Use of ICHQ3D Guideline in the Assessment of APIMFs Submitted in Support of an FPP or Prequalified API

1. BACKGROUND

ICHQ3D guideline presents a process to assess and control elemental impurities in drug products using the principles of risk assessment.

Risk assessment may be based to a large degree on the impurity profile of the active pharmaceutical ingredient (API). Therefore, at this time, WHO has decided to adopt the ICHQ3D guideline for the assessment of the elemental impurities information for new applications for both procedures: API master file (APIMF) procedure and API prequalification procedure.

Since the ICHQ3D guideline applies to the drug product, providing a risk assessment as part of the APIMF is not a mandatory requirement. However, whether a risk assessment is provided or not the principles stated on the guideline will be taken into consideration for the assessment of the information on elemental impurities from the API.

2. DOCUMENT SCOPE

This document is intended to provide guidance to applicants on the compilation of the information regarding elemental impurities on APIs in the dossiers submitted for API prequalification or APIMF procedure.

3. USE OF ICHQ3D GUIDELINE

When submitting an APIMF, the applicant has two possibilities:

- Option 1: Do not provide a risk management summary (RMS).
- Option2: Provide an RMS for elemental impurities that may be present in the final API.

The selected option should be indicated by the applicant on the application form.

1.1. Option 1: No risk assessment summary is provided

The elemental impurities intentionally added during the manufacturing process of the API and/or the starting material should be declared and the corresponding step where these elements are used should be indicated in the submitted APIMF.

Since an RMS is not provided, only the elemental impurities intentionally added in the manufacture should be discussed. This discussion should also include elemental impurities used in the preparation of the starting material.

A discussion about the levels of elemental impurities potentially to be found in the API in relation to the corresponding acceptable limits should be addressed. The limits to be applied for elemental impurities should be determined using ICHQ3D principles (using PDEs and concentrations, see section 7 of the ICHQ3D guideline. The worst-case scenario should be considered.

The control strategy should focus on the absence or presence of elemental impurities in the final API. In general it is expected that:

- Elemental impurities above 30% of the accepted limit should be controlled in the final API as a routine test regardless of the manufacturing step in which they are introduced.
- Any elemental impurity used in the last synthetic step of the manufacturing process of the API should be controlled in the API specifications. A skip test may be accepted if it is demonstrated that the level of this impurity is below 30% of the acceptable limit in three consecutive industrial batches or 6 consecutive pilot batches.
- Elemental impurities introduced prior to the last synthetic step do not require control in the final API if absence of these impurities is shown (i.e. below 30% of the acceptable limit).

1.2. APIs seeking prequalification

For APIs seeking prequalification, a statement indicating that no risk assessment for elemental impurities has been provided will be included in the confirmation of API prequalification (CPQ).

All the elements intentionally added in the manufacturing process of the API will be listed on the CPQ. Alternatively, if no elemental impurities are used in the preparation of the API, a statement to this affect will be mentioned on the CPQ.

1.3. Option 2: Risk management summary is provided

The elemental impurities intentionally added during the manufacturing process of the API including during the preparation of the starting material should be declared and the corresponding step where these elements are used should be indicated in the submitted APIMF.

In addition to the standard assessment for the control of elemental impurities a risk assessment as per the ICHQ3D guideline is also undertaken.

The following impurities should be taken into account in the risk management summary:

- All the elements that have been intentionally added in the preparation of the API including during the preparation of the starting material should be considered in the risk assessment no matter to which class they belong.
- Class 1 and class 2A elements should be considered, even if they have not been intentionally added (see ICHQ3D for Elements to be considered in the Risk Assessment).
- Other elemental impurities may be also included in the risk assessment depending on the route of administration. In case there is more than one potential route of administration, all possible routes of administration should be considered.

The risk management summary report should be included in section 3.S.2.3.2. Impurities of the APIMF in the form of a table.

See Annex 1: Risk management summary report template.

A discussion about the levels of elemental impurities found in the API in relation to the corresponding acceptable limits should be provided. The limits to be applied for elemental impurities should be determined using ICHQ3D principles, using PDEs and concentrations, see section 7 of the ICHQ3D guideline. The worst-case scenario should be considered. The proposed control strategy should focus on the absence or presence of elemental impurities in the final API.

In general it is expected that:

- Elemental impurities above 30% of the accepted limit should be controlled in the final API as a routine test regardless of the manufacturing step in which they are introduced.

- Any elemental impurity used in the last synthetic step of the manufacturing process of the API should be controlled in the API specifications. A skip test may be accepted if it is demonstrated that the level of this impurity is below 30% of the acceptable limit in three consecutive industrial batches or 6 consecutive pilot batches.
- Elemental impurities introduced prior to the last synthetic step do not require control in the final API if absence of these impurities is shown (i.e. below 30% of the acceptable limit).

1.4. APIs seeking prequalification

For APIs seeking prequalification a statement indicating that a risk assessment has been provided will be included on the CPQ.

A table summarizing the conclusion of the RMS (See Annex 1: Risk management summary report template) will be annexed to the CPQ.

4. TEST FOR HEAVY METALS

The test for heavy metals has been removed from monographs from Ph.Eur, BP and USP for substances that are within the scope of ICHQ3D. Therefore the inclusion of a test for heavy metals in the API specifications is no longer a requirement.

If applicants wish to revise their API specification in line with the corresponding monograph, an amendment application for change 11a (AAN) may be submitted at any time.

5. APIMFS ALREADY ACCEPTED

For those APIMFs that have been already accepted through the APIMF procedure or API Prequalification, the applicant can submit a RMS for elemental impurities at any time through the amendment procedure.

As stated on the APIMF amendments guideline, for such a revision applicants should submit an amendment application for change 11g (AIN). However for ongoing applications it should not be provided as part of responses, since these invariably delay the completion of the application.

6. ANNEX 1

6.1 Annex 1: Risk Management Summary (RMS) Template

Example of a Risk Management Summary

Intended route of administration / Use of the substance: ……..				
Element	Class	Is it intentionally added?	Is it considered in the risk management?	Conclusion
Cd	1	*	Yes	**
Pb	1	*	Yes	**
As	1	*	Yes	**
Hg	1	*	Yes	**
Co	2A	*	Yes	**
V	2A	*	Yes	**
Ni	2A	*	Yes	**
Tl	2B	*	*	**
Au	2B	*	*	**
Pd	2B	*	*	**
Ir	2B	*	*	**
Os	2B	*	*	**
Rh	2B	*	*	**
Ru	2B	*	*	**
Se	2B	*	*	**
Ag	2B	*	*	**
Pt	2B	*	*	**
Li	3	*	*	**
Sb	3	*	*	**
Ba	3	*	*	**
Mo	3	*	*	**
Cu	3	*	*	**
Sn	3	*	*	**
Cr	3	*	*	**

* Yes/No

** The following statements may be used: “Absent” (meaning less than 30% of ICHQ3D option 1 limit)/”maximum level: < X ppm” or “not applicable” in case the impurity has not been considered in the RMS.

For further information please contact Dr Antony Fake (fakea@who.int) and cc Dr Matthias Stahl (stahlm@who.int).