

PHARMACOPOEIAL DISCUSSION GROUP

SIGN-OFF DOCUMENT

CODE: G-07

NAME: Elemental Impurities

It is understood that sign-off covers the technical content of the draft and each party will adapt it as necessary to conform to the usual presentation of the pharmacopoeia in question; such adaptation includes stipulation of the particular pharmacopoeia's reference materials and general chapters.

Harmonised provisions:

Provision	EP	IPC	JP	USP
Introduction	+	+	+	+
Analytical Procedures 1 and 2	+	+	+	+
Requirements for Procedure Validation	+	+	+	+
Procedures for Limit Tests	+	+	+	+
Procedures for Quantitative Tests	+	+	+	+
Glossary	+	+	+	+

Legend

+ : will adopt and implement

- : will not stipulate

Non-harmonised provisions:

None.

Local requirements

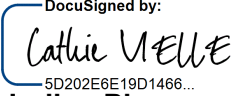
EP	IPC	JP	USP
<p><i>Sample preparation:</i></p> <ul style="list-style-type: none"> The sentence on safety considerations when using concentrated acids is omitted. Addition of a section on labware selection. <p><i>Procedure and Detection Technique</i></p> <ul style="list-style-type: none"> Inclusion of references to Ph. Eur. general chapters <p><i>Analytical procedures 1 and 2:</i></p>	<p>Detail about Elemental impurities -limits</p> <p>use of "test solution" instead of "sample solution" and "reference solution" instead of "standard solution"</p> <p><i>Introduction:</i></p> <ul style="list-style-type: none"> The note to clarify analytical methods other than the methods described in this chapter can be used if validated. 	<p><i>Introduction:</i></p> <ul style="list-style-type: none"> The sentence about the purpose of this chapter. The note to clarify analytical methods other than the methods described in this chapter can be used if validated. <p><i>Analytical Procedures 1 and 2:</i></p> <ul style="list-style-type: none"> "if necessary" will be added to "Sample stock solution" to clarify it is not necessary to add stabilizer 	<p>Addition of <i>Speciation</i> section</p> <p><i>Analytical Procedures 1 and 2:</i></p> <ul style="list-style-type: none"> "Standard solution 1" and "Standard solution 2" changed to "Standardization" solution 1" and "Standardization solution 2" <p><i>Glossary:</i></p> <ul style="list-style-type: none"> Definition of "Concentrated acid" to include Aqua regia

<ul style="list-style-type: none"> • Use of “Calibration instead of “Standardization” • Use of “test solution” instead of “sample solution” <p><i>Requirements for procedure validation:</i></p> <ul style="list-style-type: none"> • Addition of a sentence connecting with other Ph. Eur. general chapters <p><i>Glossary:</i></p> <ul style="list-style-type: none"> • Addition of a sentence on the availability of reference material. 	<p>Heading “Sample preparation” changed to “Test solution preparation”</p> <p><i>Indirect solution:</i> Added “Note- The test solution preparation scheme should yield sufficient sample to allow quantification of each element at the limit specified in the corresponding monograph or chapter”</p> <p><i>Analytical procedures 1 and 2:</i></p> <ul style="list-style-type: none"> • Inclusion of references to IP general chapters • “Standard solution 1” and “Standard solution 2” changed to “Reference solution (a)” and “reference solution (b)” • “Sample stock solution” and “sample solution” changed to “Test solution (a)” and “Test solution (b)” respectively <p><i>Requirements for procedure validation:</i></p> <ul style="list-style-type: none"> • Addition of sentence connecting with other IP general chapters <p><i>Glossary:</i></p> <p>Definition of “Cross validation,”</p>	<p>depending on the matrix.</p> <ul style="list-style-type: none"> • “Generally,” will be added to “Rinse” to clarify other acids can be used for rinse if “memory effect” is observed on the apparatus. <p><i>Requirements for Procedure Validation:</i></p> <ul style="list-style-type: none"> • The sentence to clarify the validation method and criteria may be changed depending on the content level of elemental impurities. • The sentence to explain about the difference between the JP existing general test <2.63> on ICP and this chapter. <p><i>Procedures for Quantitative Tests:</i></p> <ul style="list-style-type: none"> • The supplementary information on the preparation procedure for standard solutions and test samples. • The acceptance criterion of the Quantification Limit will be replaced by “The QL is smaller or equal to 50% of Target concentration.” <p><i>Glossary ;</i></p> <ul style="list-style-type: none"> • Different wording for “Target elements” and “Target limit or Target concentration” • Definition of “Cross validation,” 	<ul style="list-style-type: none"> • Addition of definition of “Aqua regia” <p><i>Appendix:</i></p> <ul style="list-style-type: none"> • Appropriate reference materials to include example of an NMI
---	--	--	---

