ELEMENTAL IMPURITIES

IN PHARMACEUTICALS

QUALIMETRIX

Analytical Laboratories - Quality Control

ICH Q3D Guideline

QMX stepwise approach

Qualimetrix is a customer-driven CRO that employs the Six Sigma philosophy in order to design and implement optimized processes with the aim of transforming customer inputs and requirements into "customer value". As such, the first and probably the most critical factor for a successful project is its proper definition in terms of both customer and technical requirements. To this end, a comprehensive study request form is provided to the customer with the following objectives:

- ✔ The definition of the type and scope of the study
- ✔ The provision of critical product information
- ✔ The determination of the most suitable, expedient and cost-effective approach

A customized excipient supplier form (template extracted by IPEC-Americas) is also provided to the customer in order to be filled by the excipient suppliers with all information available. The template provides a standardized format to collect information relative to Class 1, 2A, 2B and 3 elements of the ICH Q3D guideline. This information is a key part of the risk assessment process to determine the excipients of concern and thus implement an effective control strategy should the elemental impurities' levels are found to exceed the control threshold.

Risk assessment approach

Approaches to Risk Management according to the Draft EMA document "Implementation strategy of ICH Q3D guideline"

- ✔ Drug Product Approach

"The manufacturer will scan batches of the drug product for the presence of any elemental impurities to be able to do a risk assessment to support risk management and to justify a control strategy. Where necessary the control strategy will include specification(s) to the drug product tested by a validated analytical approach. **Analytical data only, without a risk assessment, will not be sufficient and the justification to omit a routine control will with this approach have to be more extensive than just data from a few batches"** ·

✔ Component Approach

"With this **preferred approach**, the contribution of elemental impurities from each component is assessed and summarised and the combined contribution of an element is compared with the PDE risk assessment and if necessary handled in the subsequent risk management and the establishment of a control strategy"

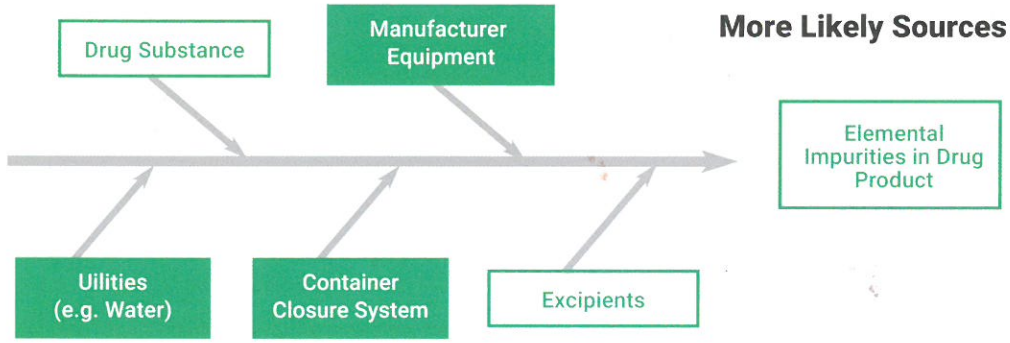
Based on the above, in cases where there is a significant lack of essential information and data that can substantiate the component approach, the evaluation stage will be performed according to the drug product approach. However, the assessment of all potential sources of elemental impurities during the identification stage and their prioritization based on a hybrid FMEA and Risk ranking and filtering approach aims at facilitating the investigation and the subsequent establishment of additional measures / controls, in case the elemental impurity levels exceed the control threshold (30% of the PDE). The risk assessment approach implemented is in fact a combination of the component approach and the drug product approach. The evaluation stage will be based on the determination of the identified metals in 3 commercial batches of the final product (or 6 representative pilot scale lots) due to the insufficient data that hinder the estimation of elemental impurities levels for the different components and in order to establish the level and variability of the identified metals.

It should be noted that in cases where no sufficient information / data are available regarding the likelihood of presence of specific metals or where either limit or no tests are employed, the final drug product will be tested for class 1, 2A and class 3 metals in order to mitigate for the underlying uncertainty and cover for a worst-case scenario which could emanate from an unpredicted increased bioavailability and/or local effects of any of the elements.

