Emprove® Operational Excellence Dossier

Documentation to support process optimization

For demonstration purposes only and should not be used for any qualification and/or registration activities.

105101

di-Potassium hydrogen phosphate anhydrous, EMPROVE® ESSENTIAL Ph Eur,BP,E 340

SAFC®

Pharma & Biopharma Raw Material Solutions

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Introduction

The Emprove® dossiers are designed to enable our customers to respond to the regulatory recommendations/requirements easily, quickly, and adequately. As a result of the Emprove® qualification processes, we offer the Emprove® Material Qualification Dossier (in line with CTD format). This dossier is designed to facilitate qualification of material for application in the pharmaceutical industry. With the Emprove® Quality Management Dossier, we assist in conducting the required risk assessments. With the Emprove® Operational Excellence Dossier, we provide supporting information to optimize processes according to the relevant regulations.

Version history
The dossier version number is indicated in the header of every page. Product quality-relevant content changes result in a full-version increase, for example version 1.0 to 2.0. Editorial or formatting changes result in a sub-version increase, for example 1.0 to 1.1.
Additionally, the Version History Report provides an overview of components which have been updated in this version.

Regulatory Framework
A key concern for final drug quality is consistent operation of the excipient manufacturing process. This is addressed for example in the EXCiPACT™ standard or similarly in ICH Q10. With the Product Quality Report, we offer an overview of quality trend analysis data to support the annual review processes, as stated in the EU guideline 2015/C 95/02.
Elemental impurities in final drug products are limited by the respective ICH Q3D Guideline. We provide information on elemental impurities of pharmaceutical raw and starting materials that can be utilized to facilitate the required risk assessment on elemental impurities. Where applicable, Technically Unavoidable Particles Profiles (TUPPs) provide additional product characterization information.
Our Stability Data section provides long-term stability data, according to the principles of ICH Q1A, which can be utilized to support safety and quality evaluations as well as life-cycle management.
Different Pharmacopoeias describe different test methods for a specific parameter for one and the same material. The use of alternative analytical methods for quality control purposes is allowed in most cases, if it has been unequivocally proven through for example cross validation that these methods provide equal performance. By providing our analytical methods, we offer transparency on the quality control of our products and the benefit of optimized methods to our customers.

Chapter 1: Elemental Impurity Information

I. Introduction

The guideline ICH Q3D presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. The risk assessment should be based on scientific knowledge and principles. According to ICH Q3D, information for this risk assessment includes, among others, information supplied by raw materials suppliers.

This information is intended to provide data to support this risk assessment. This document shall help to identify potential elemental impurities derived from intentionally added catalysts and inorganic reagents. Additionally it presents information about potential elemental impurities that may be present.

To support this, we developed ICP-MS screening methods for elemental analysis with demonstrated capability to measure the elements covered by the ICH Q3D guideline at the control threshold (30% level) of the parenteral Option 1 limits or below.

II. Intentionally added elements during the manufacturing process

No elements listed in classes 1 – 3 according to ICH Q3D are used in the manufacturing steps outlined in the manufacturing procedure for the above-mentioned item.

Please find the flow diagram of the manufacturing procedure in the Emprove® Material Qualification Dossier on our website.

III. Elemental Impurity Profile

To show the typical elemental impurity profile for the above mentioned product an elemental impurity screening has been performed on three batches.
Additional batches will be routinely tested to ensure consistency of the data.

Item No.	**105101**					
Item name:	**di-Potassium hydrogen phosphate anhydrous**					
Class	Element	Analytical method	Results			Option 1 limit for information
			AM1581401	AM1581501	AM1692701	
			(µg/g)	(µg/g)	(µg/g)	(µg/g)
1	Cd	ICP-MS				
	Pb	ICP-MS	< 0.15			
	As	ICP-MS			< 0.45	
	Hg	ICP-MS	< 0.09			
2A	Co	ICP-MS				
	V	ICP-MS				1
	Ni	ICP-MS		< 0.6		
2B	Tl	ICP-MS				0.8
	Au	ICP-MS	< 3			
	Pd	ICP-MS	< 0.3			
	Ir	ICP-MS				1
	Os	ICP-MS	< 0.3			
	Rh	ICP-MS				
	Ru	ICP-MS				
	Se	ICP-MS	< 2.4			
	Ag	ICP-MS			< 0.3	
	Pt	ICP-MS				
3	Li	ICP-MS				
	Sb	ICP-MS				
	Ba	ICP-MS	< 21			
	Mo	ICP-MS				150
	Cu	ICP-MS		< 9		
	Sn	ICP-MS				60
	Cr	ICP-MS	< 33			

Please refer to product specification for specified elements and their respective specification limits.

No elemental impurities exceeding or equal to 30% of the Option 1 limit as stated in ICH Q3D were detected.

(Quality Control Manager)

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Chapter 2: Product Quality Report

Titel: 105101_di-Potassium hydrogen phosphate_PQR_EXP_2020

Anweisendes / Übergeordnetes Dokument:
„Q033 Erstellung von Jahresberichten für APIs, Excipients, IvDs und Zellkulturmedien (CCM)“, Version 4.0, ManGO Doc ID 20246913

Product quality report
(Annual Report)

Art.-Nr. 1.05101

di-Potassium hydrogen phosphate anhydrous, EMPROVE® ESSENTIAL Ph Eur, BP, E 340

di-Kaliumhydrogenphosphat wasserfrei, EMPROVE® ESSENTIAL Ph Eur, BP, E 340

Unterschrift / Datum
(Signature / Date)

Verfasst:
Edited:

.....

