Приложения на съвременни аналитични техники в областта на клиничната химия, токсикологията и околната среда
14 Юни 2017

Анализ на онечиствания от елементи във фармацевтични продукти

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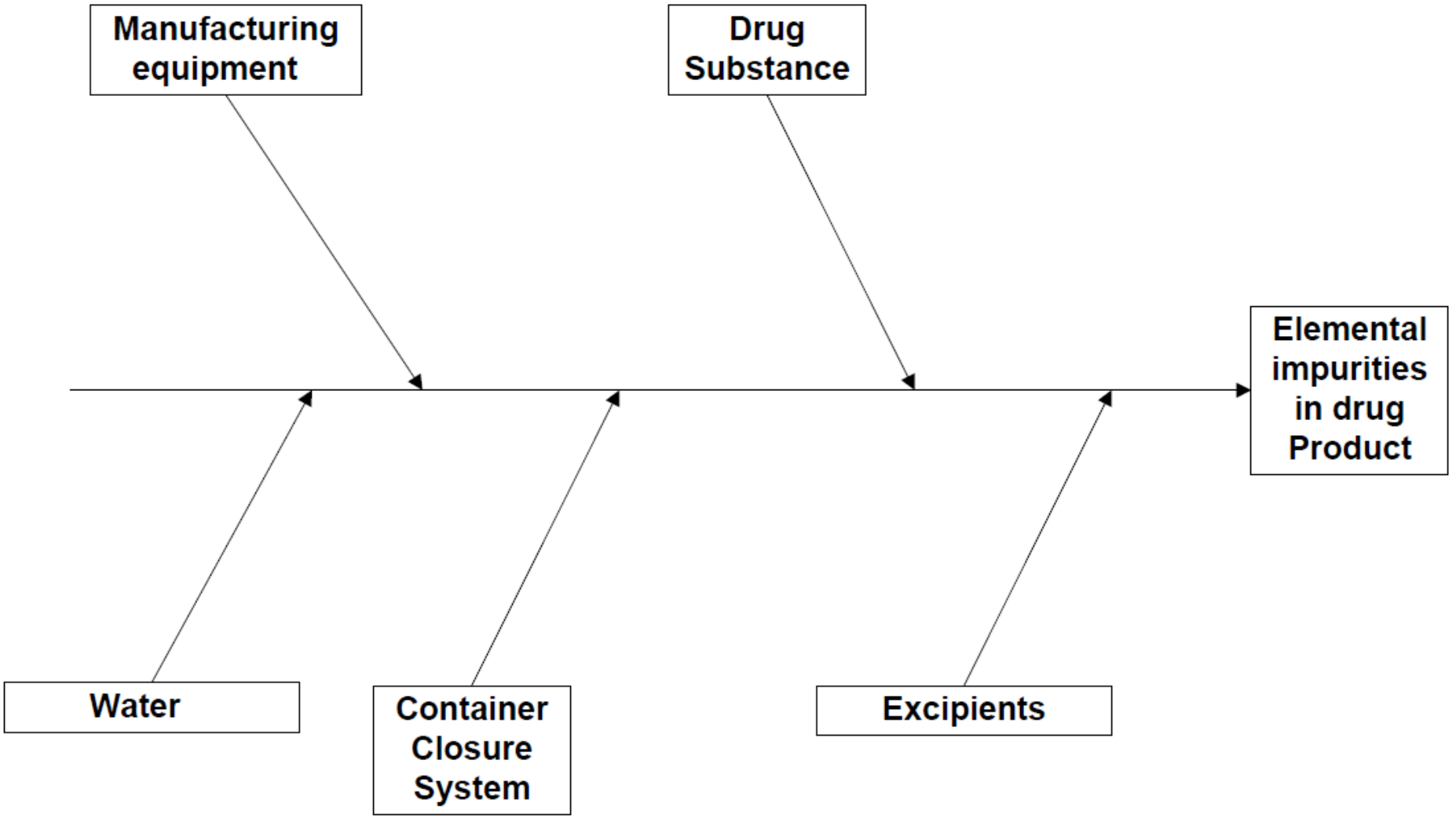
Химически факултет,
Катедра аналитична химия и компютърна химия

Източници на онечиствания от химични елементи във фармацевтичните продукти

Guideline for Elemental Impurities (ICH 3QD)



Европейски Съюз
Регулаторни органи и нормативни документи

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

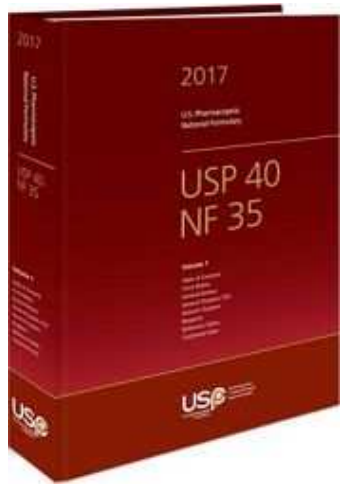
edqm

- **Европейска Агенция по Лекарствата** (EMA, European Medicines Agency)
- **Европейски Директорат по Качеството на Лекарствата** (EDQM, European Directorate for the Quality of Medicines & HealthCare
  - ***Конвенция за разработване на Европейска Фармакопея*** (Convention on the Elaboration of a European Pharmacopoeia)
  - ***European Pharmacopoeia (Ph. Eur.)***