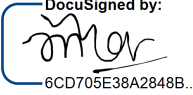
G-07

June 2024

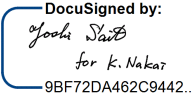
European Pharmacopoeia

Signature	Name	Date
 5D202E6E19D1466...	c. vielle	17 June 2024


Indian Pharmacopoeia Commission

Signature	Name	Date
 6CD705E38A2848B...	Gaurav Pratap Singh	19 June 2024

Japanese Pharmacopoeia

Signature	Name	Date
 9BF72DA462C9442...	Yoshiro Saito	18 June, 2024

United States Pharmacopoeia

Signature	Name	Date
 A7467E52FCC94E9...	Kevin Moore	6/13/2024

ELEMENTAL IMPURITIES

INTRODUCTION

This chapter describes two analytical procedures (Procedures 1 and 2) and validation criteria for the evaluation of the levels of elemental impurities. The chapter permits the use of any procedure that meets the validation criteria specified in this chapter. As the chemical composition of the considered substances and the specification limits for the element(s) of interest vary considerably, it is difficult to describe all suitable sample preparation and measurement methods. By means of validation studies, analysts will confirm that the analytical procedure is suitable for use on specified material. It is not necessary to verify whether or not the same result can be obtained from the corresponding analyses for the same sample against either procedure 1 or 2.

As elemental impurities may be ubiquitous, they have the potential to be present in trace amounts therefore special precautions may be necessary to avoid sample contamination.

Sample Preparation

Forms of sample preparation include *Neat*, *Direct aqueous solution*, *Direct organic solution*, and *Indirect solution*. The selection of the appropriate sample preparation depends on the material under test and is the responsibility of the analyst. When a sample preparation is not indicated in the monograph, an analyst may use any appropriately validated sample preparation procedure, including but not limited to procedures described below. In cases where spiking of a material under test is necessary to provide an acceptable signal intensity, the blank should be spiked with the same *Target elements*, and where possible, using the same spiking solution. The material or mixture under test must be spiked before any sample preparation steps are performed. Standard solutions may contain multiple *Target elements*. [Note: if intended for a quantitative test, appropriate material handling procedures should be followed e.g. volatile liquids should be pipetted, viscous liquids should be weighed.]

Neat: Used for liquids or analytical procedures that allow the examination of unsolvated samples.

Direct aqueous solution: Used when the sample is soluble in an aqueous solvent.

Direct organic solution: Used when the sample is soluble in an organic solvent.

Indirect solution: Generally, an indirect solution is obtained when a material is not directly soluble in aqueous or organic solvents. Total digestion is the preferred sample preparation approach to obtain an *indirect solution*. Digest the sample using the *Closed vessel digestion* procedure provided below or one similar to it.

Closed vessel digestion: This sample preparation procedure is designed for samples that must be digested in a *Concentrated acid* using a closed vessel digestion apparatus. *Closed vessel digestion* minimizes the loss of volatile impurities. The choice of a *Concentrated acid* depends on the sample matrix. The use of any of the Concentrated acids may be appropriate, but each introduces inherent safety risks. Therefore, appropriate safety precautions should be used at all times. [Note—Weights and volumes provided may be adjusted to meet the requirements of the digestion apparatus used.]

An example procedure that has been shown to have broad applicability is the following. Dehydrate and predigest 0.5 g of material under test in 5 mL of freshly prepared *Concentrated acid*. Allow to sit loosely covered for 30 min in a fume hood. Add an additional 10 mL of *Concentrated acid*, and digest, using a closed vessel technique, until digestion or extraction results in a clear solution. Repeat, if necessary, by adding an additional 5 mL of *Concentrated acid*. [Note—Where closed vessel digestion is necessary, follow the manufacturer's recommended procedures to ensure safe use.]

