Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) 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)

February 2018
ICH

Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)

February 2018
ICH

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION (1)[2]

Since the ICH guidance *Q11 Development and Manufacture of Drug Substances* (ICH Q11) was finalized,[3] worldwide experience with implementation of the recommendations on the development and manufacture of drug substances has given rise to requests for clarification relating to the selection and justification of starting materials.

This question-and-answer (Q&A) document is intended to provide additional clarification and to promote convergence and improve harmonization of the considerations for the selection and justification of starting materials and of the information that should be provided in marketing authorization applications and/or Master Files. The focus of the Q&A document is on chemical entity drug substances.

The scope of this Q&A document follows that of ICH Q11. ICH Q11 is applicable to drug substances as defined in the Scope sections of the ICH Q6A and Q6B guidances, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. ICH Q11 does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in ICH Q11 and this supporting Q&A document are important to consider during the investigational stages.

[1] This guidance was developed within the Expert Working Group (Quality) 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 4 of the ICH process, August 2017. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Assembly at *Step 4* of the ICH process, August 2017.

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

Generally, it is anticipated that active pharmaceutical ingredient (API) starting materials that have already been accepted by regulatory authorities (e.g., for use in authorized medicinal products) would not need to be rejustified against the ICH Q11 general principles or the recommendations included in this Q&A document, unless significant changes are made to the manufacturing processes and controls. However, a starting material accepted for one manufacturer's process may not be considered acceptable for a different manufacturer's process, if the proposal does not comply with the ICH Q11 guidance.

Applicant is used throughout the Q&A document and should be interpreted broadly to refer to the marketing authorization holder, the filing applicant, the drug product manufacturer, and/or the drug substance manufacturer. Designation of starting materials should be based on process knowledge of the intended commercial process. A decision tree is available in Annex 1 to serve as a pictorial exemplification to apply all ICH Q11 general principles for the selection and justification of a starting material.

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.

II. SCOPE (2)

There was no Q&A drafted on this section.

III. MANUFACTURING PROCESS DEVLOPMENT (3)

There was no Q&A drafted on this section.

IV. DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS (4)

There was no Q&A drafted on this section.

V. SELECTION OF STARTING MATERIALS AND SOURCE MATERIALS (5)

Q1. Should all the general principles in section 5 of ICH Q11 be considered and met in selecting and justifying starting materials? (5.1)

Applicants should consider all the ICH Q11 general principles in the selection and justification of proposed starting materials, together with the clarifications in this Q&A document, rather than choosing just a few of the general principles and using them to justify starting material selection.

If a proposed starting material does not meet all of the general principles, a rationale should be provided explaining why the starting material is considered appropriate.

Q2. Is a "starting material" as described in ICH Q11 the same as an "API starting material" as described in ICH Q7? (5.2)

Yes. ICH Q11 states that the GMP provisions described in ICH Q7 apply to each branch of the drug substance manufacturing process beginning with the first use of a "starting material." ICH Q7 states that appropriate GMP (as defined in that guidances) should be applied to the manufacturing steps immediately after "API starting materials" are entered into the process (see ICH Q7 Q&A 1.1). Because ICH Q11 sets the applicability of ICH Q7 as beginning with the "starting material," and ICH Q7 sets the applicability of ICH Q7 as beginning with the "API starting material," these two terms are intended to refer to the same material.

ICH Q7 states that an "API starting material" is a raw material, intermediate, or an API that is used in the production of an API. ICH Q7 provides guidance regarding good manufacturing practices for the drug substance, but does not provide specific guidance on the selection and justification of starting materials. When a chemical, including one that is also an API, is proposed to be a starting material, all ICH Q11 general principles still need to be considered.

Q3. Do the ICH Q11 general principles for selection of starting materials apply to the selection of starting materials for linear and convergent syntheses? (5.3)

Yes. The ICH Q11 general principles apply to the selection of starting materials for linear or convergent syntheses. The ICH Q11 general principles should be applied independently to each branch of a convergent synthesis, unless the point of convergence of the branches occurs upstream of an appropriate starting material.