Risk assessment steps

Identification

✔ The first step of the risk assessment process comprises of the identification of known and potential sources of elemental impurities that may find their way into the final product. Figure 1 below illustrates potential sources that will be considered during the evaluation.



✔ A Failure mode and effect analysis (FMEA) is performed in order to identify and assess the risk associated with each potential source of elemental impurities.

- FMEA is a highly structured, systematic technique for failure analysis. It involves the review of all components depicted in Fig.1 in order to identify failure modes and their effects.
- For each component, their failure modes and their resulting effects are recorded in a standardized FMEA sheet.
- Each failure mode is associated with a material, process or parameter that could serve as a source of elemental impurities.

- The failure effects correspond to the metals that could emanate from each source.

- The degree of severity (SEV) of the effects, their respective probabilities of occurrence (PROB), and their detectability (DET) are assessed by assigning numerical values according to a pre-defined scoring system.

- An additional weight factor (weight) is applicable for the API and excipients, based on their % proportion with respect to the total formulation weight, according to the following table. An illustrated example of the FMEA approach is depicted in Figure 2

✔ A Risk ranking and filtering approach is adopted in order to compare and rank risks. The final risk score (RPN) is calculated according to the following formula:

$$RPN = SEV \times PROB \times DET \times Weight$$

Risk Prioritization and Metals of Interest

✔ The FMEA process that is applied for all potential sources of elemental impurities, with respect to the final product, will result in a ranking similar to the one presented in the following table

Table 1: Elemental impurities sources ranking

Source of Metal	RPN
Titanium Dioxide	375.0
Kaolin, heavy	75.0
Sorbitol, liquid	50.0
Sodium polyacrylate	37.5
Carmellose sodium	37.5
API	33.2
Povidone (K90)	25.0
Disodium Edetate	25.0
Manufacturing Equipment	25.0
Methyl parahydroxybenzoate	10.0
Propyl parahydroxybenzoate	10.0
Water	10.0
Container closure	10.0
1,3-Butylene glycol	7.5
Gelatin	7.5
Tartaric acid	5.0
Aluminium glycinate	5.0
Polysorbate 80	5.0
Utilities	5.0
Propylene glycol	1.0

✔ The final ranking is based on the RPN value that reflects the risk associated with each potential source. The resulting table serves as a guide / tool, in the event that the elemental impurity levels exceed the control threshold (30% of the PDE), in order to focus all further investigation efforts and subsequent controls on the sources of higher risk (e.g. Titanium dioxide)

✔ The elements to be considered in the risk assessment emanate from Table 2 below (extracted from Table 1 of the ICH Q3D guideline) in conjunction with the metals identified as likely to be present during the components evaluation.

Table 2: Elements to be considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			oral	parental	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

Evaluation / Summary and Control Strategy

- ✔ The Component Approach (Option 2B): The levels of the identified elemental impurities are estimated / predicted based on data, provided by the suppliers, generated from similar processes, published literature and / or testing of the individual components
- ✔ The Drug Product Approach (Option 3): Using the data from the drug product testing results, obtained from 3 commercial or 6 pilot scale batches, the observed elemental impurities are calculated as a total daily amount based on the total daily dose of the drug.

Daily amount of E.I. = impurity conc.(µg/g)×mass of drug (g/day)

- ✔ The total daily amount of each elemental impurity is compared with the established Permitted Daily Exposure value (PDE)[1]. Elemental impurities consistently below the control threshold (30% of the PDE) do not require additional controls. Elemental impurities that exceed the control threshold require additional evaluation during the development of the controls.