Clear solutions are expected in the validation. In those cases where a clear solution cannot be obtained, appropriate studies should ensure that the recovery is suitable for the intended use.

Reagents: All reagents used for the preparation of sample and standard solutions should be sufficiently pure for the intended purpose.

ANALYTICAL PROCEDURES 1 AND 2

G-07
Stage 3B

CP: USP

53 System standardization and suitability evaluation using applicable reference materials should be
54 performed for each analytical sequence.

55

56 Procedure and Detection Technique

57 *Procedure 1* can be used for elemental impurities generally amenable to detection by inductively
58 coupled plasma–atomic (optical) emission spectroscopy (ICP–AES or ICP–OES). *Procedure 2* can be
59 used for elemental impurities generally amenable to detection by inductively coupled plasma-mass
60 spectrometry (ICP–MS). Before initial use, the analyst should verify that the procedure is appropriate for
61 the instrument and sample used (procedural verification) by meeting the procedure validation
62 requirements below.

63

64 Procedure 1: ICP–OES

65 **Standard solution 1:** 1.5J of the *Target element(s)* in a *matrix matched solution*

66 **Standard solution 2:** 0.5J of the *Target element(s)* in a *matrix matched solution*

67 **Sample stock solution:** Proceed as directed in *Sample Preparation* above. Allow the sample to cool, if
68 necessary. For mercury determination, add an appropriate stabilizer.

69 **Sample solution:** Dilute the *Sample stock solution* with an appropriate solvent to obtain a final
70 concentration of the *Target element(s)* within the calibrated range.

71 **Blank:** *Matrix matched solution*

72 Elemental spectrometric system

73 **Mode:** ICP

74 **Detector:** Optical detection system

75 **Rinse:** Diluent used

76 **Standardization:** *Standard solution 1*, *Standard solution 2*, and *Blank*

77 **System suitability Sample:** Standard solution of the *Target element(s)* in a *matrix matched solution* at a
78 concentration within the calibrated range

79 Suitability requirements

80 **Short term Instrumental Stability:** Compare results obtained from *System suitability sample* before
81 and after the analysis of the *Sample solution*.

82 **Suitability criteria:** NMT 20% deviation from the theoretical concentration of the system suitability
83 sample. [NOTE—If samples are high in mineral content, rinse the system well in order to minimize
84 carryover and check it by measuring a blank solution before introducing the *System Suitability Sample*.]

85 **Analysis:** Analyze according to the manufacturer's suggestions for program and wavelength. Calculate
86 and report results on the basis of the original sample size. [NOTE—Appropriate measures must be taken
87 to correct for matrix-induced interferences (e.g., wavelength overlaps).]

88

89 Procedure 2: ICP–MS

90 **Standard solution 1:** 1.5J of the *Target element(s)* in a *matrix matched solution*

91 **Standard solution 2:** 0.5J of the *Target element(s)* in a *matrix matched solution*

G-07
Stage 3B

CP: USP

92 **Sample stock solution:** Proceed as directed for *Sample Preparation* above. Allow the sample to cool,
93 if necessary. For mercury determination, add an appropriate stabilizer.

94 **Sample solution:** Dilute the *Sample stock solution* with an appropriate solvent to obtain a final
95 concentration of the *Target element(s)* within the calibrated range.

96 **Blank:** *matrix matched solution*

97 **Elemental spectrometric system**

98

99 **Mode:** ICP. [NOTE—An instrument with a cooled spray chamber is recommended. (A collision cell or
100 reaction cell may also be beneficial.)]

101 **Detector:** Mass spectrometer

102 **Rinse:** Diluent used

103 **Standardization:** *Standard solution 1, Standard solution 2, and Blank*

104 **System suitability Sample:** *Standard solution of the Target element(s) in a Matrix matched solution at*
105 *a concentration within the calibrated range*

106

107 **Suitability requirements**

108 **Short term Instrumental Stability:** Compare results obtained from *system suitability sample* before
109 and after the analysis of the *Sample solution*.