Q4. Do the ICH Q11 general principles for selection of starting materials apply to processes where multiple chemical transformations are run without isolation of intermediates? (5.4)

Yes. The ICH Q11 general principles apply to processes where multiple chemical transformations are run without isolation of intermediates. In the absence of such isolations (e.g., crystallization, precipitations), design of the manufacturing process (e.g., kinetics) and/or unit operations (e.g., extraction, distillation, the use of scavenging agents) should be in place to adequately control and/or purge impurities and be described in the application. The ICH Q11 general principles also apply to sequential chemical transformations run continuously. Non-isolated intermediates are generally not considered appropriate starting materials.

Q5. ICH Q11 states "A starting material is incorporated as a significant structural fragment into the structure of the drug substance." Why then are intermediates used late in the synthesis, which clearly contain significant structural fragments, often not acceptable as starting materials? (5.5)

The selection principle about "significant structural fragment" has frequently been misinterpreted as meaning that the proposed starting material should be structurally similar to the drug substance. However, as stated in ICH Q11, this general principle is intended to help distinguish starting materials from reagents, catalysts, solvents, or other raw materials.

The term "significant structural fragment" is not intended to dictate the selection of either a very early or a very late intermediate as the starting material. A proposed starting material may be defined downstream from a commercially available chemical, provided that there are multiple chemical transformation steps between the proposed starting material and the drug substance, and provided the justification addresses the ICH Q11 general principles. The presence of a "significant structural fragment" should not be the sole basis for starting material selection. Starting materials justified solely on the basis that they are a "significant structural fragment" probably will not be accepted by regulatory authorities, as the other general principles for the appropriate selection of a proposed starting material should also be considered.

Q6. What is the difference between a commercially available chemical and a custom synthesized chemical? (5.6)

ICH Q11 states that "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 starting material." A definition of "custom synthesized chemical" was not provided in ICH Q11, but a custom synthesized chemical is generally understood to be one that is made specifically to a drug substance manufacturer's requirement, either in-house or externally, or available for purchase but where the only use is for pharmaceutical manufacture. The reference to "non-pharmaceutical market" in the ICH Q11 description of commercially available chemicals is intended to preclude purchased intermediates from being claimed as commercially available chemicals.

ICH Q11 makes an important distinction between commercially available chemicals and custom synthesized chemicals. An applicant generally need not justify the use of a commercially available chemical as a starting material, whereas a custom synthesized chemical proposed as a starting material should be justified in accordance with the ICH Q11 general principles.

The availability of a chemical from multiple suppliers should not be the sole basis for the designation of a chemical as a commercially available starting material. This includes situations where a custom synthesized chemical has become available over time from multiple suppliers. Such chemicals should still be justified according to the ICH Q11 general principles for selection of starting materials. It can be acceptable for a starting material that is demonstrated to be a commercially available chemical to enter late in the synthesis, e.g., in the last chemical transformation prior to the drug substance.

A chemical manufactured on a small scale can be suitable as a commercially available starting material, provided that the scale is sufficient for the manufacture of the drug substance and that the chemical is also used in a pre-existing, non-pharmaceutical market.

In some cases, a chemical that does not meet the definition of a commercially available chemical (e.g., it does not have a non-pharmaceutical use) but is simple enough in structure may be accepted as a starting material (e.g., protected natural amino acids). However, in such cases, a rationale should be provided explaining why the starting material is considered appropriate (see Q&A 5.1) and why the proposed control strategy is appropriate to control impurities in the drug substance.

Q7. Q11 recommends that "manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application." At what level would a related substance or mutagenic impurity be considered to impact the impurity profile of the drug substance? (5.7)

For non-mutagenic related substances, the ICH Q3A identification threshold serves to identify the level above which a related substance is considered to have an impact on the impurity profile of the drug substance. A related substance with an acceptance criterion above the ICH Q3A identification threshold is considered to impact the drug substance impurity profile.

