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

May 2018

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

Legal Notice

Outline

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- Major Accomplishments
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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

Major Accomplishments Q & A Section 4

- 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.

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Thank you

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