[1] *Or proposed Acceptable Levels (AL) for those routes of administration not included in ICH Q3D*

Figure 2: Failure Mode and Effects Analysis for Excipients

Source of Metal	Failure Mode (Material or Parameter)	Comments / Justification	Failure Effects / Metals of Interest	SEV	Current limits	PROB	Controls	DET	Prop.	Weight	RPN
Excipients	Sorbitol, liquid	Plant derived	No metals are identified as likely to be present (refer to supplier form)	1	Pb: NMT 0.5 ppm Ni: NMT 1 ppm	5	Limit tests reported on CoA	5	40	2	50
	1,3-Butylene glycol	N/A	No metals are identified as likely to be present (refer to supplier form)	1	Heavy metals: NMT 5 ppm	1	Limit tests reported on CoA (Japanese pharmaceutical excipients)	5	10	1,5	7,5
	Sodium polyacrylate	Synthetic / The probability of presence for all metals apart from As and Pb is characterized as "unknown" (refer to supplier form). To this end the general approach employed for the API will be applied with respect to the metals of interest	Class 1: As, Pb, Cd, Hg Class 2A: V, Co, Ni Class 3: Li, Sb, Ba, Mo, Cu, Sn, Cr	5	Heavy metals: NMT 20 ppm As: NMT 2 ppm	1,5	Limit tests reported on CoA (JP Excipients)	5	4	1	37,5
	Kaolin, heavy	Mined / As, Pb, Ba, Cr, Mo are characterized as "Likely to be present" (refer to supplier form). Se has not been included due to the fact that it is a Class 2B element which has not been intentioanally added according to the supplier	Class 1: As, Pb Class 3: Ba, Mo, Cr	5	Extractable heavy metals: NMT 50 ppm	15	Limit test reported on CoA (EP) ICP-MS conc. for As, Cd, Hg, Pb, Co, Ni, Se, Ba, Cr, Cu, Li, Mo, Sb, reported on supplier form (refer to form)	1	3	1	75
	Carmellose sodium	Plant derived / Synthetic	Class 2A: Ni Class 3: Cr	5	Heavy metals: NMT 20 ppm Ni: NMT 1 ppm Cr: NMT 1 ppm	7,5	Limit test reported on CoA (EP) AAS max. conc. for Ni and Cr reported on supplier form (refer to form)	1	3	1	37,5
	Propylene glycol	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	Heavy metals: Limit value not given	1	Limit test reported on CoA (EP) ICP-MS conc. for As, Pb, Ni, Cr, Cu, Li, Sb, Sn and EDX conc. For Cd, Hg reported on supplier form (refer to form)	1	3	1	1
	Gelatin	Animal origin / As,Cr, Cu are characterized as "Likely to be present" (refer to supplier form). The probability of presence for all other metals is characterized as "unknown" (refer to supplier form). To this end the general approach employed for the API will be applied with respect to the metals of interest	Class 1: As, Pb, Cd, Hg Class 2A: V, Co, Ni Class 3: Li, Sb, Ba, Mo, Cu, Sn, Cr	5	Cr: NMT 10 ppm	1,5	Limit test reported on CoA (EP) ICP-OES conc. for As, Cd, Hg, Pb, Co, Cr, Cu, Sn and ICP-MS conc. for Ni, V, Ba, Li, Mo, Sb reported on supplier form (refer to form)	1	2	1	7,5
	Povidone (K90)	Synhetic	A statement has been provided by the supplier (BASF) declaring that no class 1,2 or 3 metals are likely to be present	5	Heavy metals: NMT 10 ppm	1	Limit test reported on CoA (EP)	5	2	1	25
	Tartaric acid	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	Heavy metals: Limit value not given As: NMT 1 ppm Pb: NMT 10 ppm	1	Limit test reported on CoA (EP) Maximum values for As and Pb according to JP17 are reported on supplier form (refer to form)	5	0,5	1	5
	Titanium Dioxide	Mined / As, Pb, Cr, Sb are characterized as "Likely to be present" (refer to supplier form). All Class 2B metals have not been included due to the fact that they have not been intentionally added according to the supplier. The probability of presence for several class 3 elements is characterized as "unknown" (refer to supplier form). To this end these metals will be included in the metals of interest (Li, Mo, Sn)	Class 1: As, Pb, Cd, Hg Class 2A: V Class 3: Li, Mo, Sn, Cr, Sb	5	Heavy metals: NMT 20 ppm Sb: NMT 100 ppm As: NMT 5 ppm Ba: Limit value not given	15	Limit tests reported on CoA (EP/JP) AAS max. conc. for As, Cd, Pb, Co, Ni, Se, Cr, Cu, Sb and ICP max. conc. for Hg, Ba reported on supplier form.	5	0,5	1	375
	Aluminium glycinate	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	Heavy metals: Limit value not given As: Limit value not given	1	Limit tests reported on CoA (Japanese pharmaceutical index)	5	0,3	1	5
	Polysorbate 80	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	Heavy metals: Limit value not given	1	Limit tests reported on CoA (EP)	5	0,2	1	5
	Disodium Edetate	Synthetic / The probability of presence for all metals apart from Cu and Pb is characterized as "unknown" (refer to supplier form). To this end the general approach employed for the API will be applied with respect to the metals of interest	Class 1: As, Pb, Cd, Hg Class 2A: V, Co, Ni Class 3: Li, Sb, Ba, Mo, Cu, Sn, Cr	5	Heavy metals: NMT 20 ppm	1	Limit tests reported on CoA (EP)	5	0,123	1	25
	Methyl parahydroxybenzoate	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	No Limits	1	No control applied	10	0,1	1	10
	Propyl parahydroxybenzoate	Synthetic	No metals are identified as likely to be present (refer to supplier form)	1	No Limits	1	No control applied	10	0,05	1	10
	Water	EP Purified water is employed / Controlled by GMP (refer to GMP certification)	Class 1: As, Pb, Cd, Hg Class 2A: V, Co, Ni Class 3: Li, Sb, Ba, Mo, Cu, Sn, Cr	1	Heavy metals: Limit value not given	1	Limit tests reported on CoA (EP)	5	29,9	2	10