For mutagenic impurities, the 30 percent threshold of the ICH M7 acceptable limit serves to identify the level above which a mutagenic impurity is considered to have an impact on the impurity profile of the drug substance. In this situation, the control strategy will generally include a test for the impurity at the acceptable limit (see section 8 of ICH M7). Any of the approaches described in section 8 of ICH M7 can be used to determine which impurities are likely to be present in the drug substance above the 30 percent threshold.

In line with ICH M7 and ICH S9, there are situations (e.g., when the drug substance is itself genotoxic, and other circumstances as described in these guidances) when the selection of the starting material for a drug substance does not need to specifically consider the mutagenic impurity profile at the levels described above. In such cases, mutagenic impurities are not considered to impact the impurity profile of the drug substance unless they are above the ICH Q3A identification threshold. Impurities that persist through multiple steps of the manufacturing process should be considered in conjunction with Q&A 5.8.

Q8. What is meant by impurities that "persist" in ICH Q11 Example 4? (5.8)

ICH Q11 recommends that "manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application." However, as described in ICH Q11 Example 4, this principle does not necessarily apply when impurities originate early and "persist" across multiple steps to the drug substance. It is normally expected that the justification for an impurity that persists will be based on it being carried across one or more manufacturing steps upstream of the proposed starting material, when these steps do not otherwise impact the impurity profile of the drug substance (for "impact," see Q&A 5.7).

In Example 4, an impurity in Compound B impacts the impurity profile of the drug substance. Steps 2 and 3 (from Compound B to Compound D) do not introduce other impurities that impact

the drug substance impurity profile. If impurities generated in Steps 2 or 3 do impact the drug substance impurity profile, these steps should also be considered for inclusion in 3.2.S.2.2 of the application.

Impurities that persist may or may not react in subsequent steps, but are not removed to the extent that they would no longer be considered to impact the drug substance impurity profile. For example, an impurity that persists might have physico-chemical properties (e.g., solubility) similar to other intermediates or the drug substance, like the enantiomer in Example 4, which could make its removal intrinsically difficult.

ICH Q11 Example 4 illustrates that when the synthetic route contains an impurity that persists, it can be acceptable to control the impurity in the starting material specification even though it impacts the impurity profile of the drug substance. Therefore, it is not always necessary to include steps that form such an impurity in section 3.2.S.2.2, provided that the other ICH Q11 general principles are addressed (ICH Q11 section 5.1.1). Example 4 is not exclusive to stereoisomers and can be applied to other types of impurities that persist.

In Example 4, there are 3 chemical transformation steps between the starting material D and the drug substance. The 3 steps in Example 4 are not intended to imply that 3 chemical transformation steps are considered enough (see Q&A 5.11) in all cases, nor that 3 chemical transformation steps are mandatory.

In the case of Example 4, application of the ICH Q11 principles includes control of the enantiomer in the specification of the proposed starting material D, in combination with the understanding that the steps immediately prior to D do not introduce other impurities that impact the impurity profile of the drug substance. The applicant should provide information in the application on the upstream process to justify the proposed starting material including control strategy of the impurity that persists.

In Example 4, there are 3 chemical transformation steps between the starting material D and the drug substance. The 3 steps in Example 4 are not intended to imply that 3 chemical transformation steps are considered enough (see Q&A 5.11) in all cases, nor that 3 chemical transformation steps are mandatory.

In the case of Example 4, application of the ICH Q11 principles includes control of the enantiomer in the specification of the proposed starting material D, in combination with the understanding that the steps immediately prior to D do not introduce other impurities that impact the impurity profile of the drug substance. The applicant should provide information in the application on the upstream process to justify the proposed starting material including control strategy of the impurity that persists.

Q9. What should an applicant consider when determining which manufacturing steps impact the mutagenic impurity profile of the drug substance, as part of the selection and justification of starting materials? (5.9)

As part of determining which manufacturing steps impact the impurity profile of the drug substance, the applicant should identify mutagenic materials that are likely to be formed or are introduced in the manufacturing process. The applicant should also determine which steps contribute mutagenic impurities to the drug substance at a level considered to impact the impurity profile (see Q&A 5.7). The Hazard Assessment Elements from ICH M7 can be used to determine which of the actual and potential impurities are considered to be mutagenic.