Überprüft und Genehmigt:
Reviewed and Approved: .....

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Titel: 105101_di-Potassium hydrogen phosphate_PQR_EXP_2020

Anweisendes / Übergeordnetes Dokument:
„Q033 Erstellung von Jahresberichten für APIs, Excipients, IvDs und Zellkulturmedien (CCM)", Version 4.0, ManGO Doc ID 20246913

Product Quality Report Summary

This report is based on the analytical results of a minimum of 5 batches produced/purchased or is created after a time period of at least 36 months.

Based on the analytical results, the batches produced/purchased and tested during the reporting period, show a consistently high quality of the product.
Yes / No / N.A.

The parameters "Assay (alkalimetric, calculated on dried substance)", "Assay (out of dried substance)", "pH-value (1 %, water)", "Potassium dihydrogen phosphate" and "Loss on drying (130 °C)" deliver continuous quantitative values (no limit test) and provide valuable information for the control of the manufacturing process. Therefore, trend analyses were conducted for these parameters.
Yes / No / N.A.

The consistent operation of the manufacturing process is demonstrated in the period under review based on the following aspects:

- All analytical parameters are within the specification limits
  Yes / No / N.A.

- During stability studies within the period of shelf-life no out of specification results have been confirmed.
  Yes / No / N.A.

If no or N.A.:

During the period under review the following significant changes have been confirmed:

a) Changes in the route of synthesis and in the type, source and quality of the starting materials used
b) Specification (if not due to compendial changes)
c) Nature of the starting materials (e.g. residual-solvent-, GMO-, BSE/TSE-, veterinary-certificates, allergen, animal origin status)
d) Manufacturing site
e) Part number
f) Significant change to package configuration
g) Others, see description

Description (Changes): -
-Implementation of the date of manufacture on the certificate of analysis (API, BIO, EXP, NUT, PHE, COD).
- Harmonization of LS Temperature storage conditions for LS-products,

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Titel: 105101_di-Potassium hydrogen phosphate_PQR_EXP_2020

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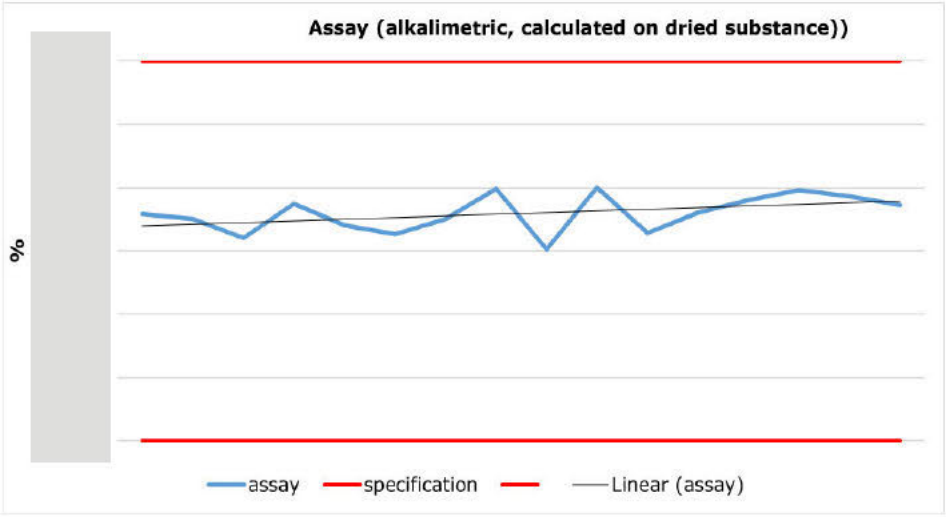
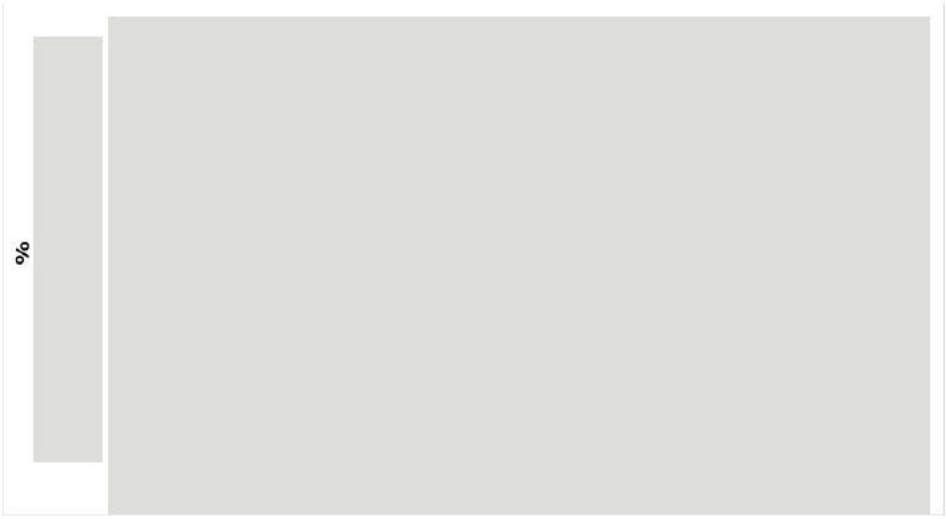
„Q033 Erstellung von Jahresberichten für APIs, Excipients, IvDs und Zellkulturmedien (CCM)", Version 4.0, ManGO Doc ID 20246913

Quality Assessment

In summary, it is confirmed, that for the described product all specified requirements are met. The product corresponds to the requirements of the declared pharmacopoeias and directives referred in the specification.

