as a stand-alone study (for example, one single dose or a short term study in rodents) or could be added as an arm into toxicology studies of the ADC. See also note 2 of ICH S6 (R1).

4.4	What are the requirements for toxicokinetic (TK) analysis? Should the free antibody and free payload be distinguished from the ADC?	Current best TK practices for ADCs are to measure the level of ADC and the payload.
4.5	Should plasma stability be included as part of the FIH study plan? If not, at what stage of development is it needed?	*In vitro* data about plasma stability of ADC in human and the toxicology species should be available to support FIH trials.
4.6	Is there a recommended approach to setting a FIH starting dose for an ADC?	A starting dose for use in cancer patients should be consistent with ICH S9. For example, for cytotoxic payloads, the starting clinical dose can be determined using either 1/10th the Severely Toxic Dose (STD) in 10% of animals (STD10) in rodents or 1/6th the Highest Non-Severely Toxic Dose (HNSTD) in non-rodents, for the ADC based on body surface area, depending on which is the most appropriate and/or sensitive species. Other approaches can be considered for new classes of ADCs.
4.7	Given the extended half-life of an ADC as compared to a cytotoxic small molecule, is a single dose toxicity study using an ADC sufficient to support a clinical dosing schedule of once every 3 weeks?	For an ADC, because of differences in the Pharmacokinetic (PK) / Pharmacodynamic (PD) compared to small molecules, a single does study to support dosing once every 3 or 4 weeks may not be sufficient. At least two doses of the ADC should be administered in order to support initial clinical trials.
4.8	If the ADC does not bind the target in the nonclinical species, what repeat dose *in vivo* toxicity study would be needed?	If the epitope is not present in nonclinical test species, a toxicology study in one species for the ADC should be sufficient.
4.9	What is the utility of tissue distribution studies with an ADC?	Tissue distribution studies of the ADC are not warranted.
4.10	In general 2 species are used for toxicology testing. For an ADC, are there situations where one species may be acceptable? If 2 species, what should be the test article in each species?	When the antibody portion of an ADC binds only to human and NHP antigens, conducting a toxicity evaluation with the ADC in only the NHP (the only relevant species) would be appropriate, as discussed in ICH S6(R1). The payload/linker only could be studied in the second species (pilot or GLP-compliant); see also response to Question 4.3

4.11	What are the requirements for TK analysis of total ADC and free payload in the 3-month nonclinical studies if there are data to demonstrate limited or no degradation peripherally?	In general, if there are data to demonstrate that the ADC is stable in plasma then for the 3-month nonclinical study the TK analysis could focus on the total ADC.
4.12	For metabolites that are human specific or present at disproportionally higher levels in humans when compared to toxicology species, what toxicology evaluation should be done?	In general, additional studies with disproportional metabolites are not needed. In rare cases where the metabolite is not produced in toxicology species and the majority of the human exposure is due to the metabolite and not the Active Pharmaceutical Ingredient (API), additional toxicology evaluation of human metabolites may be considered.
4.13	Should impurities exceeding the established limits in ICH Q3A/B be assessed in genotoxicity studies when the API is genotoxic?	Genotoxicity studies of the impurity are not warranted if the API is genotoxic.
4.14	Should impurities associated with programs being developed under ICH S.9 and exceeding the established limits in ICH Q3A/B be assessed in genotoxicity studies when the API is non genotoxic?	An assessment of genotoxicity for impurities that exceed Q3A/B should be provided. In general, any genotoxic impurity should be managed as described in Q3A/B for nongenotoxic impurities, as discussed in Section 4.4 of ICH S9. With scientific justification, limits described in Q3A/B can be exceeded on a case-by-case basis.
4.15	Is ICH M7, giving guidance for the management of mutagenic impurities, applicable to the patient population covered in the scope of ICH S9? And if not, what approach should be taken to manage mutagenic impurities in products developed under ICH S9?	The scope of ICH M7 specifically states that the guidance does not apply to "drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9". Therefore mutagenic impurities in products used for treatment of indications under the scope of ICH S9 do not have to be identified or controlled in line with the concepts and principles described in ICH M7, and could be considered for management in line with the concepts outlined in ICH Q3A/B.
4.16	Given the compressed development timelines for oncology products, drug substance manufacturing	ICH Q3A/B give some flexibility to qualification thresholds for impurities under such circumstances. A risk assessment should be conducted (considering factors like structural similarity to the parent drug, toxicology alerts in the structure, presence of the impurity at lower

	processes may not be fully mature at the time of making the marketing application. If new impurities are observed above ICH Q3A/B qualification thresholds after the completion of registration toxicology studies, how should such circumstances be handled?	levels in toxicology or clinical lots, metabolite status, patient group and dosing regimen etc.) to consider whether *in vivo* qualification studies should be considered. Such studies may not be necessary in all cases just because an impurity is found above / is specified above the Q3A/B qualification threshold when the product is being developed under ICH S9.
4.17	If a drug with an impurity is first developed in patients with late stage disease, and then moves to a different population with earlier stage disease, how should the impurities in the drug be managed?	If the impurity is non-mutagenic / non-genotoxic but not suitably qualified then the controls associated with the impurity should be considered, in the light of clinical exposure already accrued. In some cases, further qualification can be important. When the impurity is mutagenic/genotoxic the specifications may need to be re-evaluated, or additional qualifications studies may be warranted. The Threshold of Toxicological Concern (TTC) approach as described in ICH M7 should not be considered the default approach.
4.18	Is it acceptable to evaluate carcinogenicity risk of impurities by means of staged TTC which is associated with the expected duration of treatment?	Application of the staged TTC or the TTC to oncology drugs for advanced cancer is not appropriate as the TTC is based on negligible excess lifetime cancer risk (e.g. 1 in 10^5 probability) in the absence of cancer disease. For oncology indications where normal life expectancy is anticipated, recommendations according to ICH M7 should be considered.

5. ANNEX: Q&As linked to the respective Sections of ICH S9 Guideline

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