For the selection and justification of starting materials, the following approaches are recommended:

- Impurities that have been identified in the drug substance ("actual impurities") should be assessed for mutagenicity.

- Reagents and intermediates used in the synthesis from commercially available chemicals to the drug substance should be assessed for mutagenicity if they are likely to impact the impurity profile of the drug substance. Note that this may include assessment of the mutagenicity of some reagents and intermediates used in steps before the starting material that is eventually proposed.

- Mutagenic substances that are impurities in commercially available chemicals or synthetic intermediates, or that are formed as the result of side reactions during the synthesis, could also be present in the drug substance at levels relevant to safety. However, such mutagenic impurities and by-products are usually present at much lower concentrations than reagents, solvents, and intermediates. Therefore, the risk that such impurities will carry over significantly into the drug substance from early reaction steps is lower than for reagents, solvents, or intermediates from the same steps. The applicant should use risk-based reasoning to determine which steps to include in the hazard assessment for this category of potential impurity, and include a discussion of the risk assessment when identifying the point in the synthesis where these impurities and by-products are included in the assessment.

Information collected during the evaluation of potential mutagenic impurities can be submitted in an application and could be valuable for multiple purposes. For example, the justification for a proposed starting material should include information demonstrating that none of the steps immediately upstream (i.e., earlier in the synthesis) of the proposed starting material impact the impurity profile of the drug substance. Also, the suitability of the proposed control strategy can be supported with information about any mutagenic impurities formed or purged in the manufacturing steps between the proposed starting material and the drug substance, or that are controlled in the specification of the proposed starting material. The ICH Q11 exception for impurities that "persist" is also applicable to mutagenic impurities (see Q&A 5.8). In addition, steps involving mutagenic reagents or impurities may be upstream of the starting material if they do not impact the impurity profile of the drug substance (see Q&A 5.10).

The approaches outlined in this Q&A are consistent with the principles in ICH M7 concerning hazard assessment, risk characterization of mutagenic impurities, and their control. However, ICH M7 does not provide specific guidance on how mutagenic impurity assessment can be used

to justify selection of appropriate starting materials. This Q&A addresses the application of the principles in ICH M7 to the selection and justification of starting materials, based on the ICH Q11 concept of impact to the impurity profile of the drug substance.

This Q&A is not intended for the types of drug substances and indications for which ICH M7 does not apply (e.g., genotoxic drug substances, advanced cancer indications per ICH S9).

Q10. Do all steps that involve mutagenic reagents, impurities, or establish regio- or stereochemical configurations, need to be included in the process description in section 3.2.S.2.2 of the application? (5.10)

No. The ICH Q11 general principles for selection of starting materials do not include a recommendation that all steps involving mutagenic reagents or impurities should be included in the process description in section 3.2.S.2.2. Similarly, the general principles do not include a recommendation that all steps that establish regio- or stereochemical configurations (which can therefore result in regio- or stereoisomerism) should be included in section 3.2.S.2.2. However, it is expected that the other ICH Q11 general principles on impurities (see Q&As 5.7, 5.8 and 5.9) and inclusion of enough of the manufacturing process (see Q&A 5.11) be applied when deciding whether steps that involve mutagenic reagents, impurities, or establish regio- or stereochemical configurations, need to be included. As an example, a mutagenic compound could be introduced prior to the starting material, or be the starting material itself, provided the ICH Q11 general principles are addressed.

Q11. ICH Q11 states that "enough of the drug substance manufacturing process should be described in the application . . .." What considerations should an applicant apply in the selection of the proposed starting materials to assure that enough of the drug substance manufacturing process will be described in the process description in section 3.2.S.2.2 of the application? (5.11)

In deciding whether enough of the drug substance manufacturing process is described in section 3.2.S.2.2 of the application, the following considerations should be applied.

The applicant should first evaluate which chemical transformation steps in the manufacturing process impact the impurity profile of the drug substance. These steps should normally be included in section 3.2.S.2.2 (see Q&As 5.7, 5.8 and 5.9).

