



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

3 July 2017

EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1  
Committee for Medicinal Products for Human Use (CHMP)  
Committee for Medicinal Products for Veterinary Use (CVMP)

## Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances

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| Agreed by CHMP/ CVMP Quality working party   | 11 July 2014      |
| Adoption by CHMP                             | September 2014    |
| Adoption by CVMP                             | September 2014    |
| Reviewed by CHMP/ CVMP Quality working party | 21 September 2016 |
| Adoption by CHMP                             | December 2016     |
| Adoption by CVMP                             | January 2016      |

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| Keywords | Starting materials, active substance. |
|----------|---------------------------------------|



## Introduction:

This reflection paper aims to clarify some of the expectations of EU competent authorities arising from the guidance found in ICH Q11 (Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)<sup>1</sup> regarding the information to be submitted in marketing authorisation dossiers to justify the selection of starting materials. Whilst ICH Q11 is not generally applicable to veterinary products, the principles outlined in this document should apply equally for active substances destined to treat both humans and animals. The document re-produces extracts from section 5 of ICH Q11 *verbatim* in black text, and provides subsequent commentary on EU expectations in the form of explanatory notes within grey-shaded boxes.

It should be recognised that this document is not intended as a revision of ICH Q11, and rather as a reflection paper within the EU medicines regulatory network as prepared by the Quality Working Party (QWP).

## Problem statement:

Disagreements between applicants and quality assessors on the suitability of proposed starting materials have become more frequent in recent times. This suggests that the current guidelines,<sup>1-3</sup> intentionally high level to allow application to the wide range of chemical syntheses submitted to regulatory authorities, are open to interpretation. Furthermore, it is increasingly common for applicants to propose very short synthetic routes with complex custom-synthesized starting materials. Another trend is for some, or all, of the active substance manufacture to be outsourced to third parties. The use of external sources for any steps in a manufacturing process may lead to a higher degree of risk to quality of the active substance than would be expected were the full manufacturing process to be carried out by the applicant or a single active substance manufacturer alone. This document strives to expand on some of the points in ICH Q11 in order to harmonise opinions between assessors and clarify the requirements for applicants.

Additionally, the information submitted by applicants or Active Substance Master File (ASMF) holders to justify the selection of starting materials and their proposed specifications is often insufficient to allow adequate assessment of suitability.<sup>4</sup> A detailed description of the manufacturing process of the active substance is required, along with a flow chart of transformations employed to synthesize starting materials including all solvents, reagents, catalysts and processing aids used, in order to facilitate a proper assessment. Since steps deemed critical should be carried out under Good Manufacturing Practice (GMP), an appraisal of the criticality of all transformations in the full synthetic route on the quality of the active substance is needed. The description of the manufacturing process should be sufficiently detailed to demonstrate that the process and its associated control strategy will consistently provide active substance of satisfactory quality. Starting materials can only be justified once the criticality of all steps has been discussed. Often, starting materials are selected and then only subsequent steps are discussed. This is not sufficient. A scheme of synthetic steps carried out to synthesize the proposed non-commodity starting materials should be provided as part of the justification of starting material selection.

# ICH Q11 and explanatory notes:

## 5. Selection of Starting Materials and Source Materials

### 5.1 General Principles

#### 5.1.1 Selection of Starting Materials for Synthetic Drug Substances

The following general principles should be considered in determining where the drug substance manufacturing process begins (i.e., in selecting starting materials).

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance;
- The relationship between risk and number of steps from the end of the manufacturing process is the result of two factors, one concerning the physical properties of the drug substance and the other concerning the formation, fate, and purge of impurities. The physical properties of a drug substance are determined during the final crystallisation step and subsequent operations (e.g., milling, micronising), all of which occur at the end of the manufacturing process. Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance. However, in some cases (e.g., when peptides or oligonucleotides are synthesised on a solid support), there is a more limited relationship between risk and number of steps from the end of the manufacturing process;

#### Explanatory note 1:

EU competent authorities need to see how the structure of the active substance is formed. A sufficient number of chemical transformation steps, as defined in the glossary of ICH Q11 (a step involved in the synthesis of the chemical structure of the drug substance from precursor molecular fragments. Typically it involves C-X or C-C bond formation or breaking), need to be included so that the generation, fate and control of impurities can be understood. Recrystallisation and salt formation steps for late stage intermediates can significantly affect the impurity profile of the active substance. However, information on earlier synthetic steps is also necessary in order to understand the risk of impurity carryover and to demonstrate that the proposed control strategy sufficiently mitigates this risk. Therefore, neither recrystallisations nor salt formations are considered chemical transformation steps, and neither are activities unlikely to have an impact on API purity such as milling or sieving.

