Implementation of ICH Q3D in EU and US

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Implementation of ICH Q3D in EU and US

- Elemental Impurities, new in our lives?
- ICH Q3D
- The two approaches
- EMA and EDQMs guidance
- Guidance in the US
- Practical implications for API suppliers
- Conclusions

Elemental impurities – new in our lives?

- This sword was found in my home town (Oss) and dates back to 700 bC. Consists of iron and gold

Elemental impurities – new in our lives?

- The “big four”, namely cadmium (Cd), lead (Pb), mercury (Hg) and arsenic (As) are considered to be the most toxic elements in this category. Yet, we still use them in our daily lives

Elemental impurities – new in our lives?

- Even in our tap water certain amounts of these most toxic elemental impurities are deemed acceptable. According to the Dutch law the maximum allowable limits are:

- Cadmium nmt 5.0 µg/l
- Lead nmt 10 µg/l
- Mercury nmt 1.0 µg/l
- Arsenic nmt 10 µg/l

- So, following the advice to drink at least two liters per day, …or taking your oral medication with a glass of water…

Elemental impurities – new in our lives?

If we look at food, there is a European law (1881/2006) that uses the following maximum allowable amounts for humans:

- Cadmium 7 µg/kg body weight/week. For an average 60 kg person this means 60 µg/day.
- Lead 25 µg/kg body weight/week. For an average 60 kg person this means 214 µg/day.
- Mercury 1.6 µg/kg body weight/week. For an average 60 kg person this means 14 µg/day.

Elemental impurities – new in our lives?

- I think we can safely conclude that elemental impurities are already part of our daily lives for many many years

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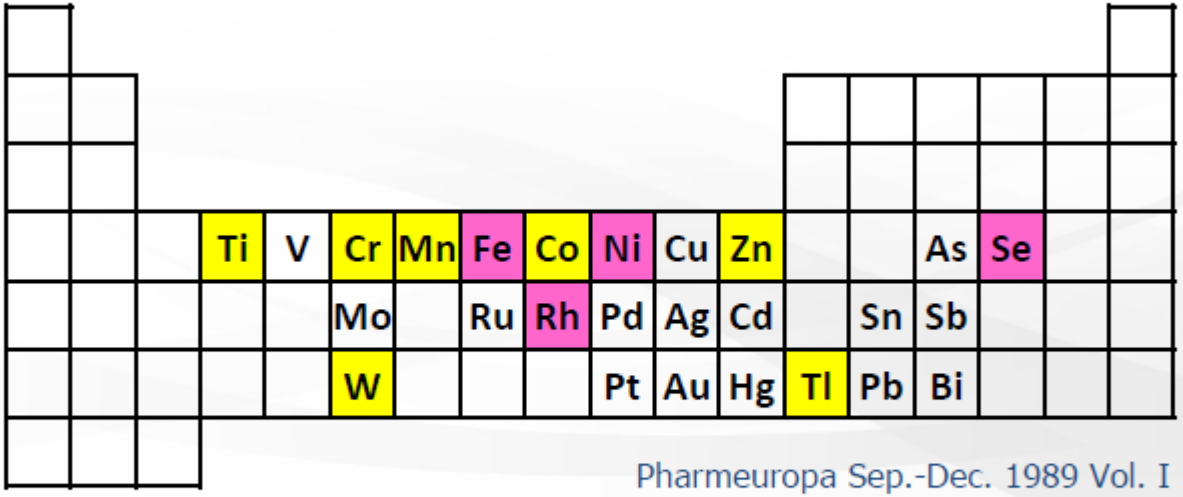
ICH Q3D

- Elemental impurities are toxic (although the level of toxicity may vary)
- In most cases there is no therapeutic benefit
- Therefore, there is a need to limit these substances
- Already for a long time this was covered (partly) by the so-called heavy metals test which was incorporated in a large number of pharmacopoeial monographs

- Disadvantages of the heavy metal test :
  - limit test for a total, no information for specific elements
  - not all relevant elements were picked up by this method
- There was a need for more state of the art analytical methods and for more relevant specifications

ICH Q3D

Ph. Eur. General Method 2.4.8. Heavy metals



Pharmeuropa Sep.-Dec. 1989 Vol. I

(rare metals not verified in this study)

⇨ Specific methods should be used

ICH Q3D

- EMA was the first authority to draft a guideline for what was at that time still called “residues of heavy metal catalysts or metal reagents”
- As you can see from the name, only two types of contribution were considered

- Lots of comments from industry organizations (including APIC) on the first draft plus a request from Industry to use a similar approach as the ICH residual solvents guideline. This was indeed done for the final version.