Next, the applicant should examine the steps immediately upstream of those steps that impact the impurity profile of the drug substance. These steps should normally also be included in section 3.2.S.2.2 if:

- They need to be carefully controlled (e.g., within narrow parameter ranges) to prevent generation of impurities that would otherwise impact the impurity profile of the drug substance.

- They include a unit operation that has been added to the manufacturing process to control specific impurities that would otherwise impact the impurity profile of the drug

substance. While starting material manufacturing processes typically contain purification operations, addition of purification steps prior to a proposed starting material in order to avoid defining an earlier, upstream compound as the starting material would not be considered appropriate.

After these considerations, if the evaluation would result in only a small number of chemical transformation steps, then it is generally appropriate to include one or more additional chemical transformation steps in section 3.2.S.2.2. This is to ensure that enough steps are conducted under GMP to appropriately mitigate risks associated with contamination and future changes to the synthetic route or supplier of the starting material. The following paragraphs provide further clarification on this risk mitigation and should be considered together.

- Although ICH Q11 does not specify how many steps should be performed under GMP, ICH Q11 recommends the inclusion of "multiple chemical transformation steps" in section 3.2.S.2.2 in order to reduce the risk of contamination and support the effective implementation of the control strategy throughout the product lifecycle. When there would be a small number of steps, there is an increased risk of contamination that needs to be addressed by the applicant in their starting material justification, and will often be best mitigated by including one or more additional steps in section 3.2.S.2.2.

- Potential risks from future changes to the starting material synthesis should also be considered (see Q&A 5.16). There is an increased risk that impurities generated as a result of a change to the manufacturing process upstream of the starting material may not be detected or purged appropriately if the starting material is only a small number of steps from the drug substance. In order to determine how many additional steps to include, the applicant may also consider other approaches to risk mitigation; for example, inclusion of analytical methodologies in the specification of the proposed starting material that are designed to detect a wide range of possible impurities based on different physical and chemical separation and detection principles. Appropriate acceptance criteria for unspecified impurities should be included in the specification.

The applicant should include in their justification of the proposed starting material a comprehensive description as to what factors were considered in deciding whether enough of the drug substance manufacturing process is provided in section 3.2.S.2.2 of the application to ensure that risks are appropriately mitigated.

Q12. What considerations are important for a starting material specification? (5.12)

Applicants should provide and justify a specification (which includes a list of tests, references to analytical procedures, and appropriate acceptance criteria) for all proposed starting materials as part of the drug substance control strategy.

The specification of a starting material should include tests for identity and purity (e.g., controls on impurities) and, where applicable, could include acceptance criteria for assay, specified, unspecified and total impurities, residual solvents, reagents, elemental impurities and mutagenic impurities. The analytical procedures used should be suitably validated. The tests and

acceptance criteria should be based on process knowledge and the drug substance control strategy. The justification of the specification should include an evaluation of the risks and the ability of the subsequent steps to adequately control and/or purge impurities.

Q13. For starting materials that are not commercially available chemicals, what information should be provided on the synthetic route? (5.13)

Information on how the proposed starting material is made (e.g., a flow chart of the starting material manufacturing process, showing all reagents, catalysts and solvents used) should be provided to help justify the controls applied to the starting material. Information about the actual and potential impurities in the proposed starting material should be provided.

Q14. What information should be included in the application about a starting material that is a commercially available chemical? (5.14)

An applicant generally need not justify the use of a commercially available chemical as a starting material (see ICH Q11 section 5.2.1). However, the applicant should provide basic information on the starting material (chemical name, chemical formula, and molecular weight), information on the impurity profile of the starting material, and how the control strategy for the drug substance manufacturing process justifies the starting material specification.

If the drug substance manufacturer needs to perform additional purification steps to ensure the consistent quality of a commercially available starting material, ICH Q11 also recommends that these steps should be included in section 3.2.S.2.2 as part of the drug substance manufacturing process.

The applicant should set appropriate controls and should justify the proposed specification for the actual and potential impurities that are reasonably expected in a proposed starting material, based on the scientific knowledge and available information.

