



1 1 July 2016  
2 EMA/404489/2016  
3 Committee for Medicinal Products for Human use (CHMP)

## 4 Implementation strategy of ICH Q3D guideline

5 Draft

Draft agreed by QWP and BWP	June 2016
Adopted by CHMP for release for consultation	June 2016
Start of public consultation	12 July 2016
End of consultation (deadline for comments)	12 August 2016

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<b>Keywords</b>	ICH Q3D guideline, Elemental impurities
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## 8 Introduction

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

### 11 *Background*

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

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

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

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

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

## 30 1. Different approaches to Risk Management

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

### 34 *Drug Product Approach*

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

### 41 *Component Approach*

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

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<sup>1</sup> EMEA/CHMP/SWP/4446/2000

47 In-house manufacturing of active substance

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

51 Out-sourced manufacturing of active substance

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

55 Other components

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

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

66 **2. Particulars for Intentionally Added Element(s)**

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

73 *Catalyst introduced in the last step of the synthesis*

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

77 *Impurities introduced or created early in the manufacturing process typically have more*  
78 *opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated*  
79 *intermediates) than impurities generated late in the manufacturing process, and are therefore*  
80 *less likely to be carried into the drug substance (Q11).*

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

88 *Drug substance manufacturers' specification*

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

### 96 **3. ASMF/CEP: dossier expectations and assessment strategy**

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

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

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

108 Two scenarios for ASMF/CEP dossiers can be envisaged:

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

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

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

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

#### 123 Additional information on the CEP

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

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

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

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

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