Ph. Eur. – график за публикуване

Commission Sessions		Edition/ Supplement	Publication schedule	Corrections to be taken into account as soon as possible and not later than	Implementation date
Session No.	Date				
153	**November 2015**	**9th Edition**	**July 2016**	**31 August 2016**	**1 January 2017**
154	March 2016	9.1	October 2016	30 November 2016	1 April 2017
155	June 2016	9.2	January 2017	28 February 2017	1 July 2017
156	November 2016	9.3	July 2017	31 August 2017	1 January 2018
157	March 2017	9.4	October 2017	30 November 2017	1 April 2018
158	June 2017	9.5	January 2018	28 February 2018	1 July 2018
159	November 2017	9.6	July 2018	31 August 2018	1 January 2019
160	March 2018	9.7	October 2018	30 November 2018	1 April 2019
161	June 2018	9.8	January 2019	28 February 2019	1 July 2019
162	**November 2018**	**10th Edition**	**July 2019**	**31 August 2019**	**1 January 2020**

Регулаторни органи и нормативни документи



- **U.S. Food and Drug Administration** (FDA)
- **U.S. Pharmacopeial Convention** (USP)
  - United States Pharmacopeia and The National Formulary (USP–NF)

Publication	Release/Posting Date	Official Date (unless otherwise indicated)
USP 40–NF 35	Nov 1, 2016	May 1, 2017
First Supplement to USP 40–NF 35	Feb 1, 2017	Aug 1, 2017
Second Supplement to USP 40–NF 35	June 1, 2017	Dec 1, 2017
USP 41-NF 36	Nov 1, 2017	May 1, 2018

ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH
harmonisation for better health

Brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.

Membership / About ICH /

Current Members and Observers

As of November 2016, the ICH Association comprises the following Members and Observers:

MEMBERS

Click here for the list of representatives

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- EC, Europe
- FDA, US
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

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- WHO

Legislative or Administrative Authorities
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- HSA, Singapore
- MCC, South Africa
- National Center, Kazakhstan
- Roszdravnadzor, Russia
- TFDA, Chinese Taipei
- TGA, Australia

Regional Harmonisation Initiatives (RHIs)
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

International Pharmaceutical Industry Organisation
- APIC

International Organisations with an Interest in Pharmaceuticals
- CIOMS
- EDQM
- IPEC
- USP

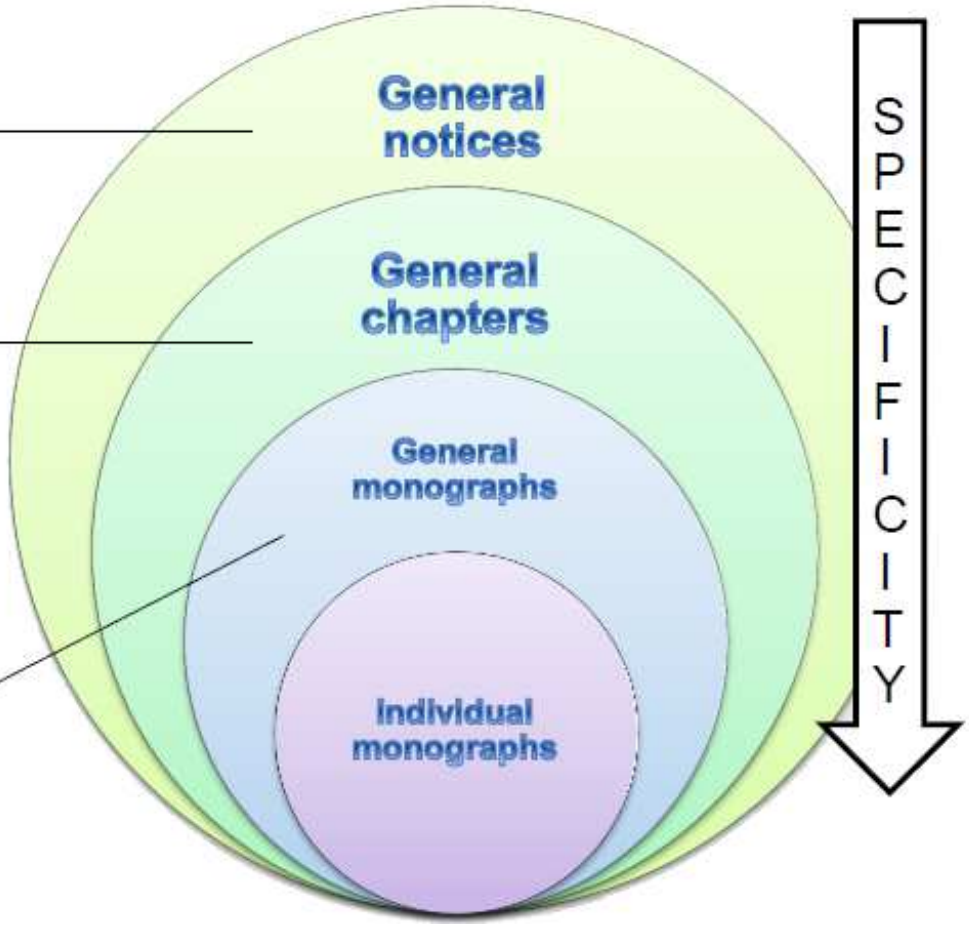
Ph. Eur. (USP-NF) – съдържание и структура

Provide basic and very general information that are true for all texts. Help to understand aspects of wording, structure and requirements of the Ph. Eur.

