S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
Questions and Answers
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2018
ICH

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Contains Nonbinding Recommendations

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers Guidance for Industry[1]

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Since the ICH guidance *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* was finalized (ICH S9 or ICH S9 guidance),[2] all parties using the guidance have experienced some challenges with implementation of the recommendations on nonclinical evaluation for anticancer pharmaceuticals. This question-and-answer guidance is intended to facilitate the implementation of ICH S9, as well as to continue progress in the 3Rs of Reduction, Refinement, and Replacement in the use of animals.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

I. INTRODUCTION – SCOPE (1)[3]

Q1. The ICH S9 guidance 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 ICH S9 guidance? (1.1)

[1] This guidance was developed within the Implementation Working Group of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Assembly at Step 2a of the ICH process, June 2016. At Step 2b of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web pages at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInvormation/Guidances/default.htm. https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

[3] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Assembly at Step 2a of the ICH process, June 2016.

As 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 Question 2 (1.2). For other initial development programs in cancer that is not resistant and refractory, ICH S9 should be used as a starting point, and other studies added as appropriate with reference to ICH M3(R2) and S6(R1). In some situations where the development pathway is not clear, regulatory agencies should be consulted. See also the answer to Question 5 (1.5).

Q2. 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 ICH S9? (1.2)

Yes.

Q3. In general, the guidance has been interpreted as applying when the patient's life expectancy is approximately 3 years. It would be useful to provide further clarity about the intended population. (1.3)

The ICH S9 guidance does not make a reference to years of life expectancy and the application of the guidance should not be based on an expectation of survival as measured in years. The intent of the scope is clarified in Questions 1 (1.1) and 2 (1.2).

Q4. Can the principles of ICH S9 be applied to non-oncology therapeutics where the disease is life-threatening with limited therapeutic options? (1.4)

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.

Q5. Are clinical trials in the adjuvant or neo-adjuvant setting covered under ICH S9? (1.5)

Yes. ICH S9 should be used as the starting point for drugs used in an adjuvant or neo-adjuvant setting even when there is a lack of detectable residual disease. Data generated in patients (e.g., when the initial program was in a refractory late stage disease) should be considered and may be used to abbreviate the nonclinical program. In cases in which there is a well understood high cure rate and a low and/or long delayed disease recurrence rate, then further studies (e.g., carcinogenicity, a complete program on reproductive and developmental toxicity) are likely to be needed prior to marketing. In cases in which these factors are less defined and recurrence is high or rapid then the need for additional studies and their timing can be addressed on a case-by-case basis, taking into account the totality of preclinical and clinical safety data, cure rate and expected time to recurrence.

If the initial development program is in the adjuvant or neo-adjuvant setting, additional nonclinical studies may be needed, including longer-term general toxicology studies.

In all cases, it is important to consider the natural course of the disease. The application of ICH S9 and any omission of studies should be justified by the sponsor. See also the response to Questions 1 (1.1), 6 (1.6), and 7 (1.7).

Q6. In the case where a therapeutic increases survival, what further toxicology work is recommended, and what is the appropriate timing of any studies? (1.6)

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. Additional toxicology studies other than general toxicology may be needed on a case-by-case basis. If additional studies are deemed important, such studies could be submitted post approval of the anticancer pharmaceutical. See also the answer to Question 7 (1.7).

Q7. 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 ICH S9 guidance, is to be applied to another oncology indication that is not immediately life-threatening, but is serious? (1.7)

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. Similar to the response under Question 6 (1.6) the clinical safety data generated in the patient population for the approved indication are 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.

II. STUDIES TO SUPPORT NONCLINICAL EVALUATION (2)

Q8. In Section 2.1 "Pharmacology," the guidance states that studies should characterize the "anti-tumor activity" of the pharmaceutical. The inference is that these are in vivo studies. Is in vivo characterization necessary to address pharmacology? (2.1)

If in vitro systems that are used for pharmacology studies of anti-tumor activity are demonstrated to generate relevant data, then they should be considered sufficient.

Q9. Should recovery groups be included in toxicology studies supporting FIH toxicology studies? (2.2)

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 or non-reversible or by including a recovery period in at least one study and one dose level, to be justified by the sponsor.

Q10. Should recovery groups be included on 3-month toxicology studies to support Phase III? (2.3)

Recovery in 3-month studies is not specifically warranted unless there is a concern from short-term toxicology or from clinical studies that recovery animals could address: for example, when a recovery group was not included in the short-term toxicology study and there was insufficient understanding whether a particular effect observed may be reversible or non-reversible. Another example is when the 3-month studies are undertaken in the absence of clinical data or with limited clinical data.

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.

Q11. 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? (2.4)

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.

