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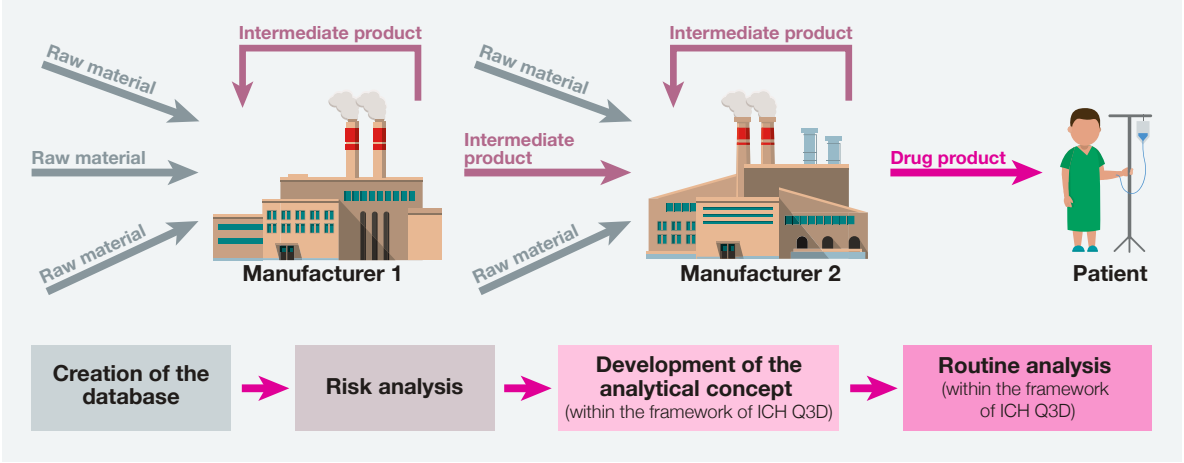
Elemental analytics according to ICH Q3D guidelines

Approach to the implementation of the ICH Q3D guidelines



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Since the announcement of the new ICH Q3D guidelines for the determination of elemental impurities in medicinal products end of 2014 the implementation of the same is a challenge for many actors in the pharmaceutical industry [1]. In particular as the ICH Q3D guidelines are connected with profound changes concerning the analytes to be investigated, specifications and analysis methods.

At Interlabor Belp AG a concept has been elaborated which allows individual solutions within the framework of ICH Q3D-compliant elemental analysis. In this way Interlabor Belp AG has the opportunity to offer a procedure tailored to the product type and manufacturing process. This aspect is of particular significance, as the ICH Q3D guidelines base on principles of risk management [2]. This means that there is in contrary to the former limit tests of Ph.Eur. 2.4.8 and USP <231> no defined number of elements, for which a product needs to be analysed according to fixed specifications. Instead a risk assessment is performed for the 24 elements affected by the guidelines. If the occurrence of certain contaminants in the product can be excluded in safety-related concentrations, it is possible to adjust the number of elements to be analysed accordingly. Another difference to the previous limit tests is the definition of the limit values. The ICH Q3D guideline defines limit values for 24 elementary contaminants in final medicinal products depending on the form of administration (oral, parenteral or inhaled) and the maximum daily dose of the corresponding medicament. The biggest change is not the analytes or the specifications, but the methodology itself. The simple, decade-long wet-chemical process of sulphide heavy metal precipitation is replaced by modern instrumental techniques, such as ICP-MS. The aim is to minimise potential weaknesses of the unspecific sulphide precipitation, such as different recovery rates of heavy metals, and to enable the specific determination of a large number of elements.
Consequently, the difficulty in the implementation of the ICH Q3D guidelines lies in the accumulation of the described changes, which require the development of an individual analytical concept.

Elemental analytics for risk assessment and knowledge building

The first step in the development of an analytical concept for implementing the ICH Q3D guidelines is to carry out a risk analysis. The main focus here is on the creation of the necessary database in order to estimate and calculate

1 The key factors of the three different screening options

Screening	Option A	Option B	Option C
Number of elements	Up to 70	24 (ICH Q3D)	24 (ICH Q3D)
Method	ICP-MS	ICP-MS	ICP-MS
Measuring range	Without limitations	Without limitations	Without limitations
Validation	No	No	Verification
Determination limit	ppm to sub-ppm	ppm to sub-ppm	ppm to sub-ppm
Quality standard	State of the art	State of the art	GMP
Suitability	Risk analysis (raw materials and intermediates)	Risk analysis (raw materials and intermediates)	Risk analysis complying with GMP (raw materials, intermediates and final products) as well as routine approvals of raw materials

the risk of potential elemental impurities of the final product by starting materials or the manufacturing process. The basis for this risk analysis form either empirical values or overview analyses of the substances concerned. For this purpose, Interlabor Belp AG has developed a screening method that can quantify up to 70 elements over a wide working range (option A). The method can be applied to both raw materials and intermediates as well as to final medicinal products in order to determine whether the contaminant content is well below the limit value, potentially endangering or even exceeding the limit value. It is also possible to carry out the screening with a reduced scope (option B and C) where only the 24 elements affected by the ICH Q3D guidelines are examined (see 1). Since the measuring range of the methods described in the Ph.Eur. and UPS is severely restricted (50 % – 150 % of the limit value), this form of pre-screening means an eminent surplus value and is definitely recommended.
Moreover, thanks to the screening data, the number of elements which must be taken into account in the analytical concept for the final pharmaceutical product can be justified, which makes it significantly more time- and cost-effective.