Furthermore, a sufficient number of purification steps need to be documented so that the fate and purge of impurities can be understood. Multiple synthetic transformations carried out in one vessel without intermediate isolations (sometimes referred to as telescoped steps or "one pot reactions") provide fewer opportunities for purification than if isolation of intermediates were carried out. As with any complex reaction, a high number of variable parameters lead to a higher risk of producing active substance of variable quality. Regulators will therefore expect a commensurately high level of process understanding and control.

For these scientific reasons, short synthetic routes will not normally be accepted.

Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate, including whether there are appropriate controls

for impurities. To conduct this assessment, enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process, how changes in the process could affect the formation, fate, and purge of impurities, and why the proposed control strategy is suitable for the drug substance manufacturing process. This will typically include a description of multiple chemical transformation steps.

#### **Explanatory note 2:**

Generally, the detailed description of the manufacturing process (i.e. from the starting materials to the active substance) should cover all the synthetic steps critical to the quality of the active substance. Discussion on the formation, fate, and purge of both actual and potential (i.e. those likely to be formed based on reaction mechanism, side reactions, degradants, as well as reagents, catalysts, and solvents used) impurities should be presented. To facilitate this, analytical techniques to detect and quantify actual and potential impurities are required.

The documentation presented should enable assessors to consider whether the manufacturing process is robust to variability, whether the process is well controlled and therefore whether it will consistently lead to active substance of appropriate quality. The specification of a starting material should contain suitable limits for known, unknown and total impurities and where appropriate, limits for solvents, reagents and catalysts used during its synthesis.

#### **Critical Steps:<sup>2</sup>**

The controls applied to steps critical for active substance quality should be described in module 3.2.S.2.4 (part 2.C.1.1.2 for veterinary applications). A critical step is defined as one where the process conditions, test requirements or other relevant parameters must be controlled within pre-determined limits to ensure that the active substance meets its specification. Difficulties to remain within pre-determined limits for processing conditions or passing in-process control tests, as well as the consequences of any excursions, should be considered when identifying critical steps.

The criticality of a given step is related to its distance (in terms of synthetic steps) from the active substance, the subsequent processing and the overall control strategy being applied. The control strategy mitigates the risk associated with a given critical step, but does not necessarily affect its criticality. Examples of possible critical steps below should be considered in the context of the whole synthesis. The following list is neither exhaustive nor intended to imply that any such step would be mandatorily included in the manufacturing process of the active substance described in section 3.2.S.2.2 of the application (part 2.C.1.1.2 for veterinary applications).

Critical steps could be for instance:

- Steps involving formation and/or purge of key impurities – if a step purges an impurity which would otherwise be present in the active substance, then it should be considered critical. This could include not only reactive chemistry steps but work-ups, phase separations and crystallisations as well;
- Steps which introduce key structural features of the active substance, for example key functional groups or stereochemistry;
- Steps where careful control of stoichiometry, temperature, pH or other process variables is crucial for active substance quality;
- Steps which employ or generate genotoxic compounds;
- Steps which employ class I solvents and/or toxic metals;

### Explanatory note 2:

- Complex chemical transformations where multiple variables could impact reaction outcome (multiple reagents, catalysts, solvents, etc.)
- The final purification step.

The applicant/manufacturer should discuss and identify those manufacturing steps that impact the impurity profile of the active substance as they should be normally included in the manufacturing process described in section 3.2.S.2.2 of the application (part 2.C.1.1.2 for veterinary applications).

An approach could be to control certain parameters in the specification of a starting material (e.g. enantiomeric purity, genotoxic impurity limits). The acceptability of such proposals will depend on the proximity of a given starting material to the active substance, and thus, the risk to active substance quality.