Diagrams (all released batches)





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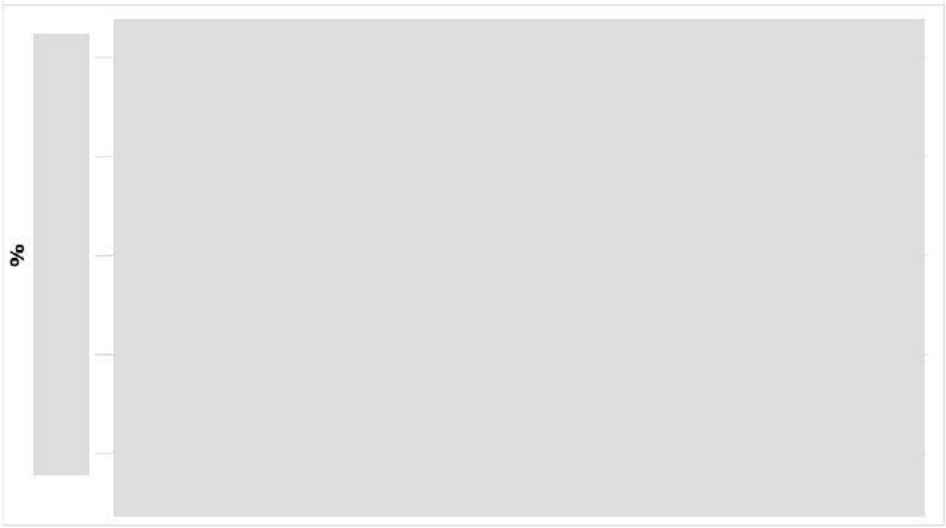

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Chapter 3: Stability Data (Long Term Data)

Stability data see in the following pages.

Titel: Formular 5: Technical report for Norm-Studies

Anweisendes / Übergeordnetes Dokument: „A037 Vorgehen zur Festlegung der Produkteigenschaft Haltbarkeit", Version 1.0, ManGO Doc ID

Technical Report for Norm-Studies			
Article number	105101		
Article name	di-Potassium hydrogen phosphate anhydrous		
Batch			
Storage conditions	25 ± 2 °C, 60 ± 5 % rel. humidity	**Container**	DPES (original)

			Analysis results after (month)						
Parameter	**Specification**	**Start 10/2012**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance of solution									passes test
Assay (alkalimetric, calc. on dried substance)									
Potassium-dihydrogen-phosphate				0.1 %				< 0.1 %	
Loss on drying (130 °C)	≤ 2.0 %				0.2 %				1.7 %

Comment: The stability tests are in progress and all results are within the specified limits. Based on the ICH-stability evaluation guideline the test results report are the worst-case values of a study with3 samplings per container.
Responsible manager from Q-unit

Titel: Formular 5: Technical report for Norm-Studies

Anweisendes / Übergeordnetes Dokument: „A037 Vorgehen zur Festlegung der Produkteigenschaft Haltbarkeit", Version 1.0, ManGO Doc ID 20269738

Technical Report for Norm-Studies			
Article number	105101		
Article name	di-Potassium hydrogen phosphate anhydrous		
Batch			
Storage conditions	25 ± 2 °C, 60 ± 5 % rel. humidity	**Container**	DPES (original)

			Analysis results after (month)						
Parameter	**Specification**	**Start 10/2012**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance of solution									passes test
Assay (alkalimetric, calc. on dried substance)	98.0-102.0 %	99.7 %							
Potassium-dihydrogen-phosphate					< 0.1 %				
Loss on drying (130 °C)							0.7 %		

Comment: The stability tests are in progress and all results are within the specified limits.
Based on the ICH-stability evaluation guideline the test results report are the worst-case values of a study with3 samplings per container.
Responsible manager from Q-unit

Titel: Formular 5: Technical report for Norm-Studies

Anweisendes / Übergeordnetes Dokument: „A037 Vorgehen zur Festlegung der Produkteigenschaft Haltbarkeit", Version 1.0, ManGO Doc ID 20269738

Technical Report for Norm-Studies			
Article number	105101		
Article name	di-Potassium hydrogen phosphate anhydrous		
Batch			
Storage conditions	25 ± 2 °C, 60 ± 5 % rel. humidity	**Container**	DPES (original)

			Analysis results after (month)						
Parameter	**Specification**	**Start 04/2013**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance of solution						passes test			
Assay (alkalimetric, calc. on dried substance)				99.8 %					
Potassium-dihydrogen-phosphate						0.2 %			
Loss on drying (130 °C)	≤ 2.0 %								

* value from batch release

Comment: Based on the ICH-stability evaluation guideline the test results reported are the worst-case values of a study with 3 samplings per container.
The stability tests are in progress and all results are within the specified limits.
Responsible manager from Q-unit Name:

Chapter 4: Analytical Procedure

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340		**Monograph** Valid from Valid to:
Item No. 105101	CAS: 7758-11-4	

Signatures

Accuracy of contents:

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

GENERAL DATA

Chemical designation

Compound

Empirical formula

Molar mass

Description

Solubility

Shelf life

Hazard (H) statements and Precautionary (P) statements

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

SPECIFICATION

Assay (alkalimetric, calc. on dried substance)	
Assay (acidimetric, from dried substance)	
Identity	
Appearance of solution	
Matter insoluble in water	
pH (1%, water)	
Chloride (Cl)	
Fluoride (F)	
Sulfate (SO_4)	
Al (Aluminium)	
As (Arsenic)	
Cd (Cadmium)	
Fe (Iron)	
Hg (Mercury)	
Na (Sodium)	
Pb (Lead)	
Potassium dihydrogen phosphate (KH_2PO_4)	
Residual solvents (ICH Q3C)	
Reducing substances	
Loss on drying (130°C)	

