SLOVENSKI STANDARD
oSIST ISO/DIS 21676:2018

01-junij-2018

Kakovost vode - Določevanje izbranih aktivnih farmacevtskih učinkovin, produktov razgradnje in drugih organskih spojin v vodi in prečiščeni odpadni vodi - Metoda tekočinske kromatografije visoke ločljivosti in masne spektrometrije (HPLC-MS/MS ali HRMS) po neposrednem injeciranju

Water quality - Determination of selected active pharmaceutical ingredients, transformation products and other organic substances in water and treated waste water - Method using high performance liquid chromatography and mass spectrometric detection (HPLC-MS/MS or - HRMS) after direct injection

Qualité de l'eau - Détermination des ingrédients pharmaceutiques actifs sélectionnés, des produits de la transformation et d'autres substances organiques dans l'eau et dans l'eau résiduaire - Méthode par chromatographie en phase liquide à haute performance et détection par spectrométrie de masse (CLHP-MS/MS ou - HRSM) après l'injection directe

Ta slovenski standard je istoveten z: **ISO/DIS 21676**

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13.060.50	Preiskava vode na kemične snovi	Examination of water for chemical substances
71.040.50	Fizikalnokemijske analitske metode	Physicochemical methods of analysis

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DRAFT INTERNATIONAL STANDARD

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Water quality — Determination of selected active pharmaceutical ingredients, transformation products and other organic substances in water and treated waste water — Method using high performance liquid chromatography and mass spectrometric detection (HPLC-MS/MS or -HRMS) after direct injection

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 147, *Water quality*, Subcommittee SC 2, *Physical, chemical and biochemical methods*.

Introduction

Pharmaceutical ingredients are essential for human and animal health. Through application or improper disposal active pharmaceutical ingredients enter the water cycle unchanged or transformed. This may happen via communal waste water treated at treatment plants. Then the active pharmaceutical ingredients and their transformation products are not removed completely from the water. Active pharmaceutical ingredients and their transformation products also travel through slurry on the ground and subsequently enter the water body depending on the nature of the ground and the active ingredients. Active pharmaceutical ingredients and their transformation products are therefore found in surface and ground water, as well as in treated waste water. This document specifies a liquid chromatography method with mass spectrometric detection for the determination of selected active pharmaceutical ingredients.

Water quality — Determination of selected active pharmaceutical ingredients, transformation products and other organic substances in water and treated waste water — Method using high performance liquid chromatography and mass spectrometric detection (HPLC-MS/MS or -HRMS) after direct injection

WARNING — Persons using this document should be familiar with normal laboratory practice. This document does not purport to address all of the safety problems, if any, associated with its use. It is the responsibility of the user to establish appropriate safety and health practices.

IMPORTANT — It is absolutely essential that tests conducted in accordance with this document be carried out by suitably qualified staff.

1 Scope

This document specifies a method for the determination of the dissolved fraction of selected active pharmaceutical ingredients and transformation products as well as other organic substances (see Table 1) in drinking water, ground water and surface water at mass concentrations ≥ 0,025 µg/l and in treated waste water at mass concentrations ≥ 0,050 µg/l.

The lower application range of this method can vary depending on the sensitivity of the equipment used and the matrix of the sample.

The method can be used to determine further organic substances or in other types of water provided that accuracy has been tested and verified for each case as well as storage conditions of both samples and reference solutions have been validated. Please refer to Table E.1 for examples of determining other organic substances.

Table 1 — Substances whose determination was tested according to this method

Common name Chemical name (IUPAC)[a]	Molecular formula	Molar mass g/mol	CAS-RN[b]
4-Acetylaminoantipyrine N-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)acetamide	$C_{13}H_{15}N_3O_2$	245,28	83-15-8
N4-Acetyl sulfamethoxazole N-{4-[(5-Methyl-1,2-oxazol-3-yl)sulfamoyl]phenyl}-acetamide	$C_{12}H_{13}N_3O_4S$	295,32	21312-10-7
Diatrizoic acid (amidotricoic acid) 3,5-Bis(acetamido)-2,4,6-triiodobenzoic acid	$C_{11}H_9I_3N_2O_4$	613,91	117-96-4
Atenolol (RS)-2-[4-[2-Hydroxy-3-(1-methylethylamino) propoxy]phenyl] ethanamide	$C_{14}H_{22}N_2O_3$	266,34	29122-68-7
Bezafibrate 2-{4-[2-(4-Chlorbenzamido)ethyl]phenoxyl}-2-methylpropanoic acid	$C_{19}H_{20}ClNO_4$	361,80	41859-67-0