Q12. Is there any guidance on the need for abuse liability studies for drugs developed under ICH S9? (2.5)

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.

Q13. What is the utility of tissue cross reactivity studies for biopharmaceuticals containing a complementary determining region (CDR) (i.e., monoclonal antibodies (mAbs), antibody drug conjugates (ADCs)) that fall under ICH S9, and do these studies need to be conducted? (2.6)

In general, tissue cross reactivity studies have little utility and are not needed with the initial first-in-human study 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 or alternative methods should be considered for the first-in-human study.

Q14. 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? (2.7)

A definitive study is generally not warranted if a dose-range finding study (including non-good laboratory practice (GLP)) shows clear evidence of embryofetal lethality or teratogenicity. This dose-ranging study in a single species would be sufficient to support marketing.

Q15. Section 2.5 describes the use of alternative assessments for biopharmaceuticals. Is there any role of alternative in vitro and in vivo assays for small molecules in reproductive toxicology assessment? (2.8)

Yes. Alternative assessments may be used to aid in the safety assessment for reproductive risk.

Q16. When the only relevant species is a non-human primate (NHP) and 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 NHPs be conducted? (2.9)

A weight-of-evidence assessment of reproductive risk should be provided. An NHP study to assess a hazard to embryofetal development (EFD) should not be considered a default approach. If the weight-of-evidence clearly indicates a risk, an EFD study in NHP is not warranted. Development toxicity studies in NHPs can only provide hazard identification according to ICH S6 (R1). The expected reproductive hazard should be appropriately indicated on the label.

Q17. Is there a need for nonclinical lactation and placental transfer studies? (2.10)

There is no specific need for lactation or placental transfer studies.

Q18. Which and how many in vitro genotoxicity studies would need to be positive in order to make the in vivo genotoxicity assays unwarranted (Section 2.6 Genotoxicity)? (2.11)

When the bacterial mutation (Ames) test is positive, then in vivo genotoxicity testing is not warranted. When the bacterial mutation assay is negative, but an in vitro chromosome damage test result (such as chromosome aberration, micronucleus or mouse lymphoma tk+/- assay) is positive, in vivo genotoxicity testing should be considered. Refer to ICH S2(R1) for additional information.

Q19. Section "2.9 Photosafety Testing" states that if initial assessment of phototoxic potential based on physicochemical properties indicates a phototoxic risk, when should nonclinical photosafety studies be conducted? (2.12)

ICH S9 should be consulted for the timing of phototoxicity studies. ICH S10 should be consulted for assessment of photosafety.

III. NONCLINICAL DATA TO SUPPORT CLINICAL TRIAL DESIGN AND MARKETING (3)

Q20. 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? (3.1)

If appropriate, a MABEL could be used for small molecules using in vivo or in vitro data. This approach should be considered if risk factors are derived from knowledge of (1) the mode of action, (2) the nature of the target, and/or (3) the relevance of animal or in vitro models.

Q21. Is use of the highest non-severely toxic dose ((HNSTD), Note 2) to select an appropriate starting dose applicable to biopharmaceuticals? (3.2)

The HNSTD may be appropriate in determining a starting dose of a biopharmaceutical (e.g., when a drug is not an immune agonist) taking into consideration differences in binding affinity between animals and humans and pharmacological properties of the biopharmaceutical (including ADCs).

Q22. 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, i.e., a 1-month or 3-month toxicology study, if the 3-month studies with the original schedule have already been conducted? (3.3)

If needed, a study of up to 1 month duration should generally be sufficient to support a change in schedule and to support marketing (see ICH S9, Table 1 for additional guidance). This study should be available prior to the initiation of the clinical trial.

Q23. What general toxicology studies are recommended for continued clinical development, including marketing, for genotoxic drugs targeting rapidly dividing cells? (3.4)

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) and are expected to be consistent across different species, toxicity studies in one rodent species of 3-month duration are considered sufficient for continued clinical development and registration.

Q24. 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 study? If needed, when would a dedicated toxicology study be recommended? (3.5)

"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 with the individual pharmaceuticals, additional nonclinical toxicology data may not be warranted. A rationale to support the combination should be provided, which can include in vitro or in vivo pharmacology data or a literature assessment.

If there are 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 agents.

For pharmaceuticals that are pharmacologically inactive in animal species, assessment of combination can be based on relevant in vitro tests and/or a mechanistic understanding of target biology.

If the available clinical and nonclinical data are insufficient to establish a safe starting dose of the combination, a dedicated toxicology study may be needed with the combination to establish a safe starting dose in humans.

Q25. Section 3.5 of ICH S9 states that data to support a rationale for the combination should be provided prior to starting the clinical study. What are "data to support a rationale for the combination study"? (3.6)

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.