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

TESTS

Description:

Identity:
passes test

Assay (alkalimetric, calc. on dried substance):

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

Assay (acidimetric, from dried substance)
≥ 98.0%

Test solution:

Appearance of solution:
passes test

Matter insoluble in water:

pH (1%, water):

Chloride (Cl):

Fluoride (F):

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

Sulfate (SO_4):

Al (Aluminium):

As (Arsenic):

Fe (Iron):

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di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**

Hg (Mercury):

Na (Sodium):

Cd (Cadmium):

Pb (Lead):

Potassium dihydrogen phosphate (KH_2PO_4):

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph**
Reducing substances: passes test	Test: Mix 5.0 mL of test solution with for 5 minutes on the water bath. Evaluation: The mixture must not become completely decolorized.
Loss on drying (130°C):	Dry about for at least 4 hours at 130°C.

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di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340	**Monograph Supplement** Valid from Valid to:
Item No. 105101 CAS 7758-11-4	

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph Supplement**

GENERAL DATA

Empirical formula	K_2HPO_4
Molar mass	174.18 g/mol
Solubility	
Hazard (H) statements	-
Precautionary (P) statements	-

REQUIREMENT	Na (Sodium)
METHOD	Flame atomic emission spectrometry
Device	e.g. FAAS spectrometer SpectrAA 280 FS

SAMPLE PREPARATION

Reagents	DI water
Preparation of sample solution	
Preparation of measuring solution	

LA00089 LS-OII-QI3

14600_EN_21
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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph Supplement**

Preparation of the external calibration curve

Blank value

Standard 1

Standard 2

Standard 3

MEASURING CONDITIONS

Burner 5-cm slit burner

Element	Wavelength λ [nm]	Flame	Slit width [nm]
Na			

PROCEDURE Open template 105101.AAWS and perform the measurement (quadratic calibration curve).

EVALUATION External calibration

Reporting of results Analysis results
Na (Sodium)
are reported as effective values.

LA00089 LS-OII-QI3

14600_EN_21
Version_3

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di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340	**Monograph Supplement** Valid from Valid to:
Item No. 105101 CAS: 7758-11-4	

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di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340 Item No. 105101	**Monograph Supplement**
GENERAL DATA	
Hazard (H) statements and Precautionary (P) statements	-
REQUIREMENTS	Al (Aluminium)
METHOD	Electrothermal atomic absorption spectrometry (Graphite furnace atomic absorption spectrometry)
EQUIPMENT	e.g.

LA00108 LS-OII-QF7.3

3574_EN_23
Version_3

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340 Item No. 105101	**Monograph Supplement**

SAMPLE PREPARATION

MEASURING CONDITIONS

Analytical program parameters

Element	Wave-length [nm]	BG compen-sation	Modifier* [µL]	Meas. volume* [µL]	Addition 1* [ng/mL]	Addition 2* [ng/mL]
Al						

*vary as required

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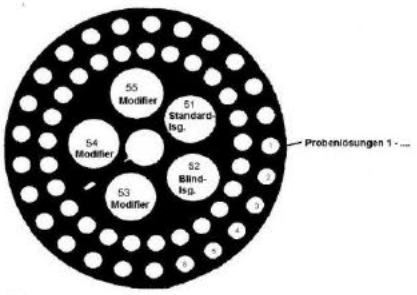
di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340 Item No. 105101	**Monograph Supplement**

Temperature program* for: Al

Step	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

Sampler name of position	Solution to be used
Pos.51	Std. solution dilution C
Pos.52	Ultrapure water
Pos.53	Modifier solution
1 - max. 45	Sample solutions
after samples	Blank solution



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Version_3

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di-Potassium hydrogen phosphate anhydrous **EMPROVE® ESSENTIAL Ph Eur, BP, E 340** Item No. 105101	**Monograph Supplement**
PROCEDURE	A calibration measurement is required for every sample.
EVALUATION	Perform the evaluation by means of the equipment software. **Reporting of analysis results** Al (Aluminium) ≥ [redacted] are reported as effective values.
SYSTEM SUITABILITY TEST	[redacted]

LA00108 LS-OII-QF7.3

3574_EN_23
Version_3

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di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340	**Monograph Supplement** Valid from Valid to:
Item No. 105101 CAS: 7758-11-4	

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Version_3

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph Supplement**

GENERAL DATA

Chemical designation	di-Potassium hydrogen phosphate anhydrous
Empirical formula	K_2HPO_4
Molar mass	174.18 g/mol
Hazard (H) statements	—
Precautionary (P) statements	—

REQUIREMENT

Hg (Mercury):

METHOD

Procedure

Test solution:

Equipment:

Measurement parameters:

LA00091 LS-OJI-QI2.2

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item No. 105101	**Monograph Supplement**

Measurement and evaluation:

Validated measuring range and reporting level:

Measurement at higher values up to the specification limit:

LA00091 LS-OII-QI2.2

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Version_3

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur, BP, E 340		**Monograph-Supplement** Valid from Valid to:
Item-No.: 105101	CAS: 7758-11-4	

Signatures

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3580_EN_72
Version_3

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item-No.: 105101	**Monograph-Supplement**

GENERAL DATA

Empirical formula	K_2HPO_4
Solubility	
Hazard statements	-
Precautionary statements	-
REQUIREMENTS	Cd (Cadmium) Pb (Lead)
METHOD	Differential pulse anodic stripping voltammetry Calibration by means of standard addition method
Instruments	e.g. Metrohm 797 VA Computrace