Elemental analytics for intermediates and final products under GMP

For the analysis of elemental impurities in intermediates intended for sale and final medicinal products, a product-specific verification or full validation of the ICP-MS method is recommended. Interlabor Belp AG relies on the requirements of the USP “Elemental Impurities – Procedures” as well as the Ph.Eur. 2.4.20 “Determination of metal catalyst or metal reagent residues”. Both chapters describe the requirements for the analytics and the scope of validation. There are no significant differences between the conditions of Ph.Eur. and USP. In contrast to other residue determinations, simplified acceptance criteria are valid for the validation of the analytical method for the determination of elemental contaminants (see 2).

2 Validation acceptance criteria according to USP <233> and Ph.Eur. 2.4.20

Parameters	Acceptance criteria
Accuracy $n = 3 \times 3$ levels (50 %, 100 %, 150 %)	70 % – 150 % (Mean value per level)
Repeatability $n = 6$ (100 %)	≤ 20 % RSD ($n = 6$)
Laboratory precision (other day, other analyst or other measuring device) $n = 6$ (100 %)	≤ 25 % RSD ($n = 12$), data from both precision series
Specification, linearity, limit of quantification (LoQ)	Complies with accuracy and precision
Work area	50 % – 150 %

For determining the limit values of the 24 elements, ICH Q3D distinguishes between three forms of administration (oral, parenteral, inhaled) and the maximum daily dose is taken into account. Based on this data and the PDE (Permitted Daily Exposure) in [µg/day] (see 3), the product-specific limit value is determined. For example, the PDE of cadmium is for oral administration at 5 µg/day. If the maximum dosage of the active substance is 10 g/day, a product-specific limit value of 0.5 ppm (µg/g) is obtained. The product-specific limit is consequently lower, the higher the maximum daily dose is, respectively, reversed.

3 PDE (Permitted Daily Exposure) according to ICH Q3D, table A.2.1

Analyte	PDE oral [µg/day]	PDE parenteral [µg/day]	PDE inhaled [µg/day]
Antimony (Sb)	1200	90	20
Arsenic (As)	15	15	2
Barium (Ba)	1400	700	300
Cadmium (Cd)	5	2	2
Chrome (Cr)	11000	1100	3
Cobalt (Co)	50	5	3
Copper (Cu)	3000	300	30
Gold (Au)	100	100	1
Iridium (Ir)	100	10	1
Lead (Pb)	5	5	5
Lithium (Li)	550	250	25
Mercury (Hg)	30	3	1
Molybdenum (Mo)	3000	1500	10
Nickel (Ni)	200	20	5
Osmium (Os)	100	10	1
Palladium (Pd)	100	10	1
Platinum (Pt)	100	10	1
Rhodium (Rh)	100	10	1
Ruthenium (Ru)	100	10	1
Selenium (Se)	150	80	130
Silver (Ag)	150	10	7
Thallium (Tl)	8	8	8
Tin (Sn)	6000	600	60
Vanadium (V)	100	10	1

Interlabor Belp AG offers two different verification and validation options for elemental analysis within the scope of ICH Q3D under GMP, which diverge considerably in terms of work and costs (see 4). Regardless of which option is selected, a screening with a wide measuring range should be carried out beforehand; it serves as a sound data basis for the determination of the number of elements to be examined. The first option for product-specific verification is an alternative to product-specific full validation. A basic validation of the ICP-MS method for three typical matrices (organic compound, plant drug and inorganic compound) is provided and used as a basis for performing a product-specific verification with a reduced scope (recovery experi-

4 The key factors of the two different options for routine analysis under GMP

Validation	Option D (verification)	Option E (full validation)
Number of elements	1 – 24 (ICH Q3D)	1 – 24 (ICH Q3D)
Method	ICP-MS	ICP-MS
Measuring range	50 – 150 % of the limit value according to EP/USP	50 – 150 % of the limit value according to EP/USP
Validation	Yes, verification	Yes, validation
Determination limit	50 % of the limit value according to EP/USP	50 % of the limit value according to EP/USP
Quality standard	GMP	GMP
Suitability	Routine analytics under GMP of intermediates and final products with verified method	Routine analytics under GMP of intermediates and final products with validated method

ments (n = 6) spiked on the limit values for the parameters accuracy, precision & specificity).

The documentation contains the data for the basic validation as well as the product-specific verification. The advantage of this approach is the reduced effort with regard to documentation and practical laboratory work compared to product-specific full validation. However, the significance of the data is dependent on the comparability of the matrices from the basic validation and that of the product. In order to rule out any potential risk associated with the non-identical matrices, however, it is necessary to carry out a product-specific full validation with the validation scope according to the specifications of the medicinal products (see 2). Both options allow routine analysis within the framework of GMP for 1 to 24 elements.

Outlook

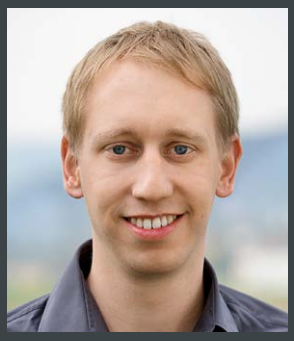
For a long-term successful implementation of the ICH Q3D guidelines, in addition to detailed knowledge about product and manufacturing process specific analytical know-how is indispensable in practice. On the one hand, an analytical concept must be developed at the outset; on the other hand, monitoring of the product quality with regard to elemental impurity must be ensured by means of appropriate control strategies in routine analysis. □

Literature

1) *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf*

2) *https://www.gmp-verlag.de/de/gmp-news/gmp-aktuell/ICHQ3D-finale-version-metallische-verunreinigungen/page/9.html*

About the author



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