Steps which have an impact on solid-state properties are always considered as critical, particularly, if the active substance is used within a solid dosage form, since they may adversely affect dissolution of the active substance thereby affecting bioavailability.

Tests and acceptance criteria, with justification based on experimental data, performed at critical steps identified in 3.2.S.2.2 of the manufacturing process, should be provided (part 2.C.1.1.2 for veterinary applications).

The opportunity to justify a short synthetic sequence exists but this should be for clear scientific reasons and is expected to be the exception rather than the norm. In such cases, steps to synthesize the starting materials should be demonstrated not to be critical (as defined above) to the quality of the active substance, and steps to avoid contamination from non-GMP steps should be integral to the control strategy.

If an intermediate in the proposed synthesis of the active substance is itself an active substance covered by a monograph of the European Pharmacopoeia (Ph. Eur.) covered by a valid CEP, then the CEP can be submitted as an alternative to submitting its process description. Documentation on the additional chemical transformation steps from the intermediate to the active substance should be provided in 3.2.S.2.2. The manufacturers involved in the process covered by the CEP should be listed in module 3.2.S.2.1 and the QP declaration.

If an intermediate in the proposed synthesis of the active substance is itself an active substance already included in a finished product authorised in the EU and documented in an ASMF or in module 3, then this can be referenced. Complete information on the manufacturing process (3.2.S.2), starting with the starting materials will still need to be submitted, either as part of a new ASMF or in the dossier.

1. 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.

### Explanatory note 3:

It therefore follows that steps critical for the purity of the active substance should be performed under GMP, which forms an integral part of any control strategy.

- Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The Good Manufacturing Practice (GMP) provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug **substance**.

#### Explanatory note 4:

In the EU, the requirements of GMP for Active Substances (ICH Q7)<sup>5</sup> have been incorporated into "The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Part II: Basic Requirements for Active Substances used as Starting Materials".<sup>6</sup>

For active substances, GMP applies to a manufacturing process from the introduction of starting materials and makes a major contribution to any control strategy.

GMP guidelines are intended to help ensure that active substances meet the requirements for quality and purity that they are claimed to possess.

EU Authorities are concerned that introduction of impurities into the active substance from non-GMP manufacture, (e.g. from poor cleaning of vessels previously used for other purposes or inadequate control of processes), which would not necessarily be picked up by routine analytical testing is a significant risk. The fewer synthetic steps carried out under GMP, the higher the risk to the quality of the active substance.

The control strategy in place for a given manufacturing route mitigates the risk associated with the manufacturing process and assures the quality of the active substance. The control strategy ensures the individual batch quality, but relies on GMP to ensure that the conditions necessary for the validity of the control strategy do not change over time. It does not follow that a short route of synthesis can be accepted if a good control strategy is in place, nor that a poor control strategy can be compensated by a longer synthetic route carried out under GMP. Specifications of starting materials, intermediates and the active substance, reaction parameters (stoichiometry, temperature, pH, reaction times, etc.), in-process controls, release testing, and working under GMP all form an integral part of the control strategy.

Although there are no objections to the manufacturers of starting materials operating under the principles of GMP, statements from applicants/manufacturers such as "we commit to carrying out manufacture of starting materials to GMP and are willing to be inspected" are not acceptable since production of the API starting material is currently excluded from application of the EU GMP Guide. Furthermore there is no current regulatory framework for inspection and no transparency exists for applicants and inspectors in steps prior to the starting materials. Likewise, assessors will not accept third party confidential information, sometimes proposed by starting material or intermediate manufacturers or suppliers of any raw materials used in the synthetic process, in order to seek approval of an advanced intermediate as a starting material. Any acceptance of GMP declarations of this nature would not translate to the lifecycle of the product where subsequent changes in the supply chain or to steps prior to the starting materials may not be subject to the same declarations which could neither be requested nor enforced.

Once approved, any subsequent change to the synthetic route involving re-definition of the starting materials must be proposed, justified and assessed according to same principles outlined in this reflection paper. Statements such as "this intermediate or starting material can be supplied by other qualified suppliers" cannot be accepted unless details of their source are provided and then only after regulatory assessment.

