ICH S9 - Nonclinical Evaluation for Anticancer Pharmaceuticals: Questions and Answers

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Outline

• Background
• Guideline Objectives
• Major Accomplishments
• Progress in the 3Rs
• Considerations

Background

• The ICH S9 Guideline was adopted by the Steering Committee in October 2009.
• Since its adoption, it became apparent that the original guideline was not specific enough in some areas regarding nonclinical development of anti-cancer pharmaceuticals:
  • Open to differing interpretations by ICH Members and Observers, leading to unnecessary nonclinical studies
  • Additional detail was needed to promote efficient pharmaceutical development in some areas briefly discussed in the original guideline; e.g., antibody-drug conjugates
• A Question and Answer (Q & A) Concept Paper to address the areas requiring clarification was endorsed by the Steering Committee in October 2014
  • An Implementation Working Group (IWG) was formed in 2015
Q & A Objectives

- The goal of the Q & A is to clarify interpretation of the original guideline and to continue the process of harmonisation, where possible.
- Questions from industry and regulators were solicited based on issues identified in the Concept Paper.
  - ICH Observers were also encouraged to provide questions.
- The IWG culled the questions (some out of scope), and rewrote some for clarification purposes.
  - Developed draft responses after soliciting feedback from stakeholders.
- The IWG also continued progress in the 3Rs, specifically to Reduce, Refine, Replace animal use.

Timeframe of Q&A Development

- **Step 2** Q&A was endorsed by the Assembly (**Step 2a**) and Regulatory Members of the Assembly (**Step 2b**) in June 2016.
- **Step 2** document tracked the original guideline:
  - Section 1: Scope – 7 Q&A
  - Section 2: Studies to support nonclinical evaluation – 11 Q&A
  - Section 3: Nonclinical data to support clinical trial design and marketing – 9 Q&A
  - Section 4: Other considerations – 18 Q&A
  - Annex: refers each Q&A to a relevant section of the guideline.
- Last regional comment period closed January 2017.
- IWG finished addressing all comments 1st Quarter 2018.
Final Guideline

• The Q & A was approved by the Assembly in April 2018
• The final Q & A tracked the original Q & A:
  • Section 1: Introduction - Scope; 7 questions
  • Section 2: Studies to support nonclinical evaluation; 12 questions
  • Section 3: Nonclinical data to support clinical trial design and marketing; 7 questions
  • Section 4: Other considerations; 15 questions
  • Section 5: Annex

Major Accomplishments Q & A Section 1

Clarified the intent of Scope:
• Apply S9 to cancer that is resistant and refractory to available therapy
• Application to other oncology settings (not resistant or refractory, adjuvant or neo-adjuvant setting) should use S9 as a starting point.
• Application of the guideline should not be based on life expectancy
• The guideline is specific to oncology and not to other therapeutic areas
• Usually no need to repeat general toxicology studies for longer duration if the pharmaceutical extends survival
Major Accomplishments Q & A Section 2

- A scientific assessment for toxicity to reverse should be provided but recovery groups are not automatically expected
- Outlined when supportive care during toxicology studies may be appropriate
- Consensus that tissue cross reactivity studies generally have little utility and are not needed unless there is a specific cause for concern
- Clarified that a dose-range finding study could be used to show clear evidence of embryofetal lethality or teratogenicity
- Confirmed that alternative in vitro and in vivo assays could be used to aid in the assessment of reproductive risks (Q2.8)

Major Accomplishments Q & A Section 3

- Consensus that a toxicology study of up to 1-month duration should generally be sufficient to support a change in the clinical schedule
- Clarified language around toxicology data to support a combination study; e.g., defined “well-studied individually”
Major Accomplishments Q & A Section 4

Clarified studies needed to support development of antibody-drug conjugates

- No need for studies with the mAb alone
- Generally no need for a separate toxicology evaluation of a linker
- The toxicity of the payload or payload with linker should be evaluated; if it is not available, then a stand alone study in one species or as an arm in a toxicology study with the ADC should be sufficient
- TK should include a measurement of the ADC and payload and an estimate the amount of free antibody
- In vitro plasma stability should be available to support FIH trials
- Consensus that toxicity studies of at least 2 doses of the ADC should be administered to support initial trials of once every 3 weeks
- In general, no need for tissue distribution studies

Clarified that impurities exceeding Q3A/B do not need to be assessed for genotoxicity unless the API is not genotoxic and the impurity exceeds the qualification threshold

Reiterated that ICH M7 does not apply to advanced cancer indications and that mutagenic impurities should be managed consistent with the concepts of Q3A/B
Progress in the 3Rs

- No need to study the antibody alone of an ADC, reducing NHP use
- The need for the use of rodent and non-rodent recovery animals is reduced
- Clarified that longer-term general toxicology studies are not a default recommendation if moving to an earlier-stage patient population or into the adjuvant or neo-adjuvant setting, reducing use of rodents and non-rodents
- Stated that alternative assays for EFD may be used in the safety assessment for reproductive risk for small molecules in addition to biopharmaceuticals and clarified when dose-range finding studies could be used in lieu of a definitive EFD study, reducing use of rodents

Considerations

- ICH S9 and the Q & A should be used as the starting point in assessing the studies needed for both advanced cancer and less advanced cancer.
- In applying ICH S9 and the Q & A to a development program, it is important to clearly define the patient population. This will also determine the extent of non-clinical studies needed to support additional indications even after approval for an initial indication in advanced cancer.
Thank you

ICH Secretariat
Route de Pré-Bois 20
1215 Geneva
Switzerland

E-mail: admin@ich.org

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