ICH Q3D

- In 2010, USP drafted revisions of chapters <232> (Elemental Impurities-Limits) and <233> (Elemental Impurities-Procedures), to become effective per 2015.
- Allthough USP stated that their proposals were based on the EMA guideline, the USP proposals were absolutely not the same which made it very hard to determine what limits (if any) should be implemented.The EMA guideline offered the possibility of an “option 2“ calculation when the daily dose was below 10 grams per day. No mandatory routine testing was required.
  The USP described the so-called „big four“ (arsenic, cadmium, lead and mercury), which should always be tested.

ICH Q3D

- In order to have one global guideline and to avoid the need for testing different parameters for different regions, there was a call to ICH to pick up this topic.
  In 2013, ICH started to work on this topic, and by the end of 2014 the step 4 document was published.

- USP and EMA in the meantime postponed their implementation date and now follow ICH.

ICH Q3D

Framework:

Four classes of elements have been defined:

- Class 1 As, Cd, Hg and Pb, typically originating from mined excipients or mined reagents. Always to be addressed in the risk assessment.
- Class 2A Co, Ni and V, high probability of occurrence. Always to be addressed in the risk assessment.
- Class 2B Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl, low probability of occurrence. Only to be addressed in the risk assessment when intentionally added during the manufacture of Drug Substance, excipients or other components of the drug product.

ICH Q3D

Framework:

- Class 3 Ba, Cr, Cu, Li, Mo, Sb and Sn, relatively low toxicity. May require risk assessment for inhalation and parenteral routes. For oral applications these only need to be considered when intentionally added during the manufacture of Drug Substance, excipients or other components of the drug product.

- So, the route of administration and the toxicity of the metal concerned determine wether the metal needs to be considered in the risk assessment.
- Class 1 and 2A always need to be considered, Class 2B only if intentionally added and for Class 3 it may depend on the route of administration.

ICH Q3D

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	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

ICH Q3D

The following potential sources of elemental impurities need to be considered by the finished dosage form manufacturer:

- Residues from elements intentionally added in the production of Drug Substances, excipients or other drug components.
- Elements that are not intentionally added but are potentially present in the drug substance, water or excipients used in drug product manufacture.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from the container closure systems (does not apply to solid substances).

ICH Q3D

- So, for the risk assessment one needs to consider which elemental impurities may find their way into the finished dosage form from either contributing source.
- The presence of such an elemental impurity may then be predicted or measured and the outcome needs to be compared with the Permitted Daily Exposure (PDE). Note: this can thus be a „paper exercise“ by the finished dosage form manufacturer! The outcome may be that additional controls are necessary, but obviously often the outcome will be that no additional controls are needed (control only needed when predicted levels are >30% of the PDE).
- The risk assessment must be documented.

ICH Q3D

Element	Class	Oral µg/g	Parenteral µg/g	Inhalation µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
AS	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Ti	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

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The two approaches

In principle there are two approaches which can be used:

1.Drug Product Approach –
the drug product manufacturer analyses several batches of drug product on the levels of each element in order to be able to perform a risk assessment and to justify a control strategy.

2.Component Approach –
the drug product manufacturer collects information from the suppliers of the various components (including APIs and excipients) and performs the “paper exercise” risk assessment, in this case there is no need for the drug product manufacturer to perform screening testing.

The Q3D guideline also allows for data from published literature and data generated for similar processes as sources of information

The two approaches

The Drug Product Approach

If the drug product manufacturer uses the first approach, a number of batches of drug product needs to be screened to see which elements are present at what levels.

Another possibillity is to screen all components that could add to the Drug Product.

As in such case the finished dosage form manufacturer does not know what to look for, he needs to test on all the elements.

This is obviously a difficult exercise!

The two approaches

The Drug Product Approach (continued)

In EU and US some companies have worked together in consortiums e.g. by sharing information on excipients commonly used.
In most cases the excipients are the major contributors of elemental impurities in the Drug Product.

It is obvious that the tests need to be repeated when new suppliers of excipients or drug substances are introduced or when the suppliers inform of major changes to their processes.

The two approaches

The Component Approach

In the component approach, the Drug Product manufacturer collects the information from all suppliers.

If he gets full information, he is able to do a “paper exercise” calculation to determine whether any specifications are necessary for the Drug Product.

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EMA and EDQMs guidance

- The EMA guidance “Implementation strategy of ICH Q3D guideline” was adopted in December 2016 (EMA/CHMP/QWP/115498/2017).
- In this guidance both approaches are described
- It is thus recognized by the guideline that sometimes it may be hard (or even impossible) to obtain information from all suppliers.

EMA and EDQMs guidance

- It is notable that specific emphasis is put on APIs, where at the same time it is noted that excipients may originate from natural (mined) origin with a higher potential of elemental impurities being present.
  Obviously, in practice APIs do often not represent the largest contribution to the finished dosage form.
- It is extensively described how a risk evaluation can be made by the API producer (obviously related to the Component Approach).