110 **Suitability criteria:** NMT 20% deviation from the theoretical concentration of the system suitability
111 sample. [NOTE—If samples are high in mineral content, rinse the system well in order to minimize
112 carryover and check it by measuring a blank solution before introducing the *System suitability sample*.]

113 **Analysis:** Analyze according to the manufacturer's suggestions for program and *m/z*. Calculate and
114 report results based on the original sample size. [NOTE—Appropriate measures must be taken to correct
115 for matrix-induced interferences (e.g., argon chloride interference with arsenic determinations).]

116

117

REQUIREMENTS FOR PROCEDURE VALIDATION

118 All procedures must be validated in accordance with the validation requirements described below. The
119 level of validation necessary to ensure that a procedure is acceptable depends on whether a limit test or a
120 quantitative determination is used. Any procedure that has been validated and meets the acceptance
121 criteria that follow is considered to be suitable for use.

122

123 During procedure validation, the system suitability requirements as established for the procedure must be
124 met.

125

126

PROCEDURES FOR LIMIT TESTS

127 The following section defines the validation parameters for the acceptability of limit tests. Meeting these
128 requirements must be demonstrated experimentally using appropriate tests and reference material. The
129 suitability of the method must be determined by conducting studies with the material or mixture under test
130 spiked with known concentrations of each *Target element* of interest at the appropriate target
131 concentration.

132

Detection Limit

133

134 The detection limit is shown to be sufficiently low by the analysis of samples with known concentrations of
135 analyte at and below the target concentration.

G-07
Stage 3B

CP: USP

136 For the purposes of this chapter, detection limit does not mean that the procedure must demonstrate
137 lowest possible analytical result.
138

139 **Standard solution: A** preparation of reference materials for the *Target element(s)* at 1.0 J in a matrix
140 *matched solution*.

141 **Spiked sample solution 1: Prepare** a solution of sample under test, spiked with appropriate reference
142 materials for the *Target element(s)* at the *Target concentration*, solubilized or digested as described in
143 *Sample Preparation*.

144 **Spiked sample solution 2: Prepare** a solution of the sample under test, spiked with appropriate
145 reference materials for the *Target element(s)* at 80% of the *Target concentration*, solubilized or digested
146 as described in *Sample Preparation*.

147 **Unspiked sample solution: A** sample of material under test, solubilized or digested in the same manner
148 as the spiked *sample solutions*.

149 **Acceptance criteria**

150 **Non-instrumental procedures:** *Spiked sample solution 1* provides a signal/response, e.g., color, or
151 intensity equivalent to or greater than that of the *Standard solution*. *Spiked sample solution 2* must
152 provide a signal /response, e.g., color, or intensity less than that of *Spiked sample solution 1*. [NOTE—The
153 signal/response, e.g., color, or intensity from each *Spiked sample solution* is NLT the *Unspiked sample*
154 *solution* determination.]

155
156 **Instrumental procedures:** The average value of the three replicate measurements of *Spiked sample*
157 *solution 1* is within $\pm 15\%$ of the average value obtained for the replicate measurements of the *Standard*
158 *solution*. The average value of the replicate measurements of *Spiked sample solution 2* must provide a
159 signal intensity or value less than that of the *Standard solution*. [NOTE—Correct the values obtained for
160 each of the spiked solutions using the *Unspiked sample solution*.]
161

162 **Specificity**

163 The procedure must be able to unequivocally assess each *Target element* in the presence of
164 components that may be expected to be present, including other *Target elements*, and matrix
165 components.
166

167 **Precision, only for Instrumental Methods (Repeatability)**

168
169 **Sample solutions:** Six independent samples of the material under test, spiked with appropriate reference
170 materials for the *Target element(s)* at the *Target concentration*.

171 **Acceptance criteria**

172 **Relative standard deviation:** NMT 20% for each *Target element*

173
174

PROCEDURES FOR QUANTITATIVE TESTS

175 The following section defines the validation parameters for the acceptability of procedures for
176 quantitative tests. Meeting these requirements must be demonstrated experimentally, using appropriate
177 tests and reference materials.