a IUPAC: International Union of Pure and Applied Chemistry

b CAS-RN: Chemical Abstracts System Registration Number

Table 1 *(continued)*

Common name **Chemical name (IUPAC)**[a]	**Molecular formula**	**Molar mass** g/mol	**CAS-RN**[b]
Bisoprolol (RS)-1-[4-(2-Isopropoxyethoxymethyl)phenoxy]-3-isopropylamino-2-propanol	$C_{18}H_{31}NO_4$	325,45	66722-44-9
Carbamazepine 5H-Dibenzo[b,f]azepine-5-carbamide	$C_{15}H_{12}N_2O$	236,27	298-46-4
Clarithromycin (2R,3R,4S,5R,8R,9S,10S,11R,12R,14R)-11-[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-5-ethyl-3,4-dihydroxy-9- [(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-12-methoxy- 2,4,8,10,12,14-hexa-methyl-6-oxacyclotetradecane-1,7-dione	$C_{38}H_{69}NO_{13}$	747,95	81103-11-9
Clofibric acid 2-(4-Chlorophenoxy)-2-methylpropanoic acid	$C_{10}H_{11}ClO_3$	214,70	882-09-7
Dehydrato-Erythromycin (anhydro-erythromycin) (2R,3R,4S,5S,8R,9S,10S,11R,12R)-11-{[4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy}-5-ethyl-3-hydroxy-9-[(5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl)oxy]-2,4,8,10,12,14-hexamethyl-6,15,16-trioxatricyclo[10.2.1.1{1,4}]hexadecane-7-one	$C_{37}H_{65}NO_{12}$	715,91	23893-13-2
Diazepam (RS)-7-Chlor-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-on	$C_{16}H_{13}ClN_2O$	284,74	439-14-5
Diclofenac 2-[2-[(2,6-Dichlorphenyl)amino]phenyl]acetic acid	$C_{14}H_{11}Cl_2NO_2$	296,15	15307-86-5
10,11-Dihydro-10,11-dihydroxy carbamazepine (5S,6S)-5,6-Dihydroxy-5,6-dihydrobenzo[b][1]benzazepie-11-carboxamide	$C_{15}H_{14}N_2O_3$	270,29	58955-93-4
Erythromycin 6-(4-Dimethylamino-3-hydroxy-6-methyl-oxan-2-yl)oxy-14-ethyl-7,12,13-trihydroxy-4-(5-hydroxy-4-methoxy-4,6-dimethyl-oxan-2-yl)-oxy-3,5,7,9,11,13-hexamethyl-1-oxacyclotetradecane-2,10-dione	$C_{37}H_{67}NO_{13}$	733,93	114-07–8
4-Formylaminoantipyrine N-(2,3-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) formamide	$C_{12}H_{13}N_3O_2$	231,25	1672-58–8
Gemfibrozil 5-(2,5-Chlorophenoxy)-2,2-methylpropanoic acid	$C_{15}H_{22}O_3$	250,34	25812-30-0
Ibuprofen (RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid	$C_{13}H_{18}O_2$	206,28	15687-27-1
Iomeprol (+/-)-N,N'-Bis-(2,3-dihydroxypropyl)-5-[(2-hydroxy-acetyl)methylamino]-2,4,6-triiodo isophthalamide	$C_{17}H_{22}I_3N_3O_8$	777,09	78649-41-9
Iopamidol (S)-N,N'-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-propanoyl)amino]-2,4,6-triiodobenzene-1,3-dicarbamide	$C_{17}H_{22}I_3N_3O_3$	777,08	60166-93-0

[a] IUPAC: International Union of Pure and Applied Chemistry

[b] CAS-RN: Chemical Abstracts System Registration Number

Table 1 *(continued)*

Common name **Chemical name (IUPAC)**[a]	**Molecular formula**	**Molar mass** g/mol	**CAS-RN**[b]
Iopromide (+/-)-N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(2-methoxyacetamido)-N-methylisophthalamide	$C_{18}H_{24}I_3N_3O_8$	791,12	73334-07-3
Metoprolol (RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol	$C_{15}H_{25}NO_3$	267,36	37350-58-6
Naproxen (S)-2-(6-Methoxy-2-naphthyl)propanoic acid	$C_{14}H_{14}O_3$	230,26	22204-53-1
Oxazepam (RS)-7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-on	$C_{15}H_{11}ClN_2O_2$	286,71	604-75-1
Phenazone 1,5-Dimethyl-2-phenyl-2,3-dihydro-1H-pyrazol-3-on	$C_{11}H_{12}N_2O$	188,23	60-80-0
Primidone 5-Ethyl-5-phenylhexahydropyrimidin-4,6-dione	$C_{12}H_{14}N_2O_2$	218,25	125-33-7
Propyphenazone 1,5-Dimethyl-4-(1-methylethyl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one	$C_{14}H_{18}N_2O$	230,31	479-92-5
Roxithromycin (3R,4S,5S,6R,7R,9R,11S,12R,13S,14R)-6-{[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy}-14-ethyl-7,12,13-trihydroxy-4-{[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-10-(2,4,7-trioxa-1-azaoctan-1-ylidene)-1-oxacyclotetradecane-2-one	$C_{41}H_{76}N_2O_{15}$	837,05	80214-83-1
Sotalol (RS)-4'-(1-Hydroxy-2-isopropylaminoethyl) methanesulfonanilide	$C_{12}H_{20}N_2O_3S$	272,36	3930-20-9
Sulfamethoxazole 4-Amino-N-(5-methyl-1,2-oxazol-3-yl)benzene-sulfonamide	$C_{10}H_{11}N_3O_3S$	253,28	723-46-6
Temazepam (RS)-7-Chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one	$C_{16}H_{13}ClN_2O_2$	300,74	846-50-4
Trimethoprim 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine	$C_{14}H_{18}N_4O_3$	290,32	738-70-5