- General methods: general recommendations for analytical procedures.
- General texts: informative texts, guidelines (e.g. microbiology, chemometrics)

Become mandatory when cited in monograph

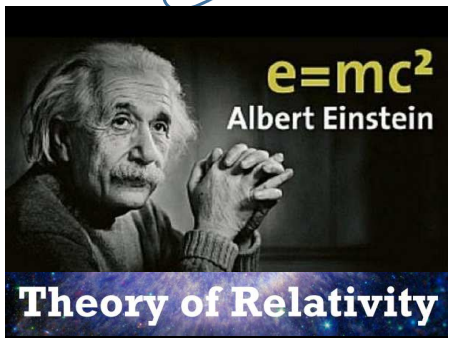
- Dosage forms: applied during licensing
- Group of products: defined by production method, risk factors or intended use. Summarises mandatory quality aspects common to a given group.



Тест за тежки метали
(Heavy Metals)

Pb, Cd, Hg, As,
Ag, Bi, Cu, Mo, Sb, Sn

от 1905



Ph. Eur. 9.0 General Method **2.4.8.**
Test (A), (B), (C), (D), (E), (F), (G), (H)

USP 40-NF 35 General Chapter **<231>**
Method I, II, III

Тест за тежки метали

EUROPEAN PHARMACOPOEIA 8.0

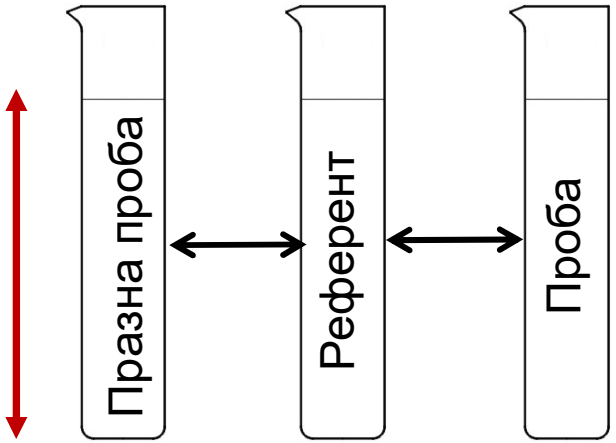
PARACETAMOL

TESTS

Heavy metals (*2.4.8*): maximum 20 ppm.

Образуване на колоидна (грубодисперсна) система при взаимодействие на „тежките метали“ със сулфидни йони, например:

$Pb^{2+} + S^{2-} \rightarrow PbS\downarrow$ (pH = 3.5)



1 или 2 ppm Pb

Недостатъци:

- Оценява се сумарното количество на всички елементи;
- Постигат се сравнително високи граници на откриване;
- Субективно заключение;

Първи стъпки за актуализация на контрола на онечистванията от елементи

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 21 February 2008
Doc. Ref. EMEA/CHMP/SWP/4446/2000

GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS

DATE FOR COMING INTO EFFECT	01 September 2008

Class exposure and concentration limits for individual metal catalysts and metal reagents

Classification	Oral exposure		Parenteral exposure		Inhalation exposure*
	PDE (µg/day)	Concentration (ppm)	PDE (µg/day)	Concentration (ppm)	PDE (ng/day)
Class 1A: **Pt, Pd**	100	10	10	1	Pt: 70*
Class 1B: **Ir, Rh, Ru, Os**	100**	10**	10**	1**	
Class 1C: **Mo, Ni, Cr, V** Metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
Class 2: **Cu, Mn** Metals with low safety concern	2500	250	250	25	
Class 3: **Fe, Zn** Metals with minimal safety concern	13 000	1300	1300	130	

* See section 4.4.
** Subclass limit: the total amount of listed metals should not exceed the indicated limit.

Първи стъпки за актуализация на контрола на онечистванията от елементи

USP Pharmacopeial Forum 2008 34(5)

Stimuli to the Revision Process: General Chapter on Inorganic Impurities: Heavy Metals

USP Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals and USP Staff*

ABSTRACT In the ICH Q3A *Impurities in Drug Substances* guidance, impurities are classified as organic, inorganic, and residual solvents. Within the inorganic impurities classification, the metals listed in *Table 1* are important to control in food, dietary supplements, and drug articles. Many toxic metal impurities found in pharmaceutical articles have been controlled for years by application of the Heavy Metals test described in *USP–NF* General Chapter *Heavy Metals* ⟨ 231 ⟩. However, the procedures and the methods contained in ⟨ 231 ⟩ lack the sensitivity, specificity, and recovery to monitor properly the levels of these metals. A number of additional chapters for the control of specific metals and other inorganic impurities are contained in *USP–NF*. This *Stimuli* article proposes a new *USP* General Chapter for the control of inorganic impurities in drug and dietary supplement articles intended for use in humans. For the purposes of this article, *inorganic impurity, metal,* and *element* all refer to those elements listed in *Table 1*. The proposed new General Chapter recommends procedures that rely on modern analytical technology and includes limits that are based on toxicity and exposure levels for the selected metals. The new General Chapter also introduces a performance-based approach for the selection of the appropriate technology. This chapter is proposed to replace ⟨ 231 ⟩ and may impact other General Chapters that control metals.

