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Implementation strategy of ICH Q3D guideline

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Introduction

The purpose of this document is to address specific considerations to enable the practical implementation of ICH Q3D Guideline for Elemental Impurities in the European Union. It is intended to provide guidance for Applicants/MAHs, drug product, drug substance and excipient manufacturers, as well as regulators. In addition to new applications, it will also apply to variations to existing authorised medicinal products.

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]. Indeed:

- the latter guideline focuses on control of metals intentionally added during the synthesis of the drug 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 Authorization 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 risk for impurities to occur in the drug 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 responsibility for an overall risk assessment/risk management of a drug product lies on the drug product manufacturer/MAH.

Analytical methods used to generate information to the risk assessment or as part of a final control strategy should be suitably validated for its intended purpose.

The summary of the risk management based on the thorough risk assessment performed and documented must be submitted in the dossier for Marketing Authorization Application (MAA) in Module 3 and discussed in the Quality Overall Summary in Module 2.

1. Different approaches to Risk Management

The PDEs in the guideline are applicable to the drug product. It is possible to comply with the guideline with limited knowledge of the possible sources of elemental impurities, but without a risk assessment based on some process and product understanding it would have to involve routine testing of all elements.

Drug Product Approach

The manufacturer will analyze 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. Analytical data, without

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

a risk assessment, will not be sufficient to justify to omit a specification for an element. With a risk assessment, depending on its outcome, the number of batches from which results are shown should be commensurate with the risk of the elemental impurities present.

Component Approach

This approach has advantages from a science and transparency point of view, and where suitable, the use of it is encouraged. The contribution of elemental impurities from each component is identified, evaluated and summarized. 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 possibilities for a drug product manufacturer to do the risk assessment may differ depending on the origin and category of the component, including but not limited to:

In-house manufacturing of drug substance

When the drug 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 drug substance

When the drug substance is not made in-house, information from the drug 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 drug substances are encouraged to find other ways of supplying similar information to be used by the drug product manufacturer in the overall risk management. This is in particular recommended for excipients from natural (mined) origin where due to their nature there is a higher potential of elemental impurities being present.

Where a supplier of a component lacks information on how the component is used, it may be difficult to set a specification for an elemental impurity present. One potential option is to set specification limits for relevant elements in compliance with Q3D Option 1 for a suitable route of administration (daily drug product intakes of not more than 10 grams) (Table A.2.2). The component can then be used in any proportion in a drug product within the scope of Option 1 of that route of administration.

If a substance with a Ph.Eur. monograph containing 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)

Any element intentionally added during the manufacturing must be included in the description of the drug substance manufacturing process in the marketing authorization dossier, an ASMF or a CEP application, as well as its fate and the need for any controls (for instance the use of a metal catalyst in the last step of the synthesis). This obligation of description 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 been the topic of a specific QWP Q&A (June 2012). 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 (ICH Q11).*

The need for a specification in the drug substance (and/or in the drug product) of an elemental catalyst used in the last synthetic step is therefore more likely than when introduced earlier in the synthesis. The absence of a specification for the drug substance (and/or for the drug product) must therefore be justified and supported by evidence that in spite of the late introduction, the catalyst is purged to levels consistently below the control threshold (<30% of the PDE). If, the amount of data is too limited and do not provide sufficient assurance that the levels are consistently below the control threshold (<30% of the PDE), 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, or an in-process control, applied by the drug substance manufacturer is a commonly used option. Such information will help the drug product manufacturer to perform the 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 drug product 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

The requirements related to the implementation of ICH Q3D and the standards of assessment are the same between an ASMF and a CEP dossier.

The route of synthesis of the drug substance must be described including information on all intentionally added catalysts and reagents. A summary of the drug substance risk assessment/risk management on the potential for intentionally added elemental impurities in the drug substance is to be 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 drug substance 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 on should be available for GMP inspections.

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

   As per Union legislation it is mandatory to submit detailed information on the synthesis of the drug 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 drug substance manufacturer, the quality 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.

Additional information on the CEP

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 drug substance or process intermediate to limit the levels of elemental impurities as applied by the drug substance manufacturer (the methods and batch results are assessed by CEP assessor while the acceptability of any limits applied by the drug substance manufacturer will be assessed but not finally concluded as that will be done when the drug product 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 with the CEP, it is understood that no such information is received by EDQM.

Manufacturers are recommended to provide the elements of information described above and to thereby take advantage of this opportunity to communicate elemental impurity risks with their customers.