Definition and justification of API starting materials

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How many questions do we raise on starting materials?

PA/PH/CEP (16) 58 (December 2016)

"Top Ten Deficiencies – New applications for certificates of suitability for chemical purity (2015-2016)"

- Publicly available on the EDQM website
- It describes what it is expected to see in the dossier

Starting materials

Redefinition of starting materials

Quality of starting materials

Fate and carryover of impurities from starting materials

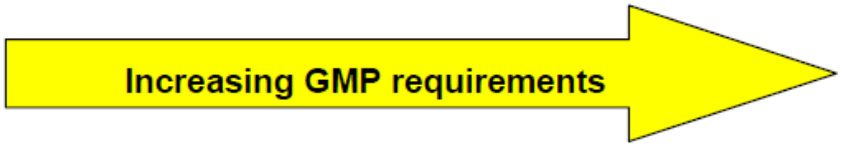
Information on starting materials

Proposed starting materials not accepted: redefinition of starting materials

ICH Q7 Good manufacturing practice guide for active pharmaceutical ingredients

- The approved starting materials are the starting point for GMP and variations and must be representative of the overall synthetic process.

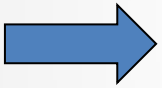
Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



Proposed starting materials not accepted: redefinition of starting materials

Criteria to define starting materials set by the **ICH Q11**

In order to assess the adequacy of control on the drug substance, its manufacturing process and control of impurities, **enough** of the process should be described.

 Relationship between risk and number of synthetic steps

- The definition of starting materials is expected to be justified by the applicant. If not acceptable, a redefinition is required. As a consequence the originally proposed starting materials become intermediates.

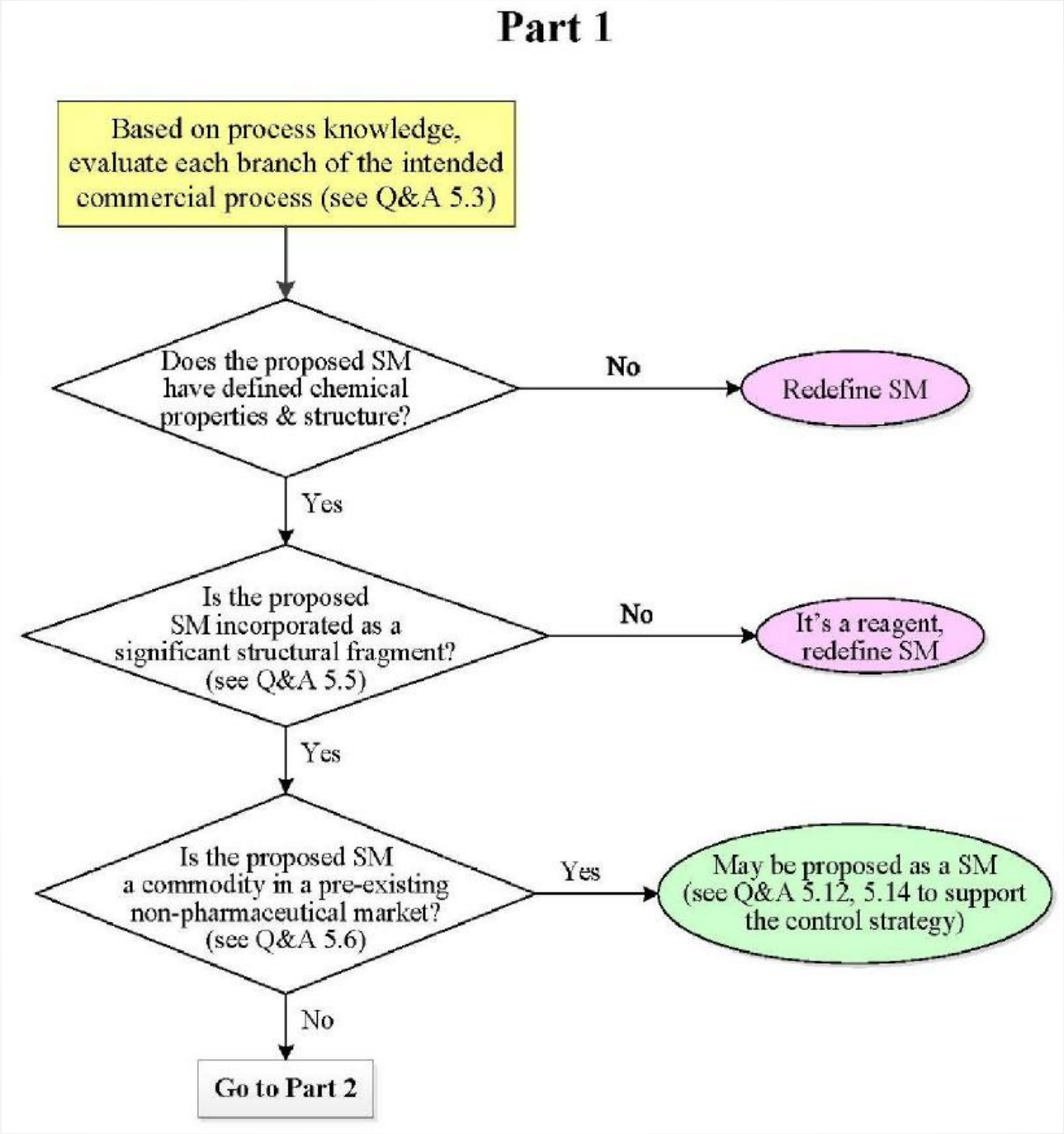
Proposed starting materials not accepted: redefinition of starting materials