Препоръка за контрол на 31 елемента:

Al, Sb, As, Be, B, Cd, Cr, Co, Cu, In, Ir, Fe, Pb, Li, Mg, Mn, Hg, Mo, Ni, Os, Pd, Pt, Rh, Rb, Ru, Se, Sr, Tl, Sn, W и Zn

Препоръки за методи за предварителна подготовка на пробите (микровълнова система със затворени съдове) и инструментални техники за детекция (ICP-OES и ICP-MS)

Ръководство ICH Q3D (Elemental Impurities)

Pure Appl. Chem., Vol. 74, No. 5, pp. 793–807, 2002.

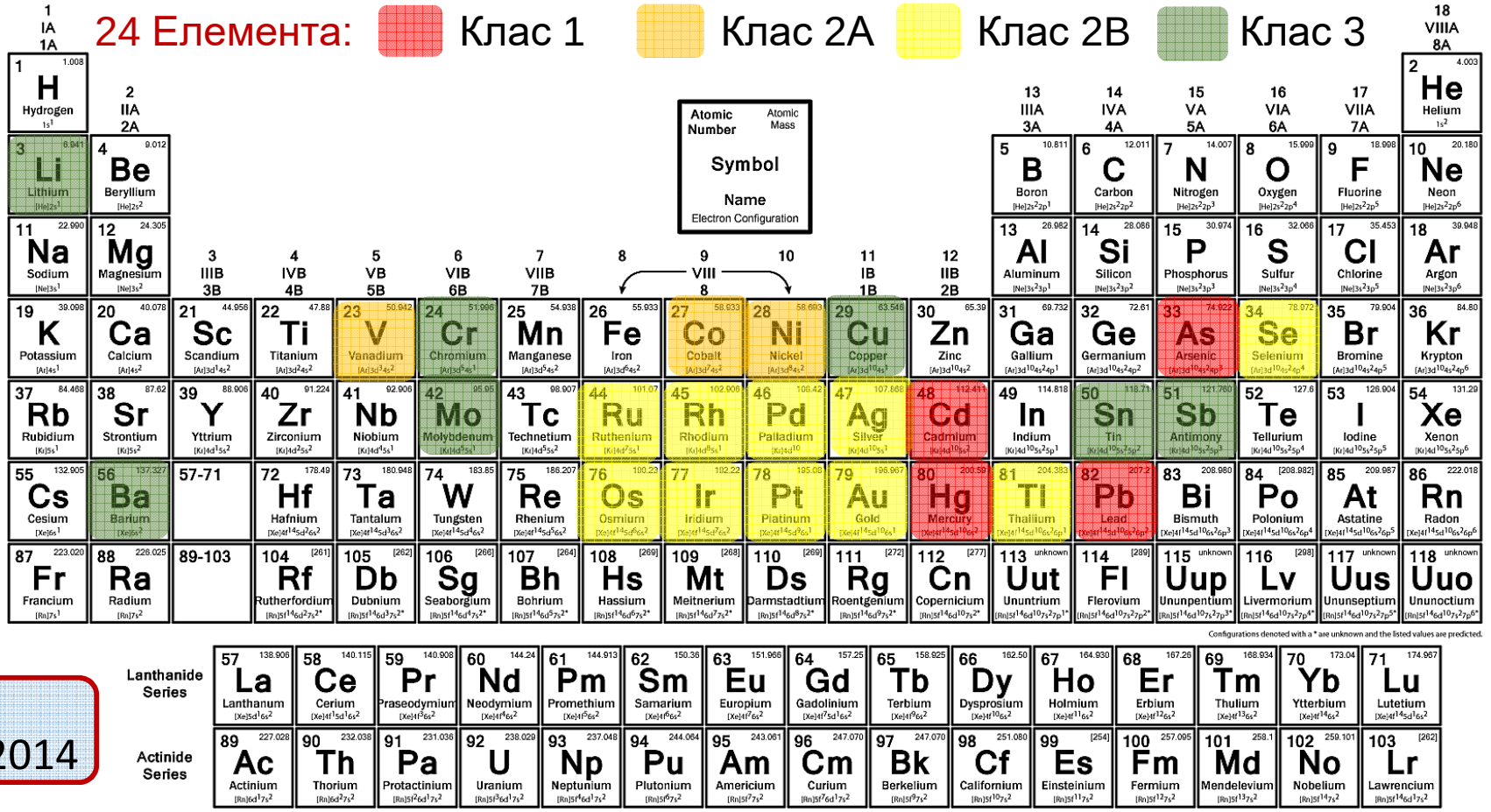
“HEAVY METALS”—A MEANINGLESS TERM?

(IUPAC Technical Report)

“Metallic impurities”?