ICH M7 states: "For starting materials that are introduced late in the synthesis of the drug substance (and where the synthetic route of the starting material is known) the final steps of the starting material synthesis should be evaluated for potential mutagenic impurities." In the case where the starting material is a commercially available chemical, then this evaluation would be used to determine the appropriate control strategy.

For all starting materials, applicants should set appropriate controls and be able to justify the proposed specifications.

Q15. Can the Lifecycle Management section of ICH Q11 (section 9) apply to starting materials? (5.15)

Yes. In addition to what is submitted in the application, changes upstream of the defined starting material should be managed under the applicant's Pharmaceutical Quality System (PQS), which should address residual risks to the drug substance quality.

The Lifecycle Management section of ICH Q11 reinforces management's responsibility described in *Pharmaceutical Quality Systems* (ICH Q10), which is applicable to starting material lifecycle management. ICH Q10 section 2.7 (Management of Outsourced Activities and Purchased Materials) recommends that

> The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials.

ICH Q7 sections 7 (Materials Management) and 13 (Change Control), ICH Q7 Q&A document sections 7 and 13, as well as ICH Q10 section 2.7 (Management of Outsourced Activities and Purchased Materials) provide guidance that can be applied to the management of starting materials and starting material suppliers.

ICH Q9 and its Annexes provide guidance on the use of principles for quality risk management which can be applied to changes related to the starting materials (e.g., new starting material suppliers, manufacturing processes, or specifications).

Q16. Does ICH Q11 include specific guidance for post-approval changes to steps upstream of the starting material (e.g., changes in synthetic route, reagents, solvents, starting material supplier)? (5.16)

No. Post-approval changes to steps upstream of starting materials are not explicitly covered in ICH Q11. However, ICH Q11 does describe fundamental science and risk-based concepts that should be used to evaluate the impact of post-approval changes to the process after the starting material (ICH Q11 section 9 – Lifecycle Management), and these same concepts should be applied to evaluate the impact of changes upstream of the starting material.

For example, changes upstream of the starting material should be evaluated for their impact on the starting material (e.g., on current and potential new impurities, including potentially mutagenic and elemental impurities) and, when appropriate, on the drug substance. The evaluation could be based on risk assessment and scientific understanding of the proposed change and its proximity to the starting material. The evaluation should include an assessment of the control strategy (e.g., adequacy of the specification for the starting material, including the ability of the analytical procedures to detect any new impurities).

As stated in ICH Q7 Q&A document section 13.1, each party in the supply chain is responsible for transferring information related to quality or regulatory changes to the next customer in the supply chain so that the information is transferred to the drug product manufacturer in a timely manner.

Post-approval changes to information on the starting material should be reported to regulatory authorities in accordance with regional regulations and guidances.

VI. CONTROL STRATEGY (6)

There was no Q&A drafted on this section.

VII. PROCESS VALIDATION/EVALUATION (7)

There was no Q&A drafted on this section.

VIII. SUBMISSION OF MANUFACTURING PROCESS DEVEOPMENT AND RELATED INFORMATION IN THE COMMON TECHNCICAL DOCUMENT (CTD) FORMAT (8)

There was no Q&A drafted on this section.

IX. LIFECYCLE MANAGEMENT (9)

There was no Q&A drafted on this section.

X. ILLUSTRATIVE EXAMPLES (10)

There was no Q&A drafted on this section.