SAMPLE PREPARATION

Reagents	Ultrapure water
	Potassium chloride sodium acetate solution acc. to

LA00089 LS-OII-QI3

3580_EN_72
Version_3

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Merck KGaA, Darmstadt, Germany

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Item-No.: 105101	**Monograph-Supplement**

MEASURING CONDITIONS

Electrodes

Parameter

Peak potentials

PROCEDURE

EVALUATION

Reporting of results

SYSTEM SUITABILITY TEST

LA00089 LS-OII-QI3

3580_EN_72
Version_3

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Merck KGaA, Darmstadt, Germany

Determination of fluoride	**General Monograph Supplement** Valid from Valid to:
Item No. A21243	

Signatures

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12176_EN_71
Version_10

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Merck KGaA, Darmstadt, Germany

Determination of fluoride Item No. A21243	**General Monograph Supplement**

GENERAL DATA

Structural formula

Molar mass

Hazard (H) statements and Precautionary (P) statements

REQUIREMENTS

Limit of quantitation

METHOD
Indication

Equipment

SPECIAL NOTES
regarding the principle of the determination

SYSTEM SUITABILITY TEST

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Reagents

[redacted]

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Volumetric solutions

[redacted]

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Review measuring station (SST) for the individual cell

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

SAMPLE PREPARATION SST

Blank value (Choice of addition: 0)	
Blank value with addition 1 (Choice of addition: 1)	
Blank value with addition 2 (Choice of addition: 2)	
If required: Reagent blank value (Choice of addition: 3)	

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Review measuring station (SST) for the individual cell

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

MEASURING CONDITIONS
SST

Method	
Method mask (Choice of addition)	
Detection	

PROCEDURE SST

Review measuring station (SST) for the individual cell

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Determination of fluoride Item No. A21243	**General Monograph Supplement**
EVALUATION SST / CALCULATION Blank value / Reagent blank value Recovery rate Specified values Blank value / Reagent blank value: Addition 1 and 2:	

Review measuring station (SST) for the sample changer

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

SAMPLE PREPARATION SST

Blank value
(Choice of addition: 0)

Blank value with addition 1
(Choice of addition: 1)

Blank value with addition 2
(Choice of addition: 2)

If required:
Reagent blank value
(Choice of addition: 3)

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Review measuring station (SST) for the sample changer

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

MEASURING CONDITIONS
SST

Method	
Method mask (Choice of addition)	0: Blank value 1: BV with addition 1 2: BV with addition 2 3: Reagent blank value
Detection	

PROCEDURE SST

-
- Enter sample data into software
- Prepare electrode(s), the immersion in the measuring sample solution is an automatic function
- Prepare buret tip(s), the immersion in the measuring sample solution is an automatic function
- Start measurement

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Review measuring station (SST) for the sample changer

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Determination of fluoride Item No. A21243	**General Monograph Supplement**
EVALUATION SST / CALCULATION Blank value / Reagent blank value Recovery rate Specified values Blank value / Reagent blank value: Addition 1 and 2: **Measurement of samples**	

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

SAMPLE PREPARATION

Preparation **A**

[redacted]

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Preparation **B**

[redacted]

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Preparation **C**

[redacted]

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Preparation **D**

[redacted]

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Determination of fluoride Item No. A21243	**General Monograph Supplement**
Preparation **E** (Acids)	
Recovery rate for acids	

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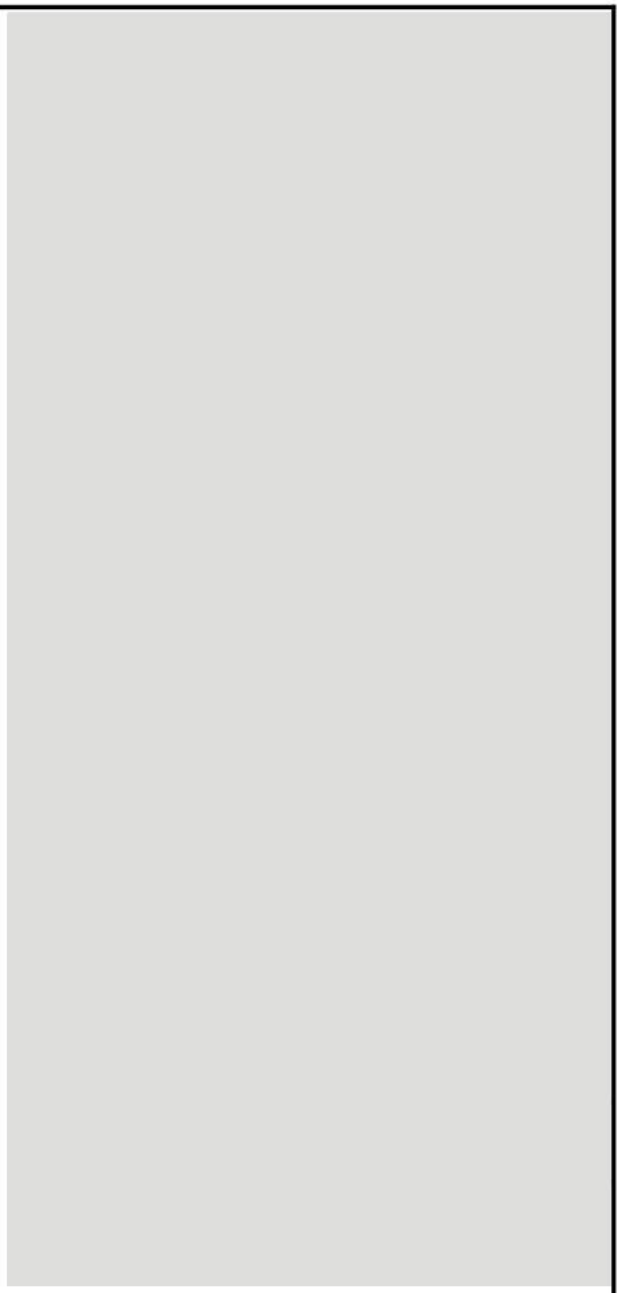
Preparation **F**
(Waste TAR)