Elemental impurities excluded from the risk assessment

✔ No further consideration

Elemental impurities that may be present below the control threshold (30% of the PDE) in the drug product

✔ No further investigation is required provided that the applicant has ***appropriately assessed*** the data and ***demonstrated adequate controls*** on elemental impurities

Elemental impurities that may exceed the control threshold but do not exceed the PDE in the drug product

✔ Additional control(s)[1] should be defined and established

Elemental impurities that may exceed the PDE in the drug product

✔ Justify higher levels
✔ Define additional control[1] / purification step

[1] In order to setup additional controls, the identification of the major source(s) of elemental impurities is of paramount importance. To this end, the combination of FMEA and Risk Ranking and Filtering methodology serve as useful aids for the prioritization of all potential sources and therefore constitute an integral part of the risk assessment process.

Control of Elemental Impurities in Pharmaceuticals – "Paradigm shift"

Impact on Ph.Eur. monographs and methods of control

In the frame of the holistic control strategy, mandated by the ICH Q3D, that focuses on the final product, numerous texts in the European Pharmacopoeia will be revised. According to EDQM's recent update on the Ph. Eur. policy on elemental impurities, the revised texts are to be published in Supplement 9.3 with an implementation date of 1st January 2018. The revision plan will include the following general texts:

- ✔ General chapter 5.20 Elemental Impurities
- ✔ General monograph on Pharmaceutical Preparations (2619)
- ✔ General monograph on Substances for Pharmaceutical Use (2034)
- ✔ General method 2.4.20 Determination of elemental impurities

Regarding the fate of specific elemental impurities tests the Ph. Eur. commission has decided to keep the published specific elemental impurities test in monographs on substances of natural origin only. Specific elemental impurities tests will be deleted from monographs on other substances (i.e. not from natural origin), unless otherwise justified. In particular, the Ph. Eur. Commission decided that, unless otherwise justified, specific tests for elemental contaminants originating from the production process will be deleted. As these elemental impurities are specific to the production process, they will remain the responsibility of the substance manufacturer.

