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4 Implementation strategy of ICH Q3D guideline

5 Draft

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Introduction

The purpose of this document is to describe the practical implementation of ICH Q3D Guideline for Elemental Impurities in the European context.

Background

In the ICH Q3D Guideline for elemental impurities, the focus of the control of elemental impurities is shifted compared to the CHMP Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents[1]. The latter guideline focuses on control of metals intentionally added during the synthesis of the active substance. The former acknowledges that this is one of the most important sources of elemental impurities, but also takes into account other sources and therefore includes elements not used as catalysts and reagents.

A consequence of this is that the Permitted Daily Exposure (PDE) levels established are applicable to the drug product, as there may be more than one source to some elemental impurities. Also, in the spirit of the principles of ICH Q8, Q9, Q10 and Q11, the new guideline states that the manufacturer of the drug product/Marketing Authorisation Holder (MAH) should base his control strategy for elemental impurities on a risk assessment which is part of an overall risk management of the potential presence for such impurities to occur in the product.

The guideline describes both a Drug Product Approach and a Drug Product Components Approach, to be chosen at the manufacturer's discretion. The choice may also be a mixture of the two.

The full responsibility for an overall risk assessment/risk management resides with the drug product manufacturer/MAH.

The regulatory expectation in the dossier for Marketing Authorisation Application (MAA) is a summary of the risk management based on the thorough risk assessment performed and documented.

1. Different approaches to Risk Management

The PDEs in the guideline are applicable to the drug product, and even if it is possible to comply with the guideline with limited knowledge of the possible sources of elemental impurities, the guideline describes the risk assessment process as based on process and product understanding.

Drug Product Approach

The manufacturer will scan batches of the drug product for the presence of any elemental impurities to be able to do a risk assessment to support risk management and to justify a control strategy. Where necessary the control strategy will include specification(s) to the drug product tested by a validated analytical approach. Analytical data only, without a risk assessment, will not be sufficient and the justification to omit a routine control will with this approach have to be more extensive than just data from a few batches.

Component Approach

With this preferred approach, the contribution of elemental impurities from each component is assessed and summarised and the combined contribution of an element is compared with the PDE in the risk assessment and if necessary handled in the subsequent risk management and the establishment of a control strategy. In the European context the conditions for a drug product manufacturer to do the risk assessment may differ depending on the origin of the component.

[1] EMEA/CHMP/SWP/4446/2000

In-house manufacturing of active substance

When the active substance is made in-house, the manufacturer assesses all potential sources of elemental impurities as outlined in the ICH Q3D guideline and uses this information in the overall risk management for the drug product.

Out-sourced manufacturing of active substance

When the active substance is not made in-house, information from the active substance manufacturer, as part of an Active Substance Master File (ASMF) or a Certificate of Suitability (CEP), may be used in the overall risk management for the drug product.

Other components

Suppliers of other components than active substances are encouraged to find other forms of supplying similar information to inform the overall risk management. This is in particular recommended for excipients from natural (mined) origin where due to their nature residual elements can be expected to be present. Where specification limits for relevant elements in compliance with Q3D Option 1 (Table A.2.2) are applied, the excipient can be used in any proportion in a drug product within the scope of Option 1.

If a substance with a Ph.Eur. monograph contains limit(s) for specific elemental impurities is used, the substance should comply with the elemental impurities limits of the monograph. The overall risk management may also conclude that tighter limits than those of the monograph are necessary.

2. Particulars for Intentionally Added Element(s)

The details of the manufacture of active substances must always be presented with a Marketing Authorisation Application or an application for a CEP. This includes that any element that is intentionally added during the manufacture must be included in the file as well as the fate of that element and the need for any controls (for instance the use of a metal catalyst in the last step of the synthesis). This is independent of whether the substance is made in-house, relies on an ASMF or on a CEP.