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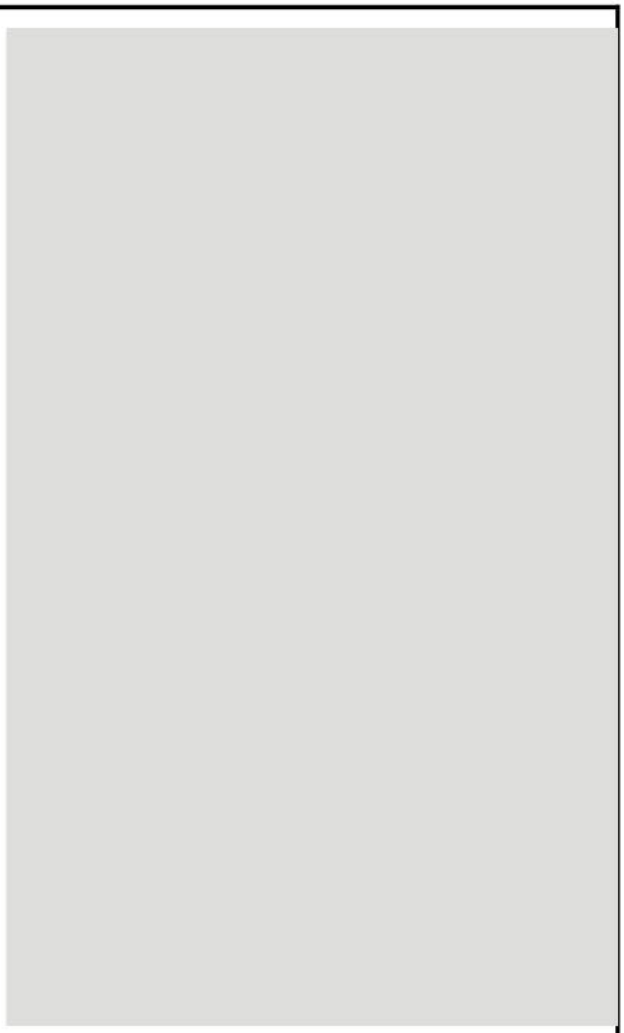
Preparation **G**
(Pigments)



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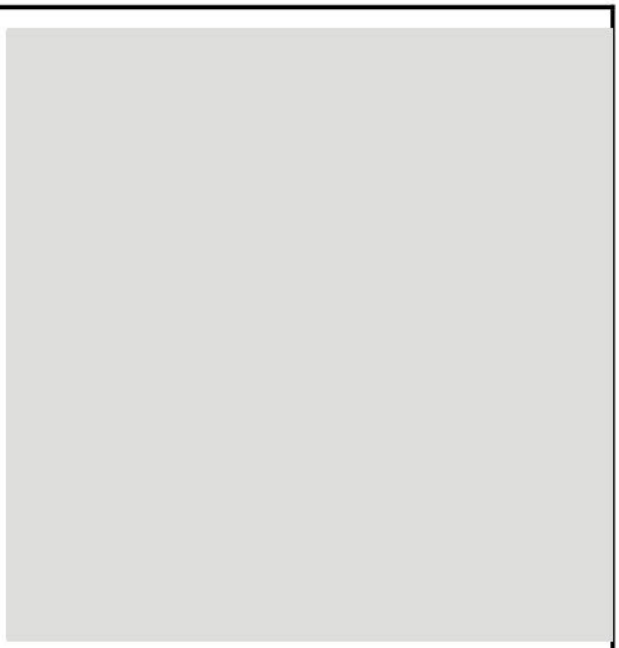
Preparation **H**
(Al salts)



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Preparation **I**
(TISAB + water)

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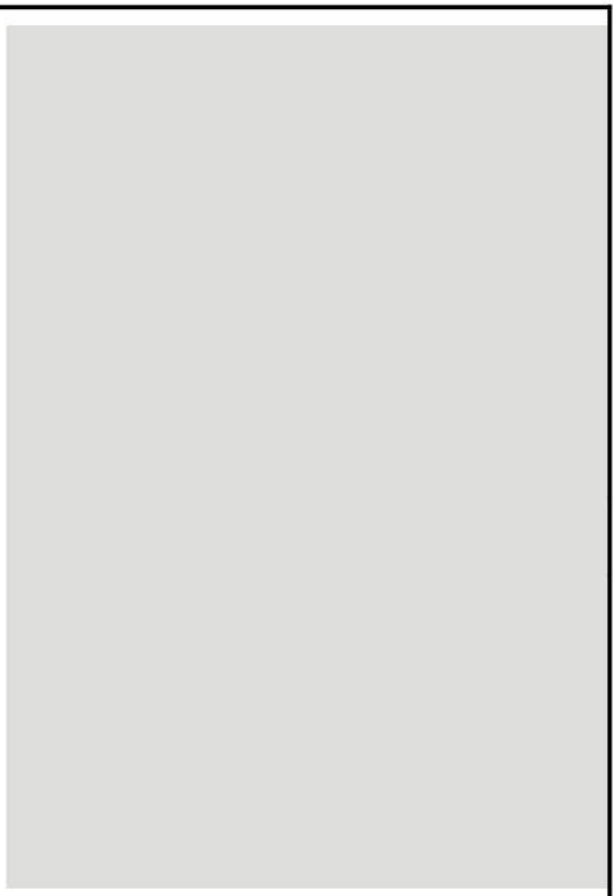
Preparation **J**
(Sodium fluoride-sodium chloride)