XI. GLOSSARY (11)

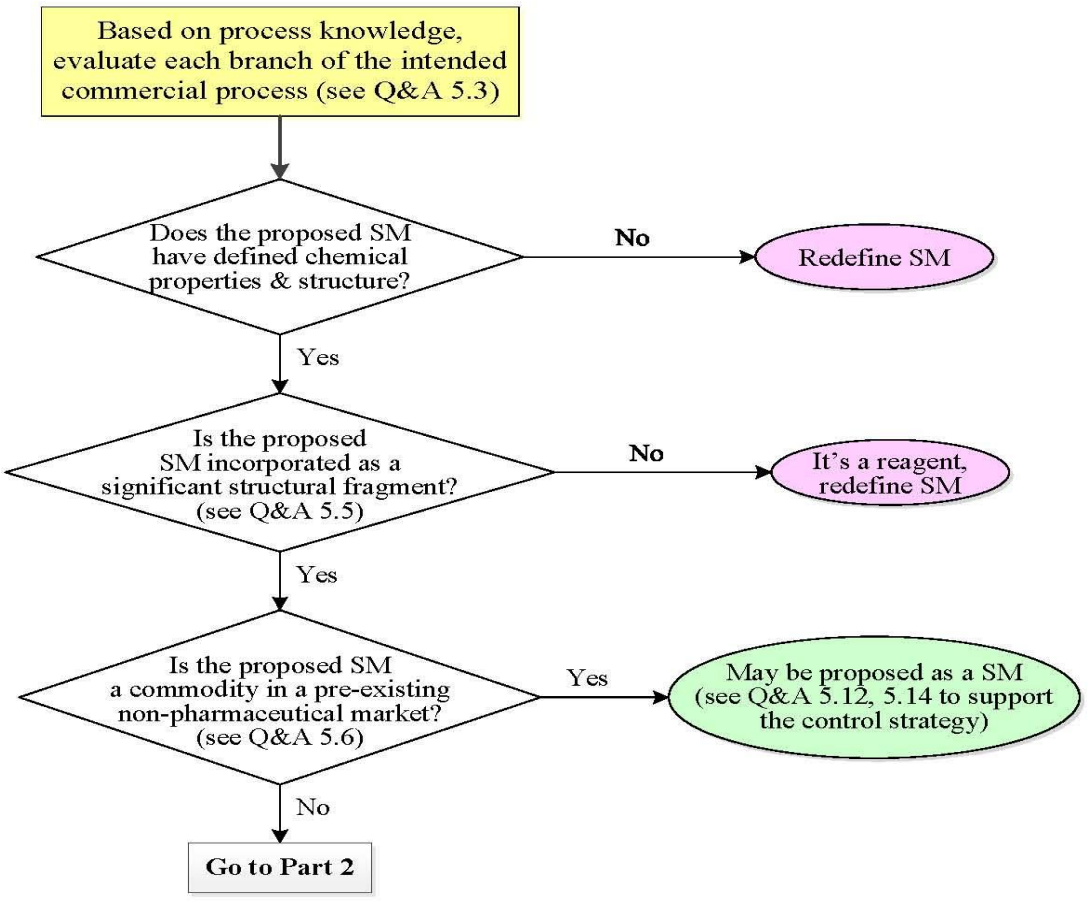
There was no Q&A drafted on this section.