ICH Q11 Q&A document with regard to selection and justification of starting materials

Implementation Working Group
ICH Q11 Guideline:
DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)
Questions and Answers

Version: 23 August 2017

Part 1


Based on process knowledge, evaluate each branch of the intended commercial process (see Q&A 5.3)
Does the proposed SM have defined chemical properties & structure?
No
Redefine SM
Yes
Is the proposed SM incorporated as a significant structural fragment? (see Q&A 5.5)
No
It's a reagent, redefine SM
Yes
Is the proposed SM a commodity in a pre-existing non-pharmaceutical market? (see Q&A 5.6)
Yes
May be proposed as a SM (see Q&A 5.12, 5.14 to support the control strategy)
No
Go to Part 2

5.2		Is a "starting material" as described in ICH Q11 the same as an "API starting material" as described in ICH Q7?	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 guideline) 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.
5.3		Do the ICH Q11 general principles for selection of starting materials apply to the selection of starting materials for linear and convergent syntheses?	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.

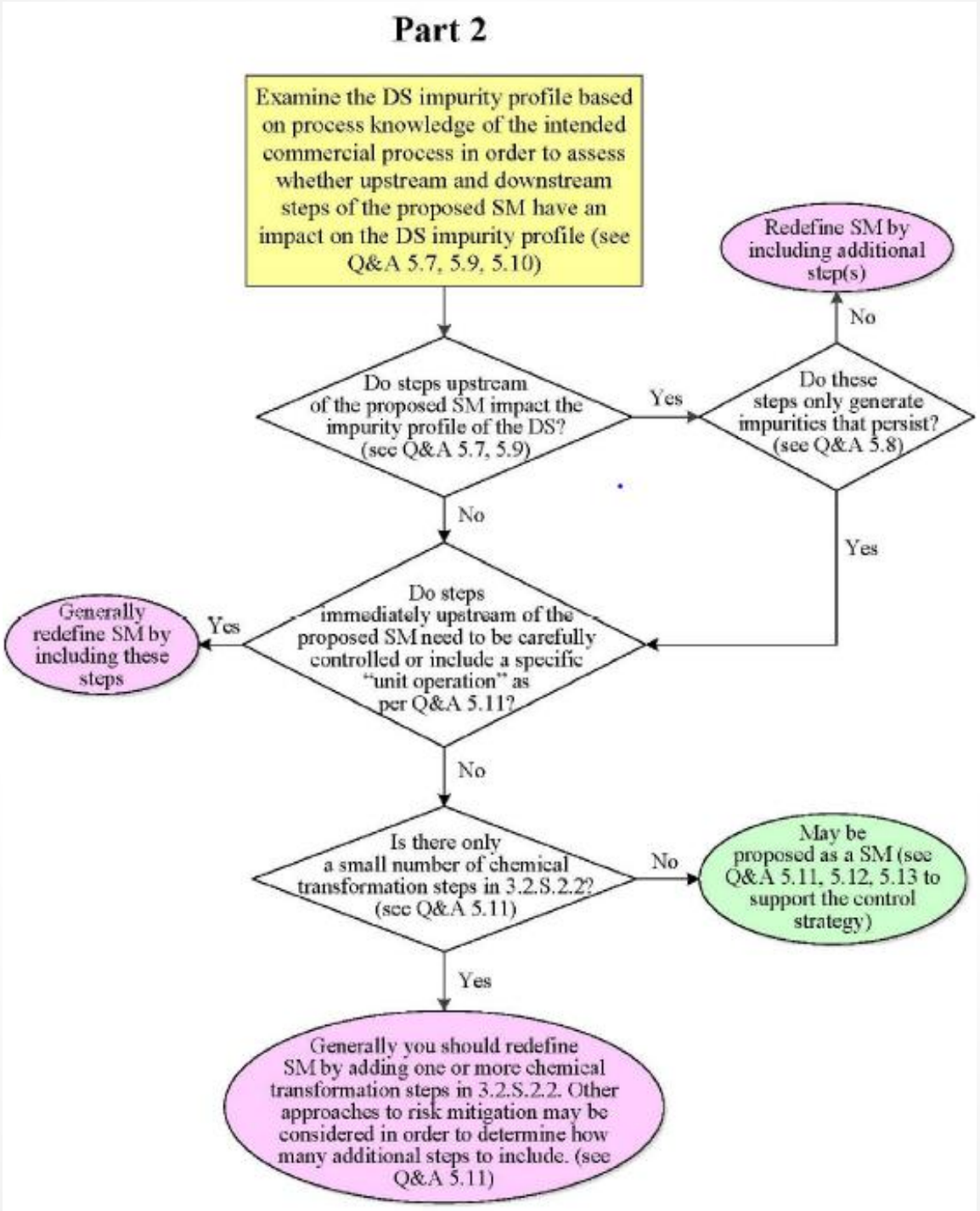
5.4		Do the ICH Q11 general principles for selection of starting materials apply to processes where multiple chemical transformations are run without isolation of intermediates?	Yes. The ICH Q11 general principles apply to processes where multiple chemical transformations are run without isolation of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

5.5		ICH Q11 states that "*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?	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.

5.6		What is the difference between a commercially available chemical and a custom synthesised chemical?	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 synthesised chemical" was not provided in ICH Q11, but a custom synthesised 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 synthesised chemicals. An applicant generally need not justify the use of a commercially available chemical as a starting material, whereas a custom synthesised 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.

5.12		What considerations are important for a starting material specification?	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.
5.14		What information should be included in the application about a starting material that is a commercially available chemical?	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.

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)
Redefine SM by including additional step(s)
No
Yes
No
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)

5.7		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.*" At what level would a related substance or mutagenic impurity be considered to impact the impurity profile of the drug substance?	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% 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% 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 guidelines) 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.
5.8		What is meant by impurities that "persist" in ICH Q11 Example 4?	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). 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.

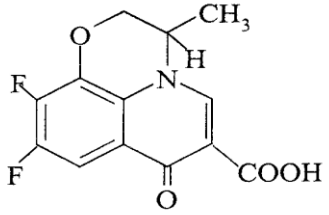
5.9		What should an applicant consider when determining which manufacturing steps impact the mutagenic impurity profile of the drug substance, as part of the selection and justification of starting materials?	As part of determining which manufacturing steps impact the impurity profile of the drug substance,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

5.10		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?	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.
5.11		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?	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.