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Determination of fluoride Item No. A21243	**General Monograph Supplement**

MEASURING CONDITIONS

Method	
Entries for the method mask (Choice of addition)	
Detection	
PROCEDURE	
EVALUATION	

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

CALCULATION

General

For Item 1.15368 TISAB

For Item 1.16754 Water

For Item 1.16770 TISAB-III

RR acid

Specified values

The result is entered into the LIMS as shown on the printout of the result.

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Determination of fluoride Item No. A21243	**General Monograph Supplement**

Explanation of formula

Formula symbols	Explanation	Unit
β	Parts by volume (of fluoride)	µg/mL or mg/L
c_A	Concentration of analyte (result from Software Tiamo as fluoride)	mmol/L
$c_{BV/RBV}$	Concentration of fluoride from blank value/reagent blank value	mmol/L
c_{ACT}	Determined concentration of fluoride	mmol/L
$c_{PF\ solution}$	Concentration of potassium fluoride solution from addition	mol/L
c_{acid}	Concentration of fluoride from measurement of acid	mmol/L
$c_{acid\ with\ addition}$	Concentration of fluoride from measurement of acid with addition	mmol/L
c_{SPEC}	Expected concentration of fluoride	mmol/L
$c_{addition}$	Concentration of fluoride from addition	mmol/L
m_E	Sample weight of substance	g
M_F	Molar mass fluoride	g/mol
$t_{PF\ solution}$	Titer of potassium fluoride solution used	-
V	Volume of solution	mL
$V_{PF\ solution}$	Volume of potassium fluoride solution from addition	mL
Vm_E	Volume of substance solution in measuring flask	mL
V_{VF}	Volume of volumetric flask	L
w	Mass proportion (of fluoride)	%
RR	Recovery rate	%

Please note:

The concentrations reported, which originate from the software as results of the standard addition, are already calculated there with the titer of the KF solution used.

$$c_A = \text{result standard addition} \frac{\text{mol}}{\text{L}} \cdot 1000 \frac{\text{mmol}}{\text{mol}} \cdot t_{PF\ solution}$$

$$c_{BV/RBV} = \text{result standard addition} \frac{\text{mol}}{\text{L}} \cdot 1000 \frac{\text{mmol}}{\text{mol}} \cdot t_{PF\ solution}$$

$$c_{acid} = \text{result standard addition} \frac{\text{mol}}{\text{L}} \cdot 1000 \frac{\text{mmol}}{\text{mol}} \cdot t_{PF\ solution}$$

$$c_{acid\ with\ addition} = \text{result standard addition} \frac{\text{mol}}{\text{L}} \cdot 1000 \frac{\text{mmol}}{\text{mol}} \cdot t_{PF\ solution}$$

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Chapter 5: Technically unavoidable Particle Profile

Technically unavoidable particle profile (TUPP)

for

di-Potassium hydrogen phosphate anhydrous EMPROVE® ESSENTIAL Ph Eur,BP,E 340 Product item-no. 105101

quality control:

production:

quality assurance:

Intention

All of the steps in the manufacturing processes for our Emprove® exp/ESSENTIAL, bio/EXPERT and API products continuously run through optimization processes with the intention preventing contamination from particulate matter. In this respect, risk assessments were conducted and mitigation strategies where put into place.

Our company is fully aware of its GMP obligations for excipients when manufacturing and handling ingredients intended for use in pharmaceutical production. Although all of these measures are well-established to prevent contamination with foreign matter, for technical reasons certain kinds of particles cannot be reduced to zero during the manufacturing processes for several products.

In line with the guide of *The International Pharmaceutical Excipient Council (IPEC) Federation* on "Technically Unavoidable Particle Profile (TUPP)", 2015, these particles will be referred to as technically unavoidable particles (TUP) in this document.

TUPs are particles that are visibly different from the bulk of the material when viewed with the naked eye within the container or against a suitable background (examples are size, shape, color, number, texture), are inherent to the excipient manufacturer`s process, product or raw materials and are technically unavoidable.

