ICH Q11 Questions & Answers – Selection & Justification of Starting Materials.

Step 4 –August 2017

Implementation Working Group

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

Legal Notice

- **Background**
- **Issues to be addressed**
- **Scope**
- **Current status of the document**

Background

ICH Q11: Development & manufacture of drug substances.

Chemical and biotechnological/biological entities

Development & manufacture

'Traditional' and 'enhanced' approaches

***Step 4*: 1 May 2012 – recommended for adoption in Europe, Japan & US.**

ICH Steering Committee endorsed the creation of a Q11 Implementation Working Group (IWG) to develop a Questions and Answers document to provide clarification on information relating to the selection and justification of starting materials. The IWG commenced activities in Jan. 2015

Why was a question & answer document needed ?

Perceived problem:

Differences in interpretation of Section 5 concerning the selection and justification of starting materials for chemical drug substances.

- Addressing issues by providing clarification on the types of information that should be provided by industry in applications regarding the selection and justification of starting materials for regulators to evaluate whether the proposed starting material, manufacturing process, and control strategy provide sufficient assurance of the quality of the drug substance;
- The objective is to provide further elaboration of the high level principles described in Q11, in order to improve the likelihood that industry proposals for SM will be acceptable to regulators
- Clarify/emphasise the need to take all of the general principles into consideration rather than the selection of a limited sub-set.

Q11 Q&A Selection & Justification of Starting Materials

The Q&A will have implications for:

Information to be submitted in the Common Technical Document on the manufacture and control of the drug substance.

Information to be submitted to regulatory authorities in respect of post approval changes.

Good Manufacturing Practices (GMPs), process validation and inspection related activities.

What is the scope of the question and answer relative to the parent guideline ?

Drug substances as defined in ICH Q6A.

Synthetic drug substances.

Selection & justification of starting materials.

Section 5.1.1 Selection of Starting Materials for Synthetic Drug Substances

6 general principles for consideration

1. **In general, changes….that occur near the beginning of the process have lower potential to impact the quality of the drug substance.**
2. **Enough of the drug substance manufacturing process should be described (ie in the CTD) to allow evaluation of the control of the process, including control of impurities.**
3. **Steps that impact the impurity profile of the drug substance should be included in section 3.2.S.2.2 .**
4. **Each branch of a convergent synthesis begins with one or more starting material**
5. **A starting material should be a substance with defined chemical properties and structure – usually isolated**
6. **A SM is incorporated as a significant structural fragment into the structure of the drug substance**

5.2.1 Justification of SM selection for synthetic drug substances

- **……..an applicant generally need not justify the use of a commercially available chemical as a starting material. A commercially available chemical is usually one that is sold as a commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as a starting material. Chemicals produced by custom synthesis are not considered to be commercially available.**

What are the main issues that need to be resolved?

Further clarification of guidance on:

Definitions:

- **Significant structural fragment**
- **Commercially available chemical v custom synthesised chemical**
- **'Starting material' – ICH Q7 v Q11**

Manufacturing steps that impact the drug substance impurity profile.

Evaluation of risk of mutagenic impurity carryover (M7 concepts).

Inclusion of enough information about the drug substance manufacturing process in the CTD.

What are the potential benefits from further guidance ?

Improve the predictability on regulatory acceptance of the proposed starting material

Clarification on the relationship between selection of SM and GMP considerations, control strategy, length of synthetic process and impact of manufacturing steps on drug substance quality.

Clarification on information to be included in CTD to justify starting material selection.

Clarify expectations for lifecycle management of the starting material.

Emphasis on the need to take all of the principles in Q11 into consideration when selecting the starting material.

What additional guidance is provided ? (1)

16 questions and answers

Clarify definitions:

- **Significant structural fragment.**
- **Commercially available v custom synthesised chemicals.**
- **Consistency between ICH Q11 and Q7.**

Risks related to carryover of impurities. Including consideration of impurities that are generated in very early upstream steps but persist over multiple synthetic steps and carryover into the final drug substance.

Specific guidance concerning mutagenic impurities.

Considerations for steps that establish regio- or stereochemical configurations.

What additional guidance is provided ? (2)

Considerations for inclusion of enough information on the manufacture of the drug substance in the CTD:

Stepwise approach to the considerations that an applicant should apply, including:

First, the steps from which impurities in the drug substance originate.

Then, consideration of the steps immediately upstream of these *if*

- they control specific impurities that would otherwise carryover or

- they require careful control to prevent generation of impurities that would impact the DS

If the considerations above would lead to only a small number of chemical transformation steps, then it is generally appropriate to add one or more additional steps under GMP to sufficiently mitigate risk associated with contamination and future changes to the upstream process. The role of analytical methods in mitigating this risk is also discussed.

What additional guidance is provided ? (3)

- **Considerations and justification for starting material specifications.**
- **Considerations for specific cases:**
  - Processes run without isolation of intermediates.
  - Linear v convergent processes.
- **Relevance of lifecycle considerations in Q11 to starting materials.**

Public consultation

- Draft Q&A document was published on ICH website in December 2016.
- Public consultations were held between December 2016 and April 2017 in Brazil, Canada, European Economic Area, Japan, South Korea, Switzerland, & USA.
- 181 comments were received by regulatory authorities and via ICH website.

Review of the draft Q&A following public consultation

- All 16 draft Q&As were retained
- Re-ordered Q&A to more logical flow
- Updating of the guidance in the various Q&A to address issues raised
- Inclusion of a decision tree to support the understanding of the Q&A
  - Note: the decision tree should be read in conjunction with the guidance within the Q&A document and the parent guideline.

Amendments to Q&As after consultation

- **Strengthen messaging on the need to take all ICH Q11 'general principles' into account when selecting a starting material, rather than using selected arguments in order to justify a late stage intermediate as the regulatory staring material.**

Amendments to Q&As after consultation

- **Further guidance/clarification on evaluating risks associated with potential mutagenic impurities in the manufacturing process of the active substance, specifically in the context of selecting a starting material for the process to be described in the regulatory dossier.**
- **The approach in the Q&A for identifying mutagenic impurities that impact the impurity profile of the DS is to be used specifically for identifying appropriate SMs.**
- **Once the SMs have been agreed upon, applicants/holders would follow the recommendations in ICH M7.**

Amendments to Q&As after consultation

- Clarification of the text of the Q&A describing ‘impurities that persist’. The answer to this question was amended to improve communication of the intended message, particularly the intended interpretation of Example 4 in the Q11 parent document.

Amendments to Q&As after consultation

- Other amendments to the text of the answers in the Q&As were editorial rather than substantial.
- All changes were intended to improve comprehension of the intended message; to reach an appropriate balance on information included in the regulatory dossier and necessary to provide reassurance of the quality of the active substance, while early stages of the process with low probability of impacting the drug substance quality are managed within the company quality system.

Amendments to Q&As after consultation

- A decision tree has been developed as an aid to the interpretation of the ICH Q11 high level principles and to support the use of the Question and Answer document.
- The decision tree is organised on 2 levels. Part 1 includes considerations related to structure and sourcing of a potential starting material. Part 2 focusses on risks to active substance quality related to carryover of impurities from the manufacturing process.

Next steps:

- The Question and Answer document will be adopted by ICH regulatory parties (*Step 5*).
- The IWG is considering the need for the development of training materials to support the finalised Q&A document on selection and justification of starting materials.

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Thank You!

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