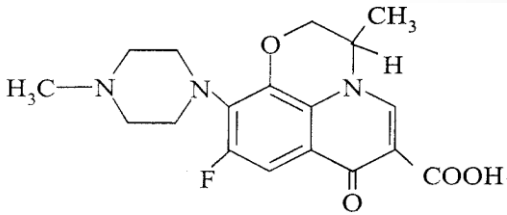
5.13		For starting materials that are not commercially available chemicals, what information should be provided on the synthetic route?	Information on how the proposed starting material is made (e.g., a flow chart of the starting material manufacturing process, showing all reagents, catalysts and solvents 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.

Proposed starting materials not accepted: redefinition of starting materials

Synthesis of ofloxacin (one synthetic step described)

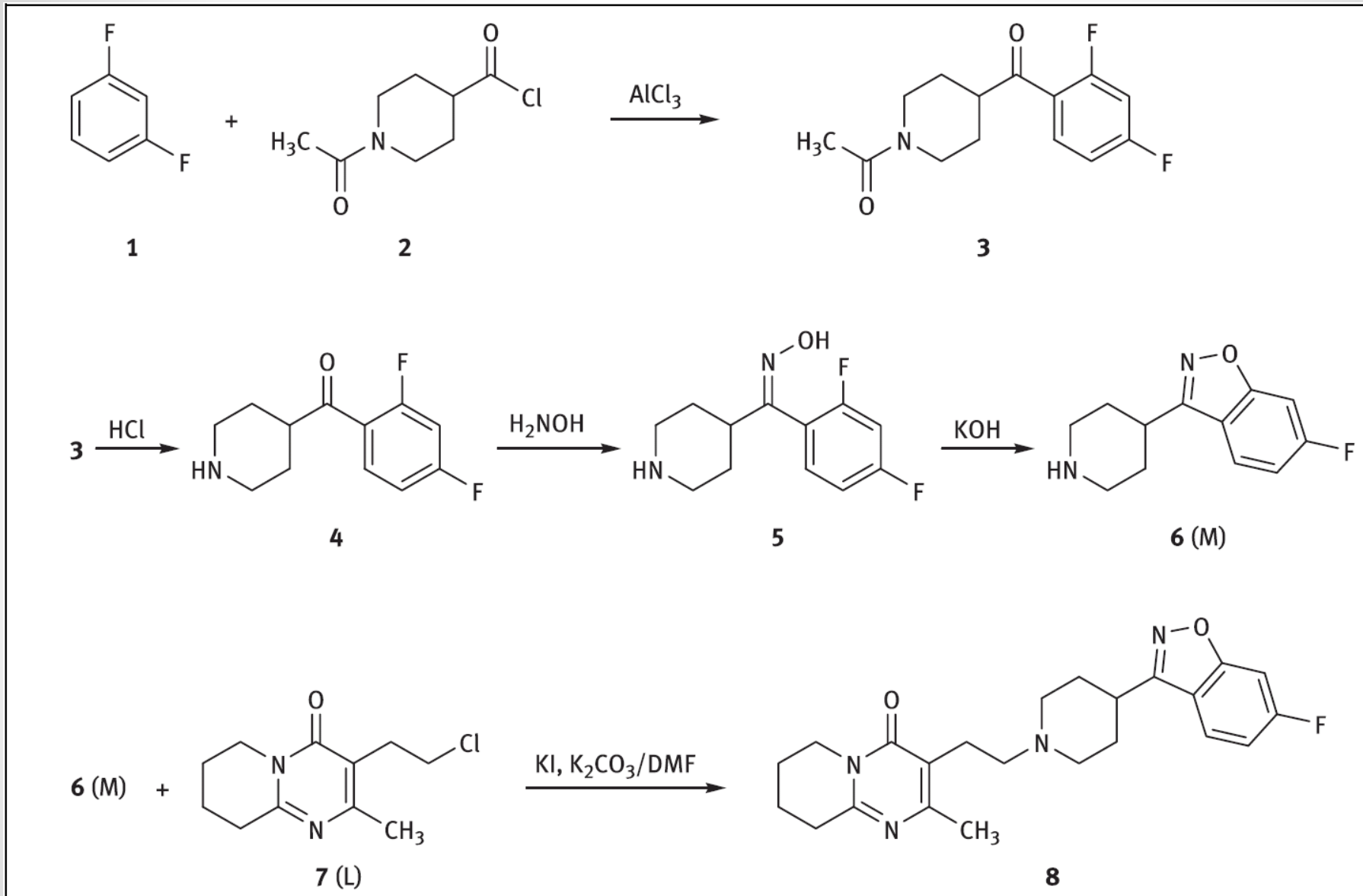


(*RS*)-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[*1,2,3-de*]-1,4-benzoxazine-6-carboxylic acid - (Q-Acid)



