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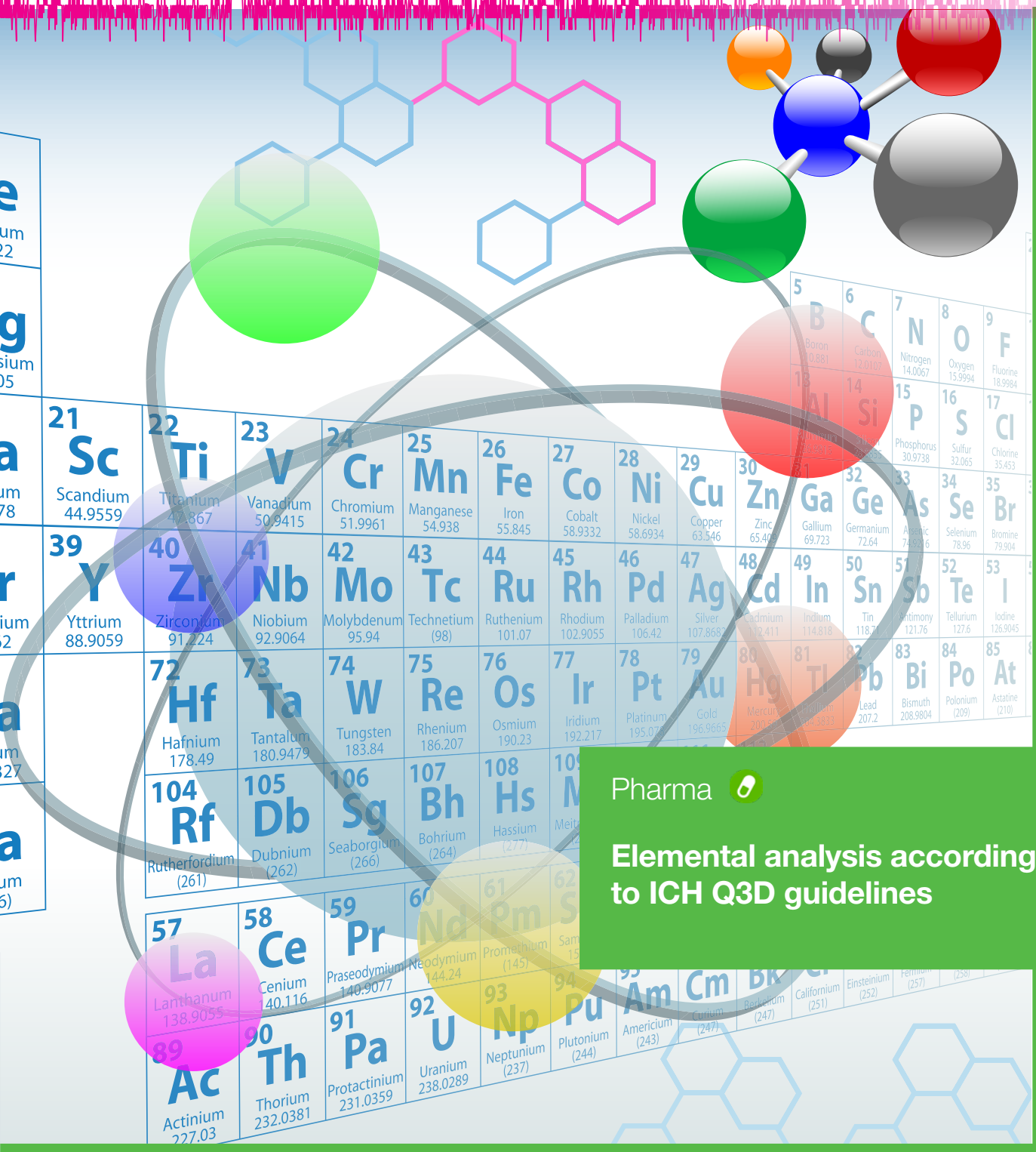

Pharma

Elemental analysis according to ICH Q3D guidelines

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Introduction

ICH Q3D is a quality guideline for the control of elemental impurities (EI) in pharmaceutical products published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Since its publication in 2014, the second revision (R2)[1] has now taken effect. On this occasion, this article is intended to provide a brief insight into the ICH Q3D, with a focus on the amendments introduced by the second revision.

At Interlabor Belp AG, the existing analytical concept was revised in order to continue to enable individual solutions for ICH Q3D compliant elemental analysis. This way, each customer can be offered a process tailored to the type of product and the manufacturing process.

Overview ICH Q3D

Elemental impurities might be introduced to a pharmaceutical product from various sources, for example through residues of catalysts or by interactions with containers and equipment. Since these (heavy) metals can have a non-therapeutic or even toxic effect on consumers, the aim of the ICH Q3D is to define standardized regulations for their control.