“Inorganic impurities”?

“Elemental Impurities”!



Step 4
16 Декември 2014

Ръководство ICH Q3D (Elemental Impurities)

Table A.2.1: Permitted Daily Exposures for Elemental Impurities

Element	Class	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Ph. Eur. – онечиствания от елементи

(р)еволюция?

Групов тест за тежки метали

Сравнителна граница:
10 или 20 ppm Pb

2008

EMA ръководство:
Specification limits for residues of metal catalysts or metal reagents

2013

ICH 3QD
Разработване и прилагане

2018

1 Април 2013

2.4.20 Determination of metal catalyst or metal reagent residues
5.20 Metal catalyst or metal reagent residues

1 Януари 2017

Премахване на теста за тежки метали от индивидуалните монографии

1 Януари 2018

2.4.20 Determination of elemental impurities
5.20 Elemental impurities (ICH 3QD)
2619 Pharmaceutical preparations
2034 Substances for pharmaceutical use

USP-NF– онечиствания от елементи

USP Pharmacopeial Forum 2008 34(5)
Stimuli to the Revision Process: General Chapter on Inorganic Impurities: Heavy Metals

USP <232>
Elemental Impurities - Limits (ICH 3QD)

USP <233>
Elemental Impurities - Procedures

В сила от:
~~1 Декември 2015~~
1 Януари 2018

Element	Class	Oral PDE µg/day	Parenteral PDE µg/day	Inhalation PDE µg/day
As	1	15	15	2
Hg	1	30	3	1

PDE – определени за неорганичните форми на елементите.
Възможност за определяне на формите на присъствие на As и Hg.

ICH 3QD: The applicant is not expected to provide speciation information; however, such information could be used to justify lower or higher levels when the identified species is more or less toxic…

Методи за определяне на онечиствания от елементи във фармацевтичните продукти

- **ICH 3QD:**
  - The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes;
  - Pharmacopoeial procedures or suitable alternative procedures for determining levels of elemental impurities should be used;

- **Ph. Eur. 2.4.20** (General Method) Determination of metal catalyst or metal reagent residues (предстои редакция в издание 9.3);

- **USP <233>** Elemental Impurities – Procedures;