EMA and EDQMs guidance

- The EMA guideline also specifically addresses the use of intentionally added elements (usually in the form of a catalyst) during API manufacturing processes.
  When such a catalyst is added during the last synthetic step it should be proven that the elements are purged to levels consistently below the threshold (which is 30% of the Permitted Daily Exposure (PDE).

EMA and EDQMs guidance

- EDQMs guideline (PA/PH/CEP (16) 23, 1R, adopted in August 2016, last revision July 2018, is a more detailed guideline, as it also covers the “how to do” aspects of filing such a risk evaluation for APIs.
- In the EDQM guidance two options are described for the CEP:
  * provide a risk evaluation
  * not provide a risk evaluation.

EMA and EDQMs guidance

- The guideline describes both options and provides information on how the information on EIs will be reflected on the CEP.

- In case of a risk evaluation, the outcome will be appended to the CEP in the format of a table (note: the CEP holder needs to draft this table).

- If there is no risk evaluation, EDQM will state on the CEP whether any elements are intentionally added during the production process.

EMA and EDQMs guidance

- Unfortunately both guidelines do not give much information on “how far should you go”…
- In the end, the amount of EIs in the drug product is the only relevant parameter and the API is only one of the contributors.
- Is there a need to address all reagents, auxiliary materials and solvents used?
  Suppliers of this type of materials are not happy with requests for information on EIs that could potentially be present in their products and do not provide information.
- Moreover, the EMA guideline describes for intentionally added elements that the risk of carryover to the API should be considered for catalysts used in the last step of the synthesis. Is there then a need to go further for other materials?

EMA and EDQMs guidance

- The combination of these aspects shows that there should also be some special consideration for the solvent used for the final crystallization.

- For the equipment used, normally API manufacturers would adapt their equipment to the type of chemistry performed (glass lined vessels vs stainless steel vessels).
- The equipment used for micronization, (where applicable) needs to be considered, as this represents the highest risk of contributing to EIs in the API.

- The container closure system should only be discussed in case you are dealing with a non-solid API.

EMA and EDQMs guidance

- Both guidances, although they do describe the two options, strongly focus on the risk evaluation provided by the API manufacturer.

- Current practice is thus that the drug product manufacturers demand such information.

- As the risk evaluation needs to be confirmed by actual data, this forces the API producer to perform testing (screening), even when this is inappropriate for the API concerned.

EMA and EDQMs guidance

- According to the EDQM guideline minimal information on the screening method is needed: method principle (e.g. ICP/MS) and a LOD/LOQ for this method.
- In case a limit test is used for the screening (this is often done), no real LOD/LOQs are available. This should be explained.
- There is no need to fully validate the methods (unless they are to be used in routine release analysis)

- In the guidelines it is stated that the option 2 approach (calculating maximum allowable concentrations) is mandatory for daily doses over 10 grams per day. It is also acceptable to use this approach for lower daily doses (e.g. for highly active APIs).

EMA and EDQMs guidance

- For highly active APIs, which are used in the magnitude of µg per daily dose, the risk assessment is thus a bit overdone.

- As an example: ethinyl estradiol is a synthetic hormone for which the most frequent use is in oral contraceptives, where the dose is usually between 20 and 40 µg per day.
  The highest daily dose of ethinyl estradiol described in literature is 3 mg per day (oral) for the palliative treatment of malignant neoplasm of the prostate.

EMA and EDQMs guidance

- Taking this 3 mg per day daily dose into account one gets funny figures. If you recalculate the acceptable concentrations for this lower daily dose it will look completely different.
  Between brackets the values for the Option 1 concentrations.

Element	Class	Oral concentration µg/g	Parenteral concentration µg/g	Inhalation concentration µg/g
Cd	1	1666 (0.5)	667 (0.2)	667 (0.2)
Pb	1	1666 (0.5)	1666 (0.5)	1666 (0.5)
As	1	5000 (1.5)	5000 (1.5)	667 (0.2)
Hg	1	10000 (3)	1000 (0.3)	333 (0.1)

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Guidance in the US

The FDA has published the following “rules”:

As of January 1, 2018:

- All new and existing NDAs and ANDAs for drug products with an official USP monograph are required to meet the requirements in USP General Chapters <232> and <233> for the control of elemental impurities.
- Applicants submitting NDAs and ANDAs for drug products without a USP monograph are expected to follow the recommendations in the ICH Q3D Elemental Impurities guideline.

Guidance in the US

- For marketed drug products not approved under an NDA or ANDA (e.g., nonprescription over-the-counter (OTC) drug products marketed under an FDA OTC monograph), compendial products are expected to meet the requirements in General Chapters <232> and <233>; those that do not have an official USP monograph should follow the recommendations in ICH Q3D.