ANNEX 1 – Decision Tree

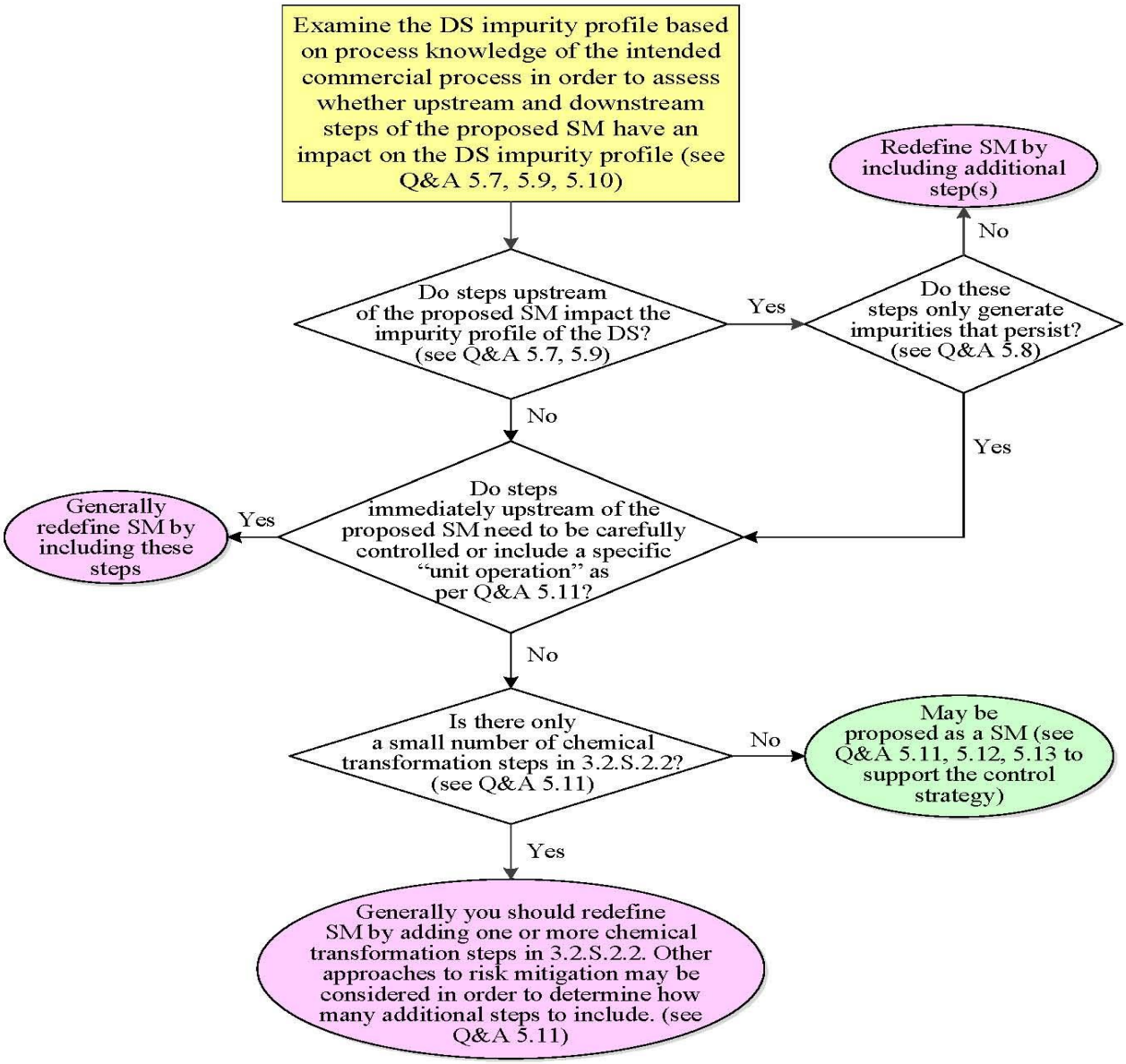
This decision tree serves as a pictorial exemplification to apply all ICH Q11 general principles for the selection and justification of a starting material (SM). Rather than being used in isolation, this decision tree should be used together with ICH Q11 and the clarifications in this Q&A document.

Part 1 of the decision tree focuses on evaluation of the proposed starting material from its chemical structure perspective. **Part 2** of the decision tree focuses on determining which manufacturing steps have an impact on the drug substance (DS) impurity profile and if enough of the manufacturing process is conducted under GMP in order to select appropriate starting materials.

Part 1



Part 2


Examine the DS impurity profile based on process knowledge of the intended commercial process in order to assess whether upstream and downstream steps of the proposed SM have an impact on the DS impurity profile (see Q&A 5.7, 5.9, 5.10)
Do steps upstream of the proposed SM impact the impurity profile of the DS? (see Q&A 5.7, 5.9)
Yes
Do these steps only generate impurities that persist? (see Q&A 5.8)
No
Redefine SM by including additional step(s)
No
Yes
Do steps immediately upstream of the proposed SM need to be carefully controlled or include a specific "unit operation" as per Q&A 5.11?
Yes
Generally redefine SM by including these steps
No
Is there only a small number of chemical transformation steps in 3.2.S.2.2? (see Q&A 5.11)
No
May be proposed as a SM (see Q&A 5.11, 5.12, 5.13 to support the control strategy)
Yes
Generally you should redefine SM by adding one or more chemical transformation steps in 3.2.S.2.2. Other approaches to risk mitigation may be considered in order to determine how many additional steps to include. (see Q&A 5.11)