#### Explanatory note 4:

The practice of shortening some of the branches of an approved synthetic route through the submission of updates or variations to an ASMF, to a CEP dossier or to Module 3.2.S (part 2.C.1.1 for veterinary applications), is often linked to the contracting out of part of the synthetic route. That means redefinition of what was previously an intermediate to be the new starting material. Accepting the new proposed starting material however, reduces regulatory oversight and may weaken the control strategy. This is especially important when linked to further lifecycle changes in the supply chain which may adversely affect the overall quality of the active substance. The shortening of manufacturing processes is therefore unlikely to be considered acceptable without a strong scientific rationale.

- A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials;
- A starting material is incorporated as a significant structural fragment into the structure of the drug substance. "Significant structural fragment" in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials. Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.

#### Explanatory note 5:

The term "significant structural fragment" is frequently misinterpreted by applicants as meaning structural proximity to the active substance. In this context however, the phrase applies to materials which contribute to the final molecular structure of the active substance, as opposed to reagents, catalysts, or solvents. Justification of a late intermediate as starting material by claiming it is a significant structural fragment is not considered a valid argument as this could apply to any intermediate in the manufacturing process.

All the general principles above should be considered in selecting Starting Material(s), rather than strictly applying each general principle in isolation (see Example 4, Section 10.4).

#### Explanatory note 6:

Scientific reasoning with appropriate justification, considering the whole synthetic approach and control strategy, and incorporating all the various principles outlined above, should be used in order to justify the selection of the starting materials. Often, applicants/manufacturers will select just a few criteria and use them to justify starting material selection, e.g.: "Compound X is a well-characterised isolated material of defined chemical properties and structure, and constitutes a significant structural fragment of the active substance. Therefore it is selected as a starting material as per ICH Q11." This line of argumentation is not comprehensive and therefore not acceptable. Control strategy **alone** is not a sufficient justification of a starting material. Equally, a long synthetic process will not necessarily compensate for a poor control strategy.

### 5.1.2 Selection of Starting Materials for Semi-Synthetic Drug Substances

For purposes of this guideline, a semi-synthetic drug substance is one in which the structural constituents have been introduced by a combination of chemical synthesis and elements of biological origin (e.g., obtained from fermentation or by extraction from botanical material). In some cases, it

might be appropriate for the applicant to describe the manufacturing process starting from the source material (microorganism or botanical material). However, if it can be demonstrated that one of the isolated intermediates in the synthetic process complies with the principles outlined above for the selection of starting materials for synthetic drug substances, that isolated intermediate can be proposed as the starting material. The applicant should specifically evaluate whether it is possible to analytically characterise the proposed starting material, including its impurity profile, and whether the fermentation or botanical material and extraction process impact the impurity profile of the drug substance. Risks from microbial and other contamination should also be addressed.

#### Explanatory note 7:

It is re-emphasised that a semi-synthetic starting material should comply with the general principles for starting materials already discussed above and summarised in **explanatory note 6**. If the fermentation step or extraction step is considered to be critical following the definition in **explanatory note 2**, and considering the potential for variability in fermentation process or extraction step, then it should be carried out under GMP.

## 5.2 Submission of Information for Starting Material or Source Material

Applicants should identify all proposed starting materials or source materials and provide appropriate specifications. Proposed starting materials for synthetic and semi-synthetic drug substances should be justified.

#### Explanatory note 8:

Information on the manufacturers and suppliers of starting materials should be provided, including name and address, and a scheme of the synthetic route used to manufacture them, showing all reagents, catalysts and solvents used. Without this information, the suitability of specifications cannot be adequately assessed.

The specification for a starting material should address impurities and is expected to consider suitable limits for known, unknown impurities and total impurities and where appropriate, limits for solvents, reagents and catalysts used during synthesis of a starting material. The acceptance criteria should be established based on origin, fate and purge of impurities present in the starting material, and where appropriate, should be designed to detect isomeric or other impurities which are potentially reactive and which may be carried through to the active substance.

Analytical methods used should be validated. A tabulated summary of the results of the validation carried out should be provided if critical for the quality of the active substance. However, it is not necessary to provide a validation report.