First, the guideline deals with toxicity studies in order to provide a classification of the elements, which can be used for the risk assessments. Furthermore, it defines the maximum permitted daily exposure (PDE) for each element and presents a risk-based approach to control these contaminants.

The classification of the elements into three different classes (see Table 1) is intended to reflect the toxicity of the element on the one hand and the probability of its occurrence in pharmaceutical products on the other hand. It serves as a basis for the risk assessment. Not all critical elements are listed in the ICH Q3D, including Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn. These are omitted from the guideline because they have different threshold values in national legislations or a rather low toxicity and only play a role in special dosage forms or patient groups (e.g. Al for patients with impaired renal function or Mn and Zn for patients with impaired liver function).

To determine the PDE values, the ICH used various approaches for the determination of the exposure values in pharmaceutical products. In addition, approved methods were applied for assessing the health risk of chemicals in alignment with national regulatory authorities such as the FDA or EMA. Four different routes of administration are distinguished: oral, parenteral, inhalation and transcutaneous. The established limit values are summarised in Table 1.

Besides the classification and determination of the maximum PDE, the ICH Q3D guideline puts a further focus on the performance of the risk assessment. The risk assessment comprises the following steps [1]:

- Identification of potential sources of elemental impurities,
- Evaluation of the presence of possible elemental impurities and comparison with the PDE,
- Summary, documentation and evaluation whether the controls built within the production process are sufficient.

If the presence of elementary contaminants has been identified within the product, a control threshold of 30 % of the PDE applies. Above this threshold, the implementation of further controls within the production process is required to limit the presence of elemental impurities. Some examples for such additional controls are given in section 6 of the guideline.
If, after completion of the assessment, the occurrence of certain contaminants in the product in safety-relevant concentrations can be excluded, it is possible to adjust the number of elements to be examined accordingly.

What is new in revision 2?

The most important change introduced by the new revision of ICH Q3D(R2)[1] are the additional PDEs for the transcutaneous administration of medicinal products on or under the skin and guidance for the risk assessment of these products. Previously, only the oral, parenteral and inhalation routes of administration were considered in the guideline.

The daily doses are calculated by means of the so-called “Cutaneous Modifying Factor” (CMF), which takes into account the absorption capacity of the skin for certain elements. It was generally assumed that 1 % of the ingredients pass through an intact skin. However, since many factors have an

influence on the skin barrier, the general value was raised to 10 % and a CMF of 10 was set for all elemental impurities. Exceptions are arsenic (CMF = 2) and thallium (CMF = 1) for which studies showed higher intakes.

The new transcutaneous limits are derived from the parenteral PDEs according to the following equation[2]:

transcutaneous PDE = parenteral PDE * CMF

In addition to the introduction of the transcutaneous PDEs, the current revision also corrects calculation errors and has adjusted the PDEs for the elements gold, silver and nickel[2]. The PDEs are derived on the basis of non-clinical and clinical data. In the case of gold, for example, it was incorrectly assumed that the underlying study referred to mice instead of rats. This changes the conversion factor and the actual maximum PDE is increased by a factor of 3 (now 300 µg/d instead of 100 µg/d).

Table 1: Limit values according to ICH Q3D (Table A.2.1 and A.5.1[1], amendments by revision 2 marked in color)

Analyte	Class	Max. oral [µg/day]	Max. parenteral [µg/day]	Max. inhalation [µg/day]	Max. (trans-)cutaneous [µg/day]
Cadmium (Cd)	1	5	2	3	20
Lead (Pb)	1	5	5	5	50
Arsenic (As)	1	15	15	2	30
Mercury (Hg)	1	30	3	1	30
Cobalt (Co)	2A	50	5	3	50
Vanadium (V)	2A	100	10	1	100
Nickel (Ni)	2A	200	20	6	200
Thallium (Tl)	2B	8	8	8	8
Gold (Au)	2B	300	300	3	3000
Palladium (Pd)	2B	100	10	1	100
Iridium (Ir)	2B	100	10	1	100
Osmium (Os)	2B	100	10	1	100
Rhodium (Rh)	2B	100	10	1	100
Ruthenium (Ru)	2B	100	10	1	100
Selenium (Se)	2B	150	80	130	800
Silver (Ag)	2B	150	15	7	150
Platinum (Pt)	2B	100	10	1	100
Lithium (Li)	3	550	250	25	2500
Antimony (Sb)	3	1200	90	20	900
Barium (Ba)	3	1400	700	300	7000
Molybdenum (Mo)	3	3000	1500	10	15000
Cooper (Cu)	3	3000	300	30	3000
Tin (Sn)	3	6000	600	60	6000
Chromium (Cr)	3	11000	11000	3	11000

ICH Q3D at Interlabor

For the determination of elemental impurities, we are currently equipped with two ICP-MS with a cooled spray chamber and He-collision cell, which comply with the recommendations of the USP[3].