Catalyst introduced in the last step of the synthesis

Catalysts introduced in the last step of the synthesis has gained special focus in the quality assessment in Europe and has been the topic of a special QWP Q&A. The basis for this is the elevated risk for impurities being carried forward in this situation as emphasized in ICH Q11.

> *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 (Q11).*

The need for a specification in the active substance of an elemental catalyst used in the last synthetic step is therefore much more likely than when introduced earlier in the synthesis. A specification in such a situation is therefore normally expected and the absence must be supported by convincing evidence that in spite of the late introduction, the catalyst is purged to levels consistently below the control threshold (<30% of the PDE). If, at the time of submission, the amount of data is limited in relation to how far below the control threshold (<30% of the PDE) the results are, a specification ensuring compliance with the PDE together with skip testing may be acceptable.

Drug substance manufacturers' specification

Where a control of an elemental impurity is likely to be necessary, a specification in the drug substance specification applied by the drug substance manufacturer is a suitable step. This will inform the drug product manufacturer's risk assessment. In the absence of information from the drug product manufacturer on a maximum intake, the drug substance manufacturer may wish to apply the Calculation Option 1 of the ICH Q3D which assumes an intake of a drug product mass of maximum 10g per day. In any case the final risk assessment has to be done by the drug product manufacturer taking into account the actual use of the drug substance in the drug product.

3. ASMF/CEP: dossier expectations and assessment strategy

Basically there is no difference in the expectations on and assessment of an ASMF or a CEP dossier.

The route of synthesis of the active substance must be described including information on all intentionally added catalysts and reagents. It is expected that a summary of the risk assessment/risk management on the potential for intentionally added elemental impurities in the active substance is included in the ASMF/CEP and made available to the drug product manufacturer allowing his overall risk management as well as the competent authority. This also includes any elemental impurity controls or mitigation steps necessary.

It is also recommended that the ASMF/CEP dossier contains a summary of a risk assessment/ management that also covers all other potential elemental impurities from other sources than the intentionally added elements to inform the drug product manufacturers overall risk assessment including any mitigation steps necessary.

Two scenarios for ASMF/CEP dossiers can be envisaged:

1. *Submission of a summary of a risk assessment/management for elemental impurities by the API manufacturer.*

   Such information would inform the drug product manufacturers overall risk management and would also be assessed by the quality assessor/CEP assessor. The internal reports and the data generated on which the summary risk assessment/management is based would be expected to be available for GMP inspections.

2. *No risk assessment/management is performed by the API manufacturer.*

In the European legislation it is nevertheless mandatory to submit detailed information on the synthesis of the active substance including information on any metal catalysts or reagents used. The quality assessor/CEP assessor will assess the use of such catalysts or reagents. If the level of an elemental impurity is routinely controlled by the active substance manufacturer, the assessor will also assess the analytical procedure but not make a final conclusion on the compliance with ICH Q3D in the ASMF/CEP assessment report, as this will be done in the context of the assessment of the drug product.

<u>Additional information on the CEP</u>

When granting a CEP the EDQM should consider the need for transparency for substances within the scope of ICH Q3D with regard to:

- The use of any elements intentionally added such as, e.g. metal catalysts (mandatory - assessed by the CEP assessor).
- Any specifications in place in the active substance to limit the levels of elemental impurities as applied by the active substance manufacturer (the methods and batch results are assessed by CEP assessor and appended to CEP while the acceptability of any limits applied by the active substance

manufacturer will be assessed but not finally concluded as that will be done when a MAA is assessed. Sufficient information will be reported on CEP to inform the drug product manufacturers overall risk management).

- Summary or outcome of manufacturers risk assessment/management on intentionally/non-intentionally added elements if it is provided by the CEP holder (appended to the CEP). If this is not provided, it is understood that no such information is received.

This approach will take advantage of the successful centralised assessment of substances made in the Certification Procedure while still not being in conflict with the ICH Q3D. Manufacturers are recommended to take advantage of this opportunity to communicate elemental impurity risks with their customers.