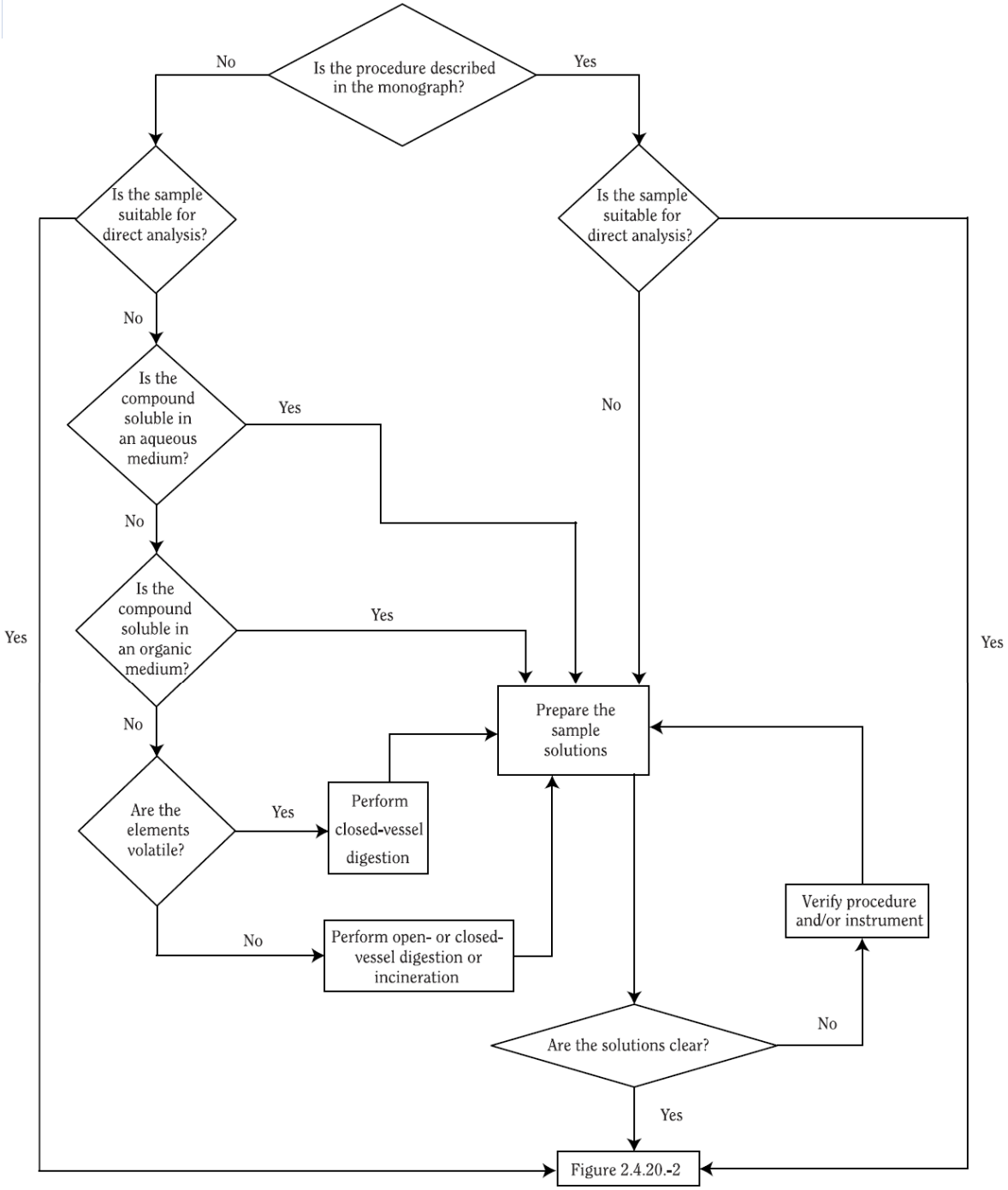


Figure 2.4.20.-1. – *Metal residues decision tree: sample preparation*

Изисква се валидиране (верифициране) на използваните аналитични методи.

Предварителна подготовка на пробата:

- Директен анализ;
- Разтваряне във вода;
- Разтваряне в органични р-ли;
- Киселинна минерализация или опепеляване в отворени системи;
- Киселинна минерализация в затворени съдове;

2.4.20 Determination of metal catalyst or metal reagent residues

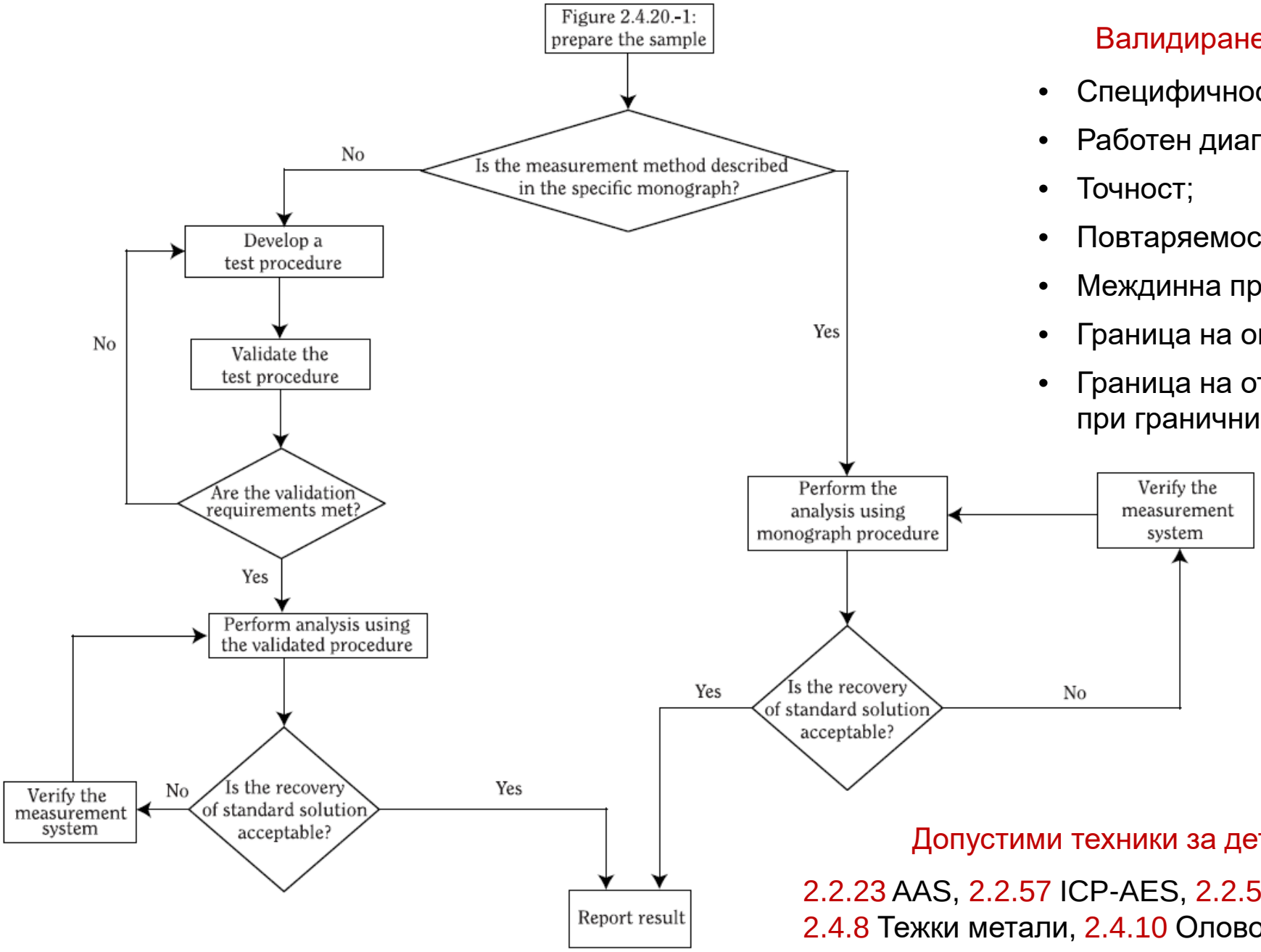


Figure 2.4.20.-2. – *Metal residues decision tree: measurement*

Валидиране на метода:

- Специфичност;
- Работен диапазон;
- Точност;
- Повтаряемост;
- Междинна прецизност;
- Граница на определяне;
- Граница на откриване (само при гранични изпитвания);

Допустими техники за детекция:

2.2.23 AAS, 2.2.57 ICP-AES, 2.2.58 ICP-MS,
2.4.8 Тежки метали, 2.4.10 Олово в захари и др.

Предварителна подготовка на проби:

- Проби анализирани без предварително третиране (Neat);
- Разтваряне във вода (Direct aqueous solution);
- Разтваряне в органични разтворители (Direct organic solution);
- Проби, които не се разтварят директно във вода или органични разтворители (Indirect solution):
  - Препоръчва се киселинна минерализация в затворени съдове.

Предложена процедура:

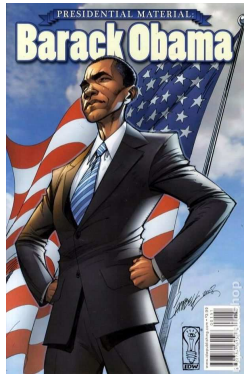
Стъпка 1 0.5 g проба + 5 ml "Концентрирана к-на" → 30 min изчакване;

Стъпка 2 Добавят се 10 ml "Концентрирана к-на" → разтваряне (екстракция) в затворени съдове;

Стъпка 3 При необходимост се добавят 5 ml "Концентрирана к-на" и се повтаря разтварянето в затворените съдове.

Микровълнова минерализация в система със затворени съдове

2008



ETHOS UP

ETHOS EASY

ULTRAWAVE

ULTRACLAVE

https://www.milestonesrl.com/lp/usp-232

Standardization solution 1: 1.5J of the *Target element(s)* in a *Matched matrix;*

Standardization solution 2: 0.5J of the *Target element(s)* in a *Matched matrix;*

Sample stock solution: Proceed as directed in *Sample Preparation* above. For mercury determination, add an appropriate stabilizer;

Sample solution: Dilute the *Sample stock solution* with an appropriate solvent to obtain a final concentration of the *Target elements* at NMT 1.5J;

Blank: *Matched matrix;*

Analysis: Analyze according to the manufacturer's suggestions for program and wavelength.

Procedure 1: ICP-OES

J: The concentration of the element(s) of interest at the *Target limit*, appropriately diluted to the working range of the instrument.

$$J = \frac{PDE}{MDD.DF}$$

PDE – Permitted daily exposure, µg/day;
MDD – Maximum Daily Dose, g/day;
DF – Dilution Factor;

Analysis of elemental impurities in drug products using the Thermo Scientific iCAP 7600 ICP-OES Duo

Grégory Lecornet, Applications Specialist, Thermo Fisher Scientific

Application Note 43149

Table 4. Method detection limits for the solid samples compared to the calculated target limit

Elements	Wavelength (nm)	MDL (µg/g)	Target limit J (µg/g)
Cadmium	214.438	0.004	12.5
Lead	220.353	0.062	2.5
Inorganic arsenic	189.042	0.070	0.75
Inorganic mercury	184.950	0.050	7.5
Iridium	212.681	0.034	50
Osmium	225.585	0.031	50
Palladium	340.458	0.055	50
Platinum	203.646	0.085	50
Rhodium	343.489	0.095	50
Ruthenium	240.272	0.051	50
Molybdenum	202.030	0.022	50
Nickel	221.647	0.015	250
Vanadium	309.311	0.012	50
Copper	324.754	0.008	500

Procedure 1: ICP-OES

Sample preparation

Drug 1 - anti-inflammatory drug;
Drug 2 - antihistamine.
The samples were prepared by dissolving 0.5 g of drug in 20 g of dimethyl sulfoxide (DMSO), sonicating the mixture for 10 minutes before making up to a final weight of 25 g with DMSO.

Standardization solution 1 (1.5J) и **2** (0.5J), **Sample stock solution, Sample solution, Blank** – аналогични с използваните при ICP-OES.

Analysis: Analyze according to the manufacturer's suggestions for program and m/z. NOTE - An instrument with a cooled spray chamber is recommended. (A collision cell or reaction cell may also be beneficial.)

Полиатомни спектрални пречения:

$^{35}Cl^{16}O^+ \rightarrow {}^{51}V^+$

$^{40}Ar^{35}Cl^+ \rightarrow {}^{75}As^+$

$^{40}Ar^{12}C^+ \rightarrow {}^{52}Cr^+$ $\quad {}^{68}Zn^{35}Cl^+ \rightarrow {}^{103}Rh^+$

PAPER www.rsc.org/jaas | Journal of Analytical Atomic Spectrometry

Microwave-assisted cloud point extraction of Rh, Pd and Pt with 2-mercaptobenzothiazole as preconcentration procedure prior to ICP-MS analysis of pharmaceutical products

Kiril Simitchiev,*[a] Violeta Stefanova,[a] Veselin Kmetov,[a] George Andreev,[a] Nikolay Kovachev[b] and Antonio Canals[b]

