Implementing the Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents (EMEA/CHMP/SWP/4446/2000)

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List of Abbreviations

AAS	Atomic absorption spectroscopy
ADI	Acceptable daily intake
API	Active pharmaceutical ingredient
CEP	European certificate of Suitability to the Monograph of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CoA	Certificate of analysis
CPMP	Committee for Proprietary Medicinal Products
GF-AAS	Graphite furnace atomic absorption spectroscopy
GMP	Good Manufacturing Practice
EMEA	European Medicines Agency
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use
ICP-AES	Inductively coupled plasma-atomic emission spectrometry
ICP-MS	Inductively coupled plasma–mass spectrometry
JP	The Japanese Pharmacopoeia
LIMS	Laboratory Information and Management System
LOEL	Lowest observed effect level
MAA	Marketing authorisation application
MDD	Maximum daily dose
NF	National Formulary (of the United States of America, merged into one volume with USP)
NOEL	No observed effect level
PDE	Permitted daily exposure
PDG	Pharmacopoeial discussion group
PF	Pharmacopeial Forum
Ph. Eur.	European Pharmacopoeia
QP	Qualified Person
QWP	Quality Working Party
TDI	Tolerable daily intake
TTC	Threshold of toxicological concern
SWP	Safety Working Party
USP	United States Pharmacopeia

1 Introduction

Metals in medicinal products or human nutrition can be viewed in different aspects: on the one hand they are used directly as active substances in drug products to exert a beneficial effect or they are necessary as minerals or trace elements. There are lots of products on the market used as dietary supplements containing trace elements like iron, copper, zinc, selenium, manganese, chromium, molybdenum, or other. Many of these metals are essential as parts of enzymes, vitamins or cofactors. Supplementation of minerals or trace elements is needed when dietary intake is deficient and may be beneficial for compensation of deficiencies. Metals used in drug substances still have importance in modern drug therapy. For example platin compounds (cisplatin, carboplatin) are administered as highly potent anticancer drugs. Aluminium is widely used in antacids, iron is used for treatment or prevention of iron deficiency and anaemia, zinc is part of insulin zinc suspensions, cobalt is part of vitamin B_{12}, gold compounds were shown to be efficacious as antirheumatoid drugs.

On the other hand, metals in medicinal products may also be present as impurities. Contamination may arise from metals deliberately added as catalysts or reagents. Natural occurrence in source materials (e.g. in minerals or herbals) or processing equipment like vessels, pipes or metal connections to tubes or hoses may be further causes for metal residues. They may exert toxicological effects and therefore they should be excluded or limited to an acceptable threshold.

1.1 Development of the EMEA Guideline on Specification Limits of Residues of Metal Catalysts or Metal Reagents

The discussion of the guideline began in June, 1998 in the Safety Working Party (SWP) of the former CPMP.[1] The guideline was developed to recommend maximum acceptable concentration limits on metal residues to assure or improve the safety of drug products. Dealing with an interdisciplinary issue also covering the quality of drug products and their starting materials, the Quality Working Party (QWP) was involved in the further course of guideline development. Only nearly 10 years later, in February, 2008, a final version was adopted first. This long period shows that, on the one hand, the development was rather complicated for the wide range of application of all source materials. On the other hand, no serious adverse events due to metal impurities have become known during this time, so that no extraordinary pressure was given for an urgent and speedy finalisation. However, heavy metals typically have a chronic toxicological impact which might be difficult to detect and to assign to a single root cause. The advantage of a long developing duration consists in the fact that the concept of the document to deal with metal residues was allowed to mature by numerous comments and revisions prior to coming into effect.

With the publication of the **first draft[1] in January, 2001** the title read still "Note for guidance on specification limits for residues of heavy metal catalysts in active substances and medicinal products". The original restriction on “heavy metals” as “catalysts” in “active substances” and “drug products” was already changed in the following draft. Thus, it becomes clear that the range of application of the current version is by far broader. It is noteworthy, that already in the first draft of the guideline all elements were included which are covered by the final version. In addition, the information on mercury included in the first draft was not longer found in the next draft. However, beginning with the first draft the scope of the guideline covered metals likely to be present due to deliberate addition to the manufacturing process, only.