General method 2.4.20 Determination of metal catalyst or metal reagent residues, makes the following statements:

"As a reference procedure is not provided for each metal, matrix and concentration, the choice of procedure, including sample preparation, detection technique and instrument parameters, is the responsibility of the user"

"All suitable sample preparation methods and measurement techniques can be used for the determination of metal residues, if the method has been verified before the initial use by a system suitability test or a validation procedure.
If no sample preparation and/or measurement method is described in the specific monograph, a suitable sample preparation and/or measurement method must be developed and validated"

The above information under the prism of the ICH Q3D "philosophy" emphasize the importance of having reliable data with respect to the elemental composition of the raw materials (e.g. API, excipients) associated with a specific final product. To this end, Qualimetrix provides analytical services for routine testing of raw materials and final products (i.e. quality control testing, stability testing and GMP batch release testing) in accordance with the general chapters of USP, 232 and 233 and the general method 2.4.20 of the European Pharmacopoeia. The analytical methods are developed and customized according to the clients' requirements and the special considerations that should be taken into account for each different matrix in terms of sample preparation and instrument parameters. Validation is a pre-requisite for the implementation of any method for testing, according to the requirements set by the relevant compendial chapters, in order to establish that the applied methodology is suitable for its intended use / purpose.

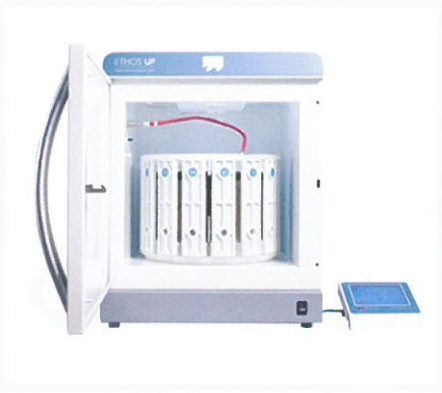
Instrumentation / Software
Laboratory Infrastructure and Equipment

✔ **Laminar Flow Work Bench:**

Provides sufficient operator protection and improved product protection in terms of contamination from ubiquitary elements (e.g. Fe, Cu from operators or Fe, Cr, Ni from corrosion of metal parts of conventional fume hoods). The Heraguard ECO clean bench installed provides both effective sample protection and clean validated air conditions

✔ ***Closed-vessel microwave digestion:***

Chapter <233> recommends the use of closed-vessel microwave digestion to completely destroy and dissolve insoluble matrices. Microwave digestion systems are the method of choice for the purpose of getting insoluble samples into solution, because they are simple to use and can rapidly process many samples in parallel, which makes them ideally suited for high sample throughput applications. The ETHOS UP system employed at our lab is specifically designed for closed vessel acid digestion as it offers a perfect integration between microwave hardware, user interface, reaction sensors and pressure vessels.



✔ ICP-MS

The NexION 350 of Perkin Elmer, employed at our CRO, provides exceptional stability and productivity as it includes an array of technical innovations that reduce background and interferences, optimize signal stability, minimize maintenance requirements and downtime and generate better results.

- The "Triple Cone Interface produces a focused ion beam and prevents sample deposition on internal components
- Quadrupole Ion Deflector turns positively charged ions 90° into the Universal Cell and filters off neutrals
- The "Universal Cell Technology" brings together the simplicity and convenience of a collision cell and the exceptional detection limits of a true reaction cell in a single ICP-MS instrument.
- The auto-sampler significantly reduces analysis times by optimizing the sample delivery process to reduce the pre- and post-measurement times.

✔ Method Validation Tool

The method validation tool provided by Perkin Elmer ensures data integrity and GMP compliance in accordance with the requirements of EU GMP Annex 11 and 21 CFR part 11.

The tool employed significantly accelerates the validation process since it automatically imports all Method Validation data while it calculates and summarizes:

- Batch Drift Checks
- Accuracy (Standards)
- Accuracy (Sample Spikes)
- Repeatability
- Ruggedness

The tool is GMP-compliant since:

- A detailed SOP covers the operation and validation of the excel.
- The tool has been developed according to a design specification (DQ) and User Requirement Specifications (URS).
- Validation has been carried out according to a formal test plan in compliance with FDA guidance on using Excel.
- All calculations have been manually checked.
- All tables in the tool output are locked and password protected eliminating risk of data falsification.
- The tool has been installed by the official and qualified supplier and a specific IQ/OQ has been performed to ensure 21 CFR part 11 and EU GMP Annex 11 compliance.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