(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (Ofloxacin)

Q-Acid is not an adequate starting material and it should be classified as an intermediate (outsourced or not).


F
F
1
+
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Cl
H_3C
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$AlCl_3$
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H_2NOH
OH
N
F
HN
F
5
KOH
N
O
HN
F
6 (M)
6 (M)
+
O
Cl
N
N
CH_3
7 (L)
KI, K_2CO_3/DMF
N
O
O
N
N
CH_3
F
8

Proposed starting materials not accepted: redefinition of starting materials

External suppliers become suppliers of intermediates and:

- GMP and willingness to be inspected declarations are necessary
- Section 3.2.S.2.1 and the application form need to be updated
- The dossier needs to be updated
- Information submitted from third parties is not acceptable. The manufacturer must be fully aware of the information supplied.

- Refusal of information from third parties in reply to EDQM's request for information (PA/PH/CEP (11) 18, March 2011)

Starting materials

Redefinition of starting materials

Quality of starting materials

Fate and carryover of impurities from starting materials

Information on starting materials

Quality of starting materials
Fate and carry-over of impurities

What is it expected?

1. The impurity profile of the starting material should be adequately characterised;
2. Analytical specifications with justified acceptance criteria should be proposed to control the impurity profile of starting materials (specified, unspecified and total impurities). Analytical specification should be representative of the process adopted;
3. Discussion on fate and carry-over of impurities.

Quality of starting materials
Fate and carry-over of impurities

Example of non-acceptable analytical specification

Chromatographic purity (By GC)	
Purity	Not less than 98.00 % (Including 4-Methoxy phenacyl chloride)
4-Methoxy acetophenone	Not more than 0.50%
Unknown single impurity	Not more than 1.00%
Total impurities	Not more than 2.00%

It is not clear what the major impurity is → risks of having uncontrolled impurities → risks for the quality of final substance

It is understandable and acceptable that there may be limitations in characterizing the impurity profile of a starting material but these limitations should not prevent the manufacturer from demonstrating that the level of characterization reached does not pose risks for the quality of the final substance.

Quality of starting materials
Fate and carry-over of impurities

Acceptance criteria in place to control impurities in starting materials should be justified by the manufacturer, taking into account fate and carry-over of impurities from starting materials to the final substance (ability of the process to purge unreacted impurities and potential by-products). Assurance should be given on the risk of having uncontrolled impurities later in the process.

Purity by HPLC		
a) Impurity at RRT 0.14	Not more than 2.5 % w/w	1.54 %
b) Single max unknown impurity	Not more than 1.0 % w/w	0.21 %
c) Total impurities	Not more than 3.0 % w/w	2.27 %

Batch data on their own DO NOT justify limits!

Other than analytical specification, it is expected to have in the Dossier a description of the analytical procedures used.

Information on the starting material

Besides analytical specification, the following information are expected in 3.2.S.2.3 part of the dossier:

-Route of the synthesis of the starting material (flow diagram of the process including solvents, reagents and catalysts used);

- Name(s) and address(es) of manufacturer(s) of the starting material should be declared (not their vendors or suppliers)

Absence of comparison of the quality of the final substance obtained with starting materials from different suppliers

- Quality equivalence should be demonstrated by means of batch data collected on the final drug substance manufactured using all the possible sources of the same starting material
- It should be demonstrated that the impurity profile of the substance is identical
- If different sources of the same starting material lead to APIs of different impurity profiles then 2 CEP's would be necessary

Thank you very much for your attention!