Guidance in the US

- In August 2018 a guidance was published: Elemental Impurities in Drug Products https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM509432.pdf

- On the FDA website there is a specific section dedicated to elemental impurities, including some questions and answers https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm590075.htm

Guidance in the US

- The most important thing to know is that –allthough FDA states full compliance to the ICH guideline-, there seems to be an expectation towards the API producers. Many APIC members have received deficiency letters from FDA asking for an elemental impurities risk assessment (even though this is not required in the Drug Product Approach according to ICH).

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Practical implications for API suppliers

In case the API supplier is requested to perfom a risk evaluation, the following is a example of “how to do”.

If we consider all the contributors for EIs in the API, the following items are of importance:

- Catalysts used
- Process aids used
- Reagents used
- Solvents used
- Equipment
- Container Closure system

Practical implications for API suppliers

Catalysts used

- Catalysts are often used in API synthesis. Examples: Palladium and Platinum. It goes without saying that the API should be screened for such elements and when necessary (meaning not below than 30% of the PDE limit) a specification should be set.

Process aids used

- Since all drug product manufacturers and all patients like white powders, tablets etc often charcoal and filter aids are used in the purification steps of API synthesis. EIs that may be present in such materials need to be covered in the screening and when necessary a specification should be set. Problem: to get information from the suppliers

Practical implications for API suppliers

Reagents used

- The API supplier is expected to evaluate all reagents used on their potential to contribute EIs to the API. Also here, reagents used in the steps closer to the API are expected to contribute more than reagents used in the earlier steps of the process. Same problem: suppliers do not always cooperate.

Solvents used (including water)

- Again an evaluation is expected with more emphasis on solvents used in the final crystallization step. Again the problem that not all suppliers are willing to provide this infomation (for them the pharmaceutical market is a very small one).

Practical implications for API suppliers

Equipment used

In fact a distinction can be made here between manufacturing equipment and particle size reduction equipment.

Manufacturing equipment

- For the equipment used, normally API manufacturers would adapt their equipment to the type of chemistry performed (glass lined vessels vs stainless steel vessels). If “harsh” chemistry (e.g. extreme pH) is applied in stainless steel vessels, the contribution should be checked.
- The equipment used for micronization, (where applicable) needs to be considered, as the forces applied there represent the highest risk of contributing EIs in the API.

Practical implications for API suppliers

Container closure system

- ICH Q3D recognizes that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment. It is generally acknowledged that this also holds for solid APIs.
- If you are dealing with non-solid APIs this point should be addressed and the EIs of concern should be incorporated in the screening studies.

Practical implications for API suppliers

- As stated not all suppliers wish to give specific information on the EIs that are potentially present in their products.

- In order to be able to still address these contributors in the risk assessment it sometimes proves helpful to check their Certificates of Analysis, their websites, or to google the specific material and find some general information on the routes of synthesis.

- All EIs that are potentially present according to the risk assessment should be screened in the API.

Practical implications for API suppliers

Screening tests

- Although the analytical method to be used is not prescribed in the guidance there are some remarks about it: The method used should provide quantitative data. Most companies use ICP/MS or ICP/OES.

- LOD/LOQ need to be provided. However, since many companies perform the screening as a limit test, there are no “real” LOD/LOQs.
  This has been considered acceptable, both in EU and the US.

Practical implications for API suppliers

Control strategy

- After defining the elements to be considered and performing screening tests in order to get information on their presence the control strategy needs to be defined.

- Depending on the outcome of the screening it should be defined per element whether or not to include a specification. As stated the element should be consistently below 30% of the PDE threshold in order to be declared “absent”. If not absent, a specification should be set. Skip testing may be acceptable.

Practical implications for API suppliers

Pharmacopoeial specifications

- Both in EU and US, the pharmacopoeial requirements for heavy metals are in most cases deleted from the monographs.
  Of course it is the expectation that if the elemental impurities risk assessment warrants so, specific tests for relevant impurities will replace the former heavy metals test. No regulatory action is required to delete the heavy metals test.

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Conclusions

- Guidelines (both Q3D and regional EU and US guidelines) describe two acceptable approaches (the Drug Product Approach and the Component Approach) but at the same time guidelines strongly focus on this component approach.
- Drug product manufacturers therefore often request their API and excipient suppliers to perform a risk assessment and provide them with the outcome (component approach), even though ICH Q3D does not specifically require that.
- For excipients that are widely used in the Pharmaceutical industry, work has sometimes been shared between pharmaceutical companies.
- API manufacturers are often expected to do their own risk assessment and provide the information to their customers.

APIC active pharmaceutical ingredients committee
25 years of promoting patient safety