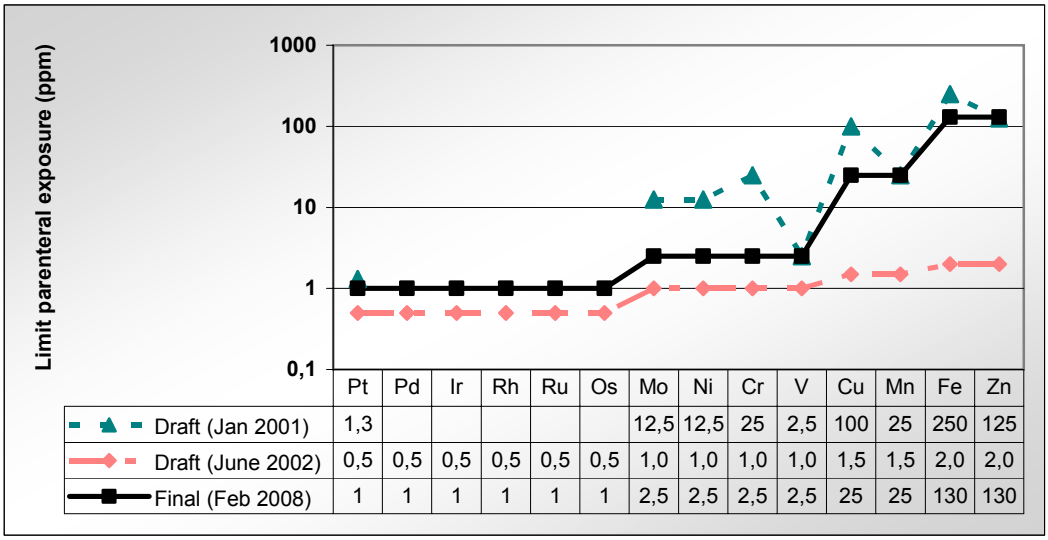
In analogy to the guideline on residual solvents (ICH Q3C(R4)),[2] the so called PDE (Permitted Daily Exposure) is used for the calculation of the concentration limits. The PDE is defined "*as the pharmaceutically maximum acceptable exposure to a metal on a chronic basis that is unlikely to produce any adverse health effect*." This concept was first introduced with ICH Q3C and is there similarly defined as "*as a pharmaceutically acceptable intake of residual solvents*". The PDE is determined by use of a body weight of 50 kg, security factors and toxicological dimensions (NOEL = No Observed Effect Level, LOEL = Lowest Observed Effect Level) or data on the typical exposure of metals like Acceptable Daily Intake (ADI) or Tolerable Daily Intake (TDI).

In the first draft of the guideline CHMP/SWP/4446/2000[1] the PDE was not yet calculated with reference to a body weight of 50 kg. Thus, the maximum acceptable concentration limits had to be calculated for the single metals not only with the daily dose but also with the body weight. However, this principle was not applied consequently: for the PDE of mercury and iron the body weight was already integrated, with mercury the acceptable intake was given per week, and not per day. All this made the calculation of specific limits complicated. Moreover, the manufacturers of active substances or excipients are not necessarily aware of the maximum daily dose of the drug product. In the final version this is simplified by introduction of an “option 1 limit”, which assumes a daily dose of 10 g and a body weight of 50 kg. Only if the daily dose of 10 g should be exceeded or the metal content should be higher than the option 1 limit, an option 2 limit will be applicable alternatively. Basis for the calculation of the option 2 limit, information on the maximum daily dose and detailed information on composition of the drug product is necessary.

In the **second draft[3] from June, 2002** the title "heavy metal catalyst" was replaced by "metal catalyst", and the terms "in active substances and in medicinal products" were deleted. This resulted in the new title: "Note for guidance on specification limits for residues of metal catalysts". The title still restricted the scope to catalysts and incorporated APIs as well as

excipients. The limits for the single metals were calculated based on a daily dose for the drug product of 10 g and a body weight of 50 kg (option 1 limit).

With this draft it was suggested that only a fraction of the PDE should be used for the calculation of the concentration limits. These percentages compensate for dietary intake as well as other sources of exposure, such as polypharmacy. Particular for the metals of the toxicological less critical classes 2 (copper and manganese) and 3 (zinc and iron), the concentration limits were thereby lowered significantly. This has undergone correction in the final version. The acceptance criteria for these metals were raised again on a level which corresponds nearly to that of the first draft (Figure 1).



	Pt	Pd	Ir	Rh	Ru	Os	Mo	Ni	Cr	V	Cu	Mn	Fe	Zn
Draft (Jan 2001)	1,3						12,5	12,5	25	2,5	100	25	250	125
Draft (June 2002)	0,5	0,5	0,5	0,5	0,5	0,5	1,0	1,0	1,0	1,0	1,5	1,5	2,0	2,0
Final (Feb 2008)	1	1	1	1	1	1	2,5	2,5	2,5	2,5	25	25	130	130

The limits regarding the draft of Jan 2001 are calculated with a body weight of 50 kg and a daily dose of 10 g

Figure 1: Comparison of the limits during the development of the guideline

After the second draft of June, 2002, one corrected version was published in December, 2002.[4] However, the acceptance criteria remained unchanged to the version of June, 2002. The next draft of this guideline was published not earlier than four years later, in January, 2007.[5] This version was completely revised and the content has developed close to the **final version of February, 2008**.[6] Compared to the draft of January, 2007, primarily the specific requirements on pharmaceutical substances with inhalation exposure have been complemented and in the title of the guideline the term “Metal Reagents” was added.