### 5.2.1 Justification of Starting Material Selection for Synthetic Drug Substances

The applicant should provide a justification for how each proposed starting material is appropriate in light of the general principles for the selection of starting materials outlined above in Section 5.1.1. This can include information on:

- The ability of analytical procedures to detect impurities in the starting material
- The fate and purge of those impurities and their derivatives in subsequent processing steps



- How the proposed specification for each starting material will contribute to the control strategy

#### Explanatory note 9:

The suitability of a starting material needs to be justified against the principles in section 5.1 as a whole, rather than against selected individual bullet points. Critical to satisfactory justification of a starting material, and for the assessment of the justification, is the description of the formation, fate and purge of impurities. The dossier must contain an appropriate discussion on known and unknown impurities including residual solvents, catalysts, metals and reagents. The starting material specifications should include tests and acceptance criteria for specified, unspecified and total impurities (including (potential) genotoxins) and where appropriate, limits for solvents, reagents and catalysts used during their synthesis. An inadequate discussion on impurities renders evaluation of the proposed starting materials and their specifications impossible.

The applicant should provide, as part of the justification, a flow diagram outlining the current synthetic route(s) for the manufacture of the drug substance, with the proposed starting materials clearly indicated. Changes to the starting material specification and to the synthetic route from the starting material to final drug substance are subject to regional, post-approval change requirements. In addition, regional requirements concerning starting material suppliers may also be applicable.

#### Explanatory note 10:

The quality of the proposed starting material must be sufficient, in combination with the control strategy, to ensure the quality of the active substance. The manufacturing route of a starting material and information on manufacturers\* should also be provided to allow an adequate assessment of the suitability of starting materials and their specification. If any synthetic steps used to manufacture the starting materials are considered critical and are either close to the active substance (in terms of number of synthetic steps) or impact its impurity profile, then the re-definition of starting materials to an earlier point should be considered, bearing in mind the whole synthetic route and the control strategy (see **explanatory note 2**).

It is emphasized that it is the legal responsibility of the marketing authorisation holder to maintain the quality of the active substance throughout its lifecycle. Implicit in this is that changes to the synthetic route to the starting materials should always be assessed for their impact on the quality of the active substance, and any resultant modifications such as changes to specifications or manufacturers of the starting material(s) should be applied for by way of appropriate variations. The active substance manufacturer, which may frequently be independent of the applicant, has a very important role to play in this and is also responsible for ensuring the quality of the active substance it manufactures.

\* When ICH Q11 mentions starting material suppliers, this is interpreted within the EU as manufacturers.

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 starting material. Chemicals produced by custom syntheses are not considered to be commercially available. If a chemical from a custom synthesis is proposed as a starting material, it should be justified in accordance with the general principles for the selection of starting materials outlined above in Section 5.1.1.

In some instances, additional purification steps by the drug substance manufacturer might be called for to ensure the consistent quality of a commercially available starting material. In these instances, the additional purification steps should be included as part of the description of the drug substance

manufacturing process. Specifications should normally be provided for both incoming and purified starting material.

#### **Explanatory note 11:**

A statement that a material is commercially available may not be considered sufficient to justify it as a starting material without additional supporting information. It is the responsibility of the applicant to show that a commercially available starting material is not custom synthesised, but a commodity material used in a non-pharmaceutical market, and to provide supportive documentation in the dossier demonstrating so. It is also a requirement to demonstrate that the quality of a commercially available starting material is adequate for use in the manufacture of an active substance. To enable the assessment of any requirement for further purification of a commercially available material, the information on the impurity profile should be presented for assessment.

### **5.2.2 Justification of Starting Material Selection for Semi-Synthetic Drug Substances**

If an isolated intermediate is proposed as the starting material for a semi-synthetic drug substance, the applicant should provide a justification that explains how the proposed starting material complies with the general principles for the selection of starting materials outlined above in Section 5.1.1. Otherwise, the applicant should describe the manufacturing process starting from the microorganism or botanical material, as appropriate, and these materials should be qualified.

#### **References:**

1. ICH Guideline Q11 on Development and Manufacture of Drug Substances (chemical entities and biotechnological / biological entities) CHMP/ICH/425213/2011 (ICH Q11)
2. Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1)
3. Chemistry of active substances 3AQ5A
4. Active substance-master-file procedure CHMP/QWP/227/02
5. ICH Guideline Q11 on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients CPMP/ICH/4106/00 (ICH Q7)
6. The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Part II: Basic Requirements for Active Substances used as Starting Materials