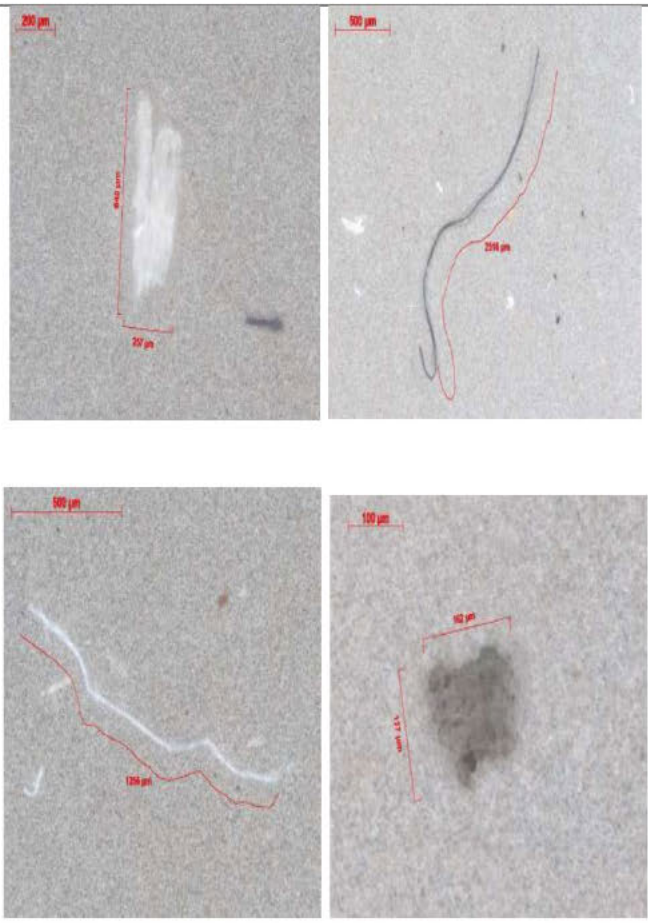
Due to the manufacturing process and the manufacturing-conditions, these particles shown in this report have been present for a long time in the product`s history and, thus, do not pose a threat in its ultimate application because of the contaminates found. The technical root-causes for the origin of these particles and, in general, because of the statistical behavior of these events with low probabilities, most of these particles cannot be considered to be homogeneously distributed within the product; nevertheless a guesstimate on their occurrence can be made.

The intention of this document is to share with our customers information about the known technically, unavoidable particles which will enable a quick and reliable risk-assessment for their applications. This may help to avoid production delays, complaints or situations of incapacities whenever one or more of these particles are found. It is not the intention of this document to negotiate or to refuse any GMP obligation of the manufacturer of pharmaceutical excipients and active pharmaceutical ingredients.

Further technical progress might lead to a situation where some of the originally documented, TUPs listed can be excluded from the report. Conversely, newly discovered, technically unavoidable particles might be added as well.

Manufacturing process of 105101 di-Potassium hydrogen phosphate anhydrous

For information on the manufacturing process of the product handled in this document, please consult the EMPROVE Material Qualification dossier on our webpage.



Product code:	105101
Product name:	di-Potassium hydrogen phosphate anhydrous
TUP size:	Fibres up to Particles up t
TUP composition:	

	Product code:	105101
	Product name:	di-Potassium hydrogen phosphate anhydrous
	TUP size:	Fibres up to Particles up
	TUP composition:	

	Product code:	105101
	Product name:	di-Potassium hydrogen phosphate anhydrous
	TUP size:	up to
	TUP composition:	

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	Product code:	105101
	Product name:	di-Potassium hydrogen phosphate anhydrous
	TUP size:	up to
	TUP composition:	

Amount of particles and insoluble foreign matter found in 105101 di-Potassium hydrogen phosphate anhydrous

Known guideline limits

According to the "APIC Guidance on Insoluble Matter and Foreign Particles in APIs chapter 6.3.2" which proposes: "A limit between 10 and 100 ppm is proposed for the maximum amount of particles allowable."

The preferred method for quantification is filtration. The amount of particles and insoluble foreign matter has been determined by filtration.

Mass balance of foreign material

The total typical particle-burden was calculated for 3 batches after dissolving 1000 g to 4000 g of the substance in DI water and filtration through a tared filter (at least: 16 µm) by sucking. After washing with DI water, the filter was dried. The amount for foreign matter was determined by weighing.

None of the obtained results did exceed 10 ppm.

Reference-no.: 00001

TUP composition:

Solubility, removal:

Ingredient	Solubility in water	Typical particle size	removal
			filtration

Additional risk of microbial / viral burden:

Same as product (low risk).

Additional BSE/TSE-risk:

Same as product (low risk).

Mitigation strategy

-
-

Reference-no.: 00003

TUP composition:

PP (Polypropylene) - white fibers and particles

Solubility, removal:

Ingredient	Solubility in water	Typical particle size	removal
		Fibres up to Particles up to	filtration

Additional risk of microbial / viral burden:

Same as product (low risk).

Additional BSE/TSE-risk:

Same as product (low risk).

Mitigation strategy

-
-

Reference-no.: 00004

TUP composition:

PE (Polyethylene) – white particles.

Solubility, removal:

Ingredient	Solubility in water	Typical particle size	removal
			filtration

Additional risk of microbial / viral burden:

Same as product (low risk).

Additional BSE/TSE-risk:

Same as product (low risk).

Mitigation strategy

-
-

Reference-no.: 00007

TUP composition:

PTFE (Polytetrafluoroethylene) - white and dark particles

Solubility, removal:

Ingredient	Solubility in water	Typical particle size	removal
			filtration

Additional risk of microbial / viral burden:

Same as product (low risk).

Additional BSE/TSE-risk:

Same as product (low risk).

Mitigation strategy

-
-

Annex

References:

ICH HARMONISED GUIDELINE FOR ELEMENTAL IMPURITIES Q3D(R2)
Current version

ICH HARMONISED TRIPARTITE GUIDELINE STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A
Current version

ICH HARMONISED TRIPARTITE GUIDELINE PHARMACEUTICAL QUALITY SYSTEM Q10
Current version

ICH HARMONISED TRIPARTITE GUIDELINE DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES Q11
Current version

The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients 2017

EXCiPACT™ Certification Standards for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices (GMP), Good Distribution Practices (GDP), Good Warehousing Practices (GWP), Requirements for Auditor Competency and Third-Party, Organisations Providing Certification of the Management System 2021

EudraLex
The Rules Governing Medicinal Products in the European Union Volume 4
EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 5 Production

EU Guideline 2015/C 95/02: Guidelines of 19 March 2015 on the formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 6 November 2001 on the Community code relating to medicinal products for human use

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