[a] IUPAC: International Union of Pure and Applied Chemistry

[b] CAS-RN: Chemical Abstracts System Registration Number

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition referenced applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 1042, *Laboratory glassware — One-mark volumetric flasks*

ISO 3696, *Water for analytical laboratory use — Specification and test methods*

ISO 4796-2, *Laboratory glassware — Bottles — Part 2: Conical neck bottles*

ISO 5667-4, *Water quality — Sampling — Part 4: Guidance on sampling from lakes, natural and man-made*

ISO 5667-5, *Water quality — Sampling — Part 5: Guidance on sampling of drinking water from treatment works and piped distribution systems*

ISO 5667-6, *Water quality — Sampling — Part 6: Guidance on sampling of rivers and streams*

ISO 5667-11, *Water quality — Sampling — Part 11: Guidance on sampling of groundwaters*

ISO 8466-1, *Water quality — Calibration and evaluation of analytical methods and estimation of performance characteristics — Part 1: Statistical evaluation of the linear calibration function*

3 Terms and definitions

No terms and definitions are listed in this document.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org./obp

4 Principle

The water sample is injected directly into the analysis system. The identification and quantitative determination is performed using high performance liquid chromatography coupled with mass spectrometric detection (HPLC-MS/MS, HPLC-HRMS).

5 Interferences

5.1 Interferences during sample preparation

Loss of analytes can occur during filtration of the sample as a result of sorption.

5.2 Interferences during high performance liquid chromatography and mass spectrometry

Peak tailing, peak fronting and/or wide peaks are indications of malfunctioning of HPLC and/or interferences occurring during chromatography.

Interferences from accompanying substances (matrix) can occur in both ionisation modes depending on the measured compound (e.g. diclofenac in negative ESI mode).

Accompanying substances (matrix) can affect the ionization of the target substances (e.g ion suppression or signal enhancement). This can result in underestimation or overestimation of concentration during quantification. These interferences can be detected and corrected for as needed using analyte recovery (11.2) and/or internal standardization (10.3 and Table D.3).

6 Reagents

6.1 General

If available, reagents of purity grade "for analysis" or "for residue analysis" are used. The amount of impurities contributing to the blank value or causing signal interference shall be negligible. This shall be checked regularly (9.4).

Solvents, water and reagents intended for use as elution agents shall be compatible with HPLC and mass spectrometry.

NOTE Special qualities are available commercially.

6.2 Water, complying with the requirements of ISO 3696, grade 1 or equivalent without any interfering blank values.

6.3 Methanol, CH_3OH.

6.4 Acetonitrile, CH_3CN.

6.5 Acetic acid, $w(CH_3COOH) = 100$ %.

6.6 Formic acid, $w(HCOOH)$ not less than 98 %.

6.7 Ammonium acetate, $w(CH_3COONH_4)$ not less than 99 %.

6.8 Ammonium formate, $w(HCOONH_4)$ not less than 99 %.

6.9 Sodium thiosulfate pentahydrate, $Na_2S_2O_3 \cdot 5H_2O$.

6.10 Operating gases for the mass spectrometer, according to the specifications of the instrument manufacturer.

6.11 Reference substances

Substances as listed in Table 1, with known mass fraction.

6.12 Internal standard substances, preferably isotope-marked compounds of reference substances (see Table D.3).

The internal standards shall not lead to analyte interferences (9.4).

6.13 Preparation of solutions

6.13.1 General

Solutions of internal standard substances are needed only once calibration and evaluation have been performed according to 10.3 and 12.3.

Test the accuracy of the reference substance solutions against a control standard (6.13.9), e.g. during calibration (10.1).

NOTE Reference substance solutions and internal standard substances are available commercially.

6.13.2 Stock solutions (reference substances / internal standard substances)

Prepare solutions with a mass concentration of e.g. 0,1 mg/ml of each substance.

For this use e.g. 5 mg amounts of a substance (6.11) in separate 50 ml volumetric flasks (7.3), dissolve them in acetonitrile (6.4) or methanol (6.3), and then add solvent to solution until it reaches the mark.

NOTE Alternatively, commercially available (or custom made) stock solutions of individual reference substances (or internal standard substances) in acetonitril can be used for preparing further dilutions.