178 **Accuracy**

179 **Standard solutions: Prepare** solutions containing the *Target element(s)* at three concentrations ranging
180 from 0.5 J to 1.5 J, using appropriate reference materials, in a Matrix matched solution.

G-07
Stage 3B

CP: USP

181 **Test samples: Prepare** 3 independent sample preparations of the material under test spiked with
182 appropriate reference materials for the *Target element(s)* at the target concentration, *J*, before any sample
183 preparation steps (digestion or solubilization). Spike concentrations should range from 0.5 *J* to 1.5 *J* and
184 should include at least 3 individual concentrations.
185

186 **Acceptance criteria**

187 **Spike recovery:** 70%–150% for the mean of three independent sample preparations at each
188 concentration

Precision

REPEATABILITY

191 **Test samples:** Six independent samples of material under test (taken from the same lot) spiked with
192 appropriate reference materials for the *Target element(s)* at the Target concentration or at least 9
193 determinations (e.g. 3 replicates of 3 concentrations) covering the specified range.

194

195 **Acceptance criteria**

196 **Relative standard deviation:** in both cases, NMT 20% for each *Target element*

197 INTERMEDIATE PRECISION (RUGGEDNESS)

198 Perform the *Repeatability* analysis again, either on a different day, with a different instrumentation, with a
199 different analyst, or a combination thereof. Combine the results of this analysis with the *Repeatability*
200 analysis.

201

202 **Acceptance criteria**

203 **Relative standard deviation:** NMT 25% for each *Target element*

204

205 **Specificity**

206 The procedure must be able to unequivocally assess each *Target element* in the presence of components
207 that may be expected to be present, including other *Target elements*, and matrix components.

208

209 **Range and Linearity**

210 Demonstrated by meeting the *Accuracy* requirement.

211

Quantitation Limit

212 Use the results from the accuracy study.

213

214 QL of 0.5 *J* is confirmed when the accuracy acceptance criteria for 0.5 *J* spiked solution is met.

215

216 Acceptance criterion: the QL is less than or equal to 0.5 *J*.

217

218

219

GLOSSARY

220 **Concentrated acid: Concentrated** ultra-pure nitric, sulfuric, hydrochloric, hydrofluoric acids or any other
221 acid or mixture of acids that is demonstrated to be suitable.

G-07
Stage 3B

CP: USP

222 **Matrix matched solution:** Solutions having the same solvent composition as the *Sample solution*. In the
223 case of an aqueous solution, *Matrix matched solution* would indicate that the same acids, acid
224 concentrations, and mercury stabilizer are used in both preparations.

225 **Target elements:** Elements which must be evaluated according to the requirements defined in other
226 chapters.

227 **Target limit or Target concentration:** The acceptance value for the elemental impurity being evaluated.
228 Exceeding the *Target limit* indicates that a material under test exceeds the acceptable value. [NOTE—
229 *Target limits* can be approximated by dividing the *permitted daily exposures (PDEs)* by the maximum
230 daily dose of the drug product.].]

231 **J: Final** concentration of the Target element(s) in the standard and the sample solutions. It corresponds
232 to the concentration (w/v) of the Target element(s) at the *Target limit*, appropriately diluted to the working
233 range of the instrument. If a dilution is not necessary J is equal to the target concentration. For example, if
234 the target elements are lead and arsenic for an analysis of an oral solid drug product with a daily dose of
235 10 g/day using inductively coupled plasma–mass spectrometry (ICP–MS), the target limit for these
236 elements would be 0.5 µg/g and 1.5 µg/g. However, in both cases, the linear dynamic range of the ICP–
237 MS is known to extend from 0.01 ng/mL to 0.1 µg/mL for these elements. Therefore, a dilution factor of at
238 least 1:100 is required to ensure that the analysis occurs in the linear dynamic range of the instrument. *J*
239 would thus equal 5 ng/ml and 15 ng/mL for lead and arsenic, respectively (Note: the density of the sample
240 solution may have to be considered).

241 **Appropriate reference materials:** Where *Appropriate reference materials* are specified in the chapter,
242 certified reference materials (CRM) from a national metrology institute (NMI), or reference materials that
243 are traceable to the CRM of an NMI should be used.