Q26. Does the ICH S9 guidance apply to the drug itself having no anti-tumor activity, such as an enhancer, that is intended to be developed as the pharmaceutical combined only with the certain anti-tumor pharmaceutical for the treatment of patients with advanced disease in late stage development? If ICH S9 does apply, which nonclinical studies are recommended for a first in human, clinical development and marketing application? (3.7)

Yes, these pharmaceuticals are within the scope of ICH S9 if they are intended to treat cancer. Data to show that the enhancer is non-active should be provided. General toxicology, safety pharmacology, and reproductive toxicology assessments should be done for the combination. The enhancer alone may have a more limited safety assessment either as an arm in the general toxicology combination study or as a stand-alone general toxicology study of up to 1 month duration (see Table 1 in ICH S9). Genotoxicity studies may be conducted with each

pharmaceutical alone or with the combination, as relevant. The timing of the studies should follow ICH S9.

IV. OTHER CONSIDERATIONS (4)

Q27. Section 4.1 of the guidance 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? (4.1)

The "unconjugated material" in Section 4.1 of ICH S9 refers to the payload.

The whole ADC molecule should be tested in at least one species. See Question 29 (4.3) for a discussion of the payload.

Q28. If the antibody of an ADC has not been separately characterized, should an arm of the antibody only be included in a toxicology study? (4.2)

In general, studies of the mAb alone are not warranted.

Q29. Are studies with the payload and/or linker only recommended? (4.3)

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 GLP study of the payload or payload with linker may not be warranted or could be further abbreviated. If the toxicity of the payload or payload with linker has not been characterized, the payload or payload with linker could be evaluated in one species as a stand-alone study or could be added as an arm into toxicology studies of the ADC. See also note 2 of ICH S6 (R1).

Q30. What toxicokinetic (TK) analysis should be performed? Should the free antibody and free payload be distinguished from the ADC? (4.4)

Current best TK practices for ADCs are to measure the level of ADC and the payload, and an estimate of the amount of free antibody should be provided.

Q31. Should plasma stability be included as part of the FIH study plan? If not, at what stage of development is it needed? (4.5)

In vitro data about plasma stability of ADC in human and toxicology species should be available to support FIH trials.

Q32. Is there a recommended approach to setting an FIH starting dose for an ADC? (4.6)

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 percent 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.

Q33. 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? (4.7)

At least two doses of the ADC should be administered to support initial clinical trials of once every 3 or 4 weeks.

Q34. If the ADC does not bind the target in the nonclinical species, what repeat dose in vivo toxicity study would be needed? (4.8)

If the epitope is not present in nonclinical test species, a toxicology study in one species for the ADC should be sufficient. Alternative models such as transgenic animals or use of a homologous molecule is usually not warranted.

Q35. What is the utility of tissue distribution studies with an ADC? (4.9)

In general, tissue distribution studies of the ADC are not warranted.

Q36. Generally, two species are used for toxicology testing. For an ADC, are there situations where one species may be acceptable? (4.10)

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). For the payload, see the response to Question 29 (4.3).

Q37. 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? (4.11)

In general, additional studies with disproportional metabolites are not needed. In cases where the metabolite is not produced in toxicology species and a relatively high amount 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.

Q38. Should impurities exceeding the established qualification limits in ICH Q3A/B be assessed in genotoxicity studies: When the API is genotoxic? When the API is non-genotoxic? (4.12)

API genotoxic?	Impurity exceeds the ICH Q3A/B qualification threshold?	Proposed action
Yes	No	None
Yes	Yes	None
No	No	None
No	Yes	Genotoxicity assessment of impurities should be conducted.

Q39. Is ICH M7, giving guidance for the management of mutagenic impurities, applicable to the patient population covered in the scope of ICH S9? (4.13)

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 should be considered for management consistent with the concepts outlined in ICH Q3A/B (see Question 4.12).

Q40. Given the compressed development timelines for oncology products, drug substance manufacturing 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? (4.14)

ICH Q3A/B gives 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 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. Identifying a no observed adverse effect level in a qualifying study is usually not warranted.

Q41. If a drug with an impurity is first developed in patients with late-stage disease, and later moves to a different population with long-expected survival (e.g., those administered pharmaceuticals on a chronic basis to reduce the risk of recurrence of cancer), how should the impurities in the drug be managed? (4.15)

When an anticancer pharmaceutical is further investigated in cancer patient populations with long expected survival, ICH Q3A/B and ICH M7 should both be considered for the control of impurities.

V. ANNEX: QUESTIONS AND ANSWERS LINKED TO THE RESPECTIVE SECTIONS OF ICH S9 GUIDANCE (5)

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