J. Anal. At. Spectrom., 2008, **23**, 717–726 | 717

Procedure 2: ICP-MS

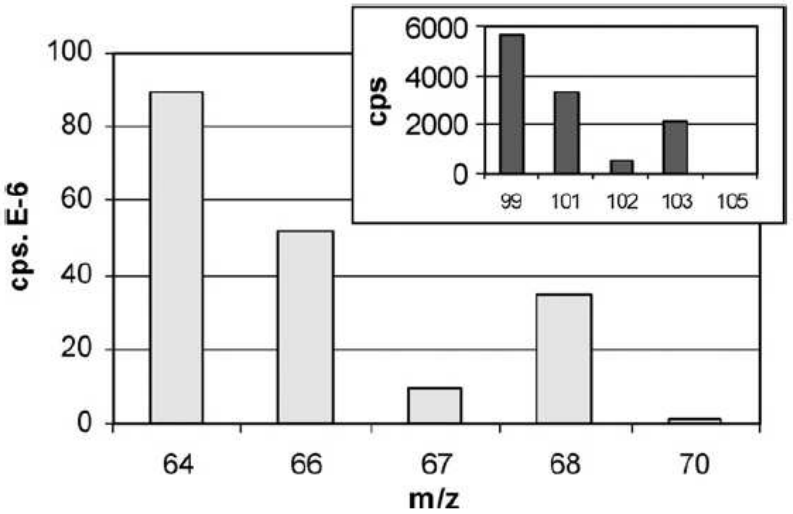


Fig. 7 Fingerprint of Zn isotope signals in a solution of *Laprilen* and corresponding signals assigned to $^{x}Zn^{35}Cl$ polyatomic ions.

Инструментални решения за премахване на спектрални пречения при ICP-MS

Thermo Scientific iCAP Qnova Series ICP-MS

Thermo Scientific™ iCAP™ RQ ICP-MS (launched at Pittcon 2016)

Simplicity, productivity and robustness for routine labs

The iCAP RQ ICP-MS delivers the reliability, analytical performance and ease of use needed to meet the demands of the highest throughput labs.

Thermo Scientific™ iCAP™ TQ ICP-MS (launched at WPC Feb 2017)

Redefining triple quadrupole technology with unique ease of use

The first, future proof triple quadrupole ICP-MS solution delivering enhanced performance and uncompromised ease of use for demanding routine analysis and challenging research applications.

Analysis of Pharmaceutical Products for their Elemental Impurities with the Thermo Scientific iCAP RQ ICP-MS

Application Note 43325

Julian Wills and Daniel Kutscher
Thermo Fisher Scientific, Bremen, Germany

Procedure 2: ICP-MS

Table 3. Instrumental detection limit (LOD, based on 3 x the standard deviation of the calibration blank), background equivalent concentration (BEC) (reported as ng/g) and resulting MDLs (reported as µg/g) for the USP <232> defined elements.

Isotope	LOD (ng/g)	BEC (ng/g)	MDL (µg/g)	Target limit J (µg/g)
^{51}V	0.0035	0.0629	0.014	10
^{52}Cr	0.007	0.042	0.008	1100
^{60}Ni	0.0012	0.0163	0.100	20
^{63}Cu	0.0049	0.0910	0.186	300
^{75}As	0.0009	0.0087	0.0005	1.5
^{95}Mo	0.0026	0.0013	0.027	300
^{101}Ru	0.0003	0.00005	0.025	10
^{103}Rh	0.0001	0.00005	0.026	10
^{105}Pd	0.0036	0.0351	0.044	10
^{111}Cd	0.00001	0.00009	0.006	0.5
^{189}Os	0.0007	0.0003	0.043	10
^{193}Ir	0.0005	0.0045	0.023	10
^{195}Pt	0.0001	0.0002	0.024	10
^{202}Hg	0.0099	0.0290	0.018	3
^{208}Pb	0.0009	0.0035	0.009	0.5

Sample preparation

Drug A: a phytotherapeutic (herbal) medicine
Drug B: a vascular medicine
Drug C: an anti-anxiety medicine
All three drugs were brought into solution via a microwave digestion procedure using an UltraWAVE closed vessel microwave digestion system (Milestone Inc., Shelton, CT, USA).

Requirements for alternate procedure validation

If the specified compendial procedures do not meet the needs of a specific application, an alternative procedure may be developed. Alternative procedures must be validated and shown to be acceptable, in accordance with the validation requirements for alternative procedures as described below:

За процедура за количествен анализ

- Точност;
- Прецизност;
  - Повтаряемост;
  - Междинна прецизност;
- Специфичност;
- Граница на определяне;
- Линейност и работен диапазон;

Затруднения при валидирането на аналитичните методи:

Липса на подходящи сертифицирани сравнителни материали (CRM)!

https://tools.thermofisher.com/content/sfs/brochures/USP-Primer-eBook.pdf

thermoscientific

USP

the
Medicine Maker

Големите промени по отношение на контрола на онечиствания от химични елементи във фармацевтичните продукти се случват в настоящия момент!

2017 → 2018

Благодаря Ви за вниманието!

Благодарности:
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