Interlabor Belp AG offers two different options for the determination of elemental impurities within the framework of ICH Q3D, which differ substantially from each other in the scope of work and costs.

Option A is recommendend for raw materials and intermediates that are not intended for direct administration and do not have fixed daily doses. This option is suitable to get an overview for possible risk assessments. A semi-quantitative analysis is performed for the 24 elements listed in the ICH Q3D guideline (see Table 2). From this data, the risk of a potential elemental contamination in the finished product can be evaluated. If required, the analysis can also be extended to include further elements. This option is also suitable for the analysis of intermediate products intended for sale.

Option B is recommended for products with a maximum daily dose as well as a defined route of administration. This option is suitable for the control of defined limits and risk assessments. A quantitative analysis is performed for 1 - 24 elements (see Table 3). In order to cover the control threshold, we recommend a measuring range of 30 - 150 % of the limits listed in Table 1.

ICH Q3D under GMP

For the analysis of elemental impurities in intermediate products and finished products intended for sale, a product-specific full validation is recommended in order to exclude a potential risk due to influences by the matrix on the analytical results. We rely here on the specifications from USP <233> "Elemental Impurities - Procedures"[3] and on Ph. Eur. 2.4.20 "Determination of Elemental Impurities" [4]. Both chapters describe the analytical requirements and the scope of validation. The contents of the Ph. Eur. and the USP are almost identical with regard to the acceptance criteria and the scope of validation. In contrast to other residue determinations, simplified acceptance criteria apply to the validation of the analytical method for the determination of elemental contaminants (Table 4).

Table 2: Overview of Option A for the analysis of raw materials and intermediates

Option	A-1	A-2
Number of elements	24 (ICH Q3D)	24 (ICH Q3D)
Technology	ICP-MS	ICP-MS
Measuring range	semi-quantitative	semi-quantitative
Validation	not required	required
Limit of quantification	ppm to sub-ppm	ppm to sub-ppm
Documentation	test report	test report, validation documents, customer-specific SOP
Quality standard	state of the arte	GMP
Suitability	risk / overview analysis **without** consideration of a max. daily dosage or form of administration; for raw materials and intermediates	

Table 3: Overview of Option B for the analysis of pharmaceutical products with a maximum daily dose and defined form of administration

Option	B-1	B-2
Number of elements	1 - 24 (ICH Q3D)	1 - 24 (ICH Q3D)
Technology	ICP-MS	ICP-MS
Measuring range	50 - 150 % of the limit value according to EP/USP; recommandation: lowest measuring range 10 - 30 % for risk management	
Validation	not required	required
Limit of quantification	optional: 50 % of the limit value according to EP/USP, on request lower levels possible (see measuring range)	
Documentation	test report	test report, validation documents, customer-specific SOP
Quality standard	state of the art	GMP
Suitability	risk assessment / limit control for products with a max. daily dosage as well as a defined form of administration (oral, inhalation, parenteral or transcutaneous); also suitable for raw materials with undefined PDE (in this case a theoretical value of 10 g is used)	

Table 4: Overview of validation acceptance criteria according to USP <233>[3] and Ph. Eur. 2.4.20[4]

Parameter	Acceptance criteria
Accuracy *n* = 3 x 3 Levels (50 %, 100 %, 150 %) of the limit	70 % - 150 % (mean value per level)
Repeatability *n* = 6 (100 %)	≤ 20 % RSD (*n* = 6)
Laboratory precision (different day, different analyst and second measuring device). *n* = 6 (100 %)	≤ 25 % RSD (*n* = 12), data from both precision series
Specificity, linearity, limit of quantification (LoQ), robustness	fullfilled with accuracy and precision
Measuring range	50 % - 150 % lower range possible from 10 %

Conclusion

In the years since the introduction of the ICH Q3D, Interlabor Belp AG has continuously improved its analytical concept to support customers in monitoring their product quality with regard to elemental impurities.

With the expansion of our instrumental equipment, our customers currently have two qualified, redundant analytical instruments available for analysis. The current updates to the ICH Q3D guideline are taken into account, as well as individual questions and customised solutions.

Please contact our customer advisors with your request. They will be happy to assist you.

References

[1] *„Guideline for elemental impurities Q3D(R2)“, in: Internetseite ich.org, 26.04.2022, URL: https://database.ich.org/sites/default/files/Q3D-R2_Guideline_Step4_2022_0308.pdf, Abruf am 21.11.2022.*

[2] *„ICH Q3D(R2) Elemental Impurities Step 4 document – to be implemented“, in: Internetseite ich.org, 27.05.2022, URL: https://database.ich.org/sites/default/files/ICH_Q3D%28R2%29_Step4Presentation_2022_0527.pdf, Abruf am 21.11.2022.*

[3] *USP-NF <233> „Elemental Impurities – Procedures“ (01.05.2018)*

[4] *Ph. Eur. 07/2018:20420 „Determination of elemental impurities“*

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