1.2 Why this guideline is necessary

Since there is no therapeutic benefit from metal residues in pharmaceutical products unless administered therapeutically they should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based criteria. For the setting of product specifications in general only pharmacopoeial monographs have set binding limits for metal residues in a material and no general guidance for pharmaceuticals was available until this guideline has been issued. A pharmacopoeial monograph does not necessarily take

into account the current manufacturing process and possibly does not cover all metals that are likely to be present in the substance. The metals used in the manufacturing process belong to the potential impurities. Hence, a need exists for uniform principles on how these impurities are to be controlled to an acceptable level. The impurities of metal residues are a special case not specifically covered in terms of qualification and providing thresholds by the ICH guidelines Q3A(R2)[7] and Q3B(R2)[8]. Although ICH Q3A(R2) is basically applicable for organic as well for inorganic impurities there are no explicit acceptance criteria for metallic residues provided. Regarding inorganic impurities merely the following advice is mentioned:

Acceptance criteria should be based on pharmacopoeial standards or known safety data. (ICH Q3A(R2), page 3)

This is not supportive to obtain binding criteria for a specification which is accepted by a marketing authorisation application. In addition, some metals can be unusually potent or produce toxic or unexpected pharmacological effects so that lower concentration limits than the general limits given in ICH Q3A(R2) have to be applied. Metallic impurities may exert directly an undesirable effect on health. Another point to consider is the possible impact on the stability of the drug substance by facilitating degradation processes, e.g. due to oxidative or hydrolytic catalysis.

2 Issues under examination

2.1 Overview about requirements on impurities in pharmaceutical substances

A specification is a quality standard. It establishes the criteria to which a substance should conform to be considered acceptable for the manufacture of medicinal products.[9] Thus, the specification includes a list of tests, references to analytical procedures and appropriate acceptance criteria for the tests described. Conformance to specifications is defined as meeting the acceptance criteria when tested according to the listed analytical procedures. Substances intended for pharmaceutical purposes are used as active ingredients, as excipients (auxiliary substances present in the drug product), or as the pharmaceutical excipients used during the manufacture of the drug product but no longer present in the drug product itself.

For many existing substances approved specifications are provided by the pharmacopoeias in each region, such as the European Pharmacopoeia (Ph. Eur.),[10] United States Pharmacopeia (USP)[11] and the Japanese Pharmacopoeia (JP).[12] The requirements of the pharmacopoeias consist not only of that described in the specific monograph of the substance. Additional requirements are described in the general chapters and general monographs and have also to be taken into account. For new active substances general recommendations are provided in the guideline ICH Q3A(R2)[7] (Impurities in New Drug Substances). This guideline in fact was initially intended for new active ingredients only.

However, with implementing the principles of this guideline in the Ph. Eur. general monograph "Substances of pharmaceutical use"[13] the requirements on impurities are now mandatory for all existing active pharmaceutical ingredients, too. Therewith the ICH Q3A(R2) concepts and thresholds for reporting, identification and qualification of impurities have been adopted for all APIs. In the guideline CPMP/QWP/1529/04[14] it is clarified that these principles are also applicable to active substances with "old monographs" in the pharmacopoeia. The "old monographs" do not have a list of impurities or a suitable analytical method for a state of the art control of related substances by which the required limits could be reached.

The guideline ICH Q3C(R4) recommends acceptable amounts for residual solvents and is valid for active substances, excipients and medicinal products. EMEA announced adoption of ICH Q3C for existing products. Consequently Ph. Eur. included the guideline as a general chapter 5.4 with a general analytical method 2.4.24 coming into effect as of July 2000.

2.1.1 Impurities in pharmaceutical starting materials

An impurity in a drug substance as defined by the guideline ICH Q3A(R2)[7] is any component of the drug substance that is not the chemical entity defined as the drug substance. Quite similar is the definition for an impurity in a drug product. It is any component of the new drug product that is not the drug substance or an excipient in the drug product (ICH Q3B(R2)).[8] The impurities which are already controlled in the drug substance need not to be monitored or specified in the drug product again, unless they are also degradation products (ICH Q6A).[9]

Impurities are generally arising from the manufacturing process or from degradation of the substance (Figure 2). Many impurities represent substances, which are already introduced in the manufacturing process. Starting materials of the manufacturing process, as well as the added reagents, solvents and catalysts belong to that group. The substances which are already included as impurities in the added starting materials, solvents or reagents may be counted to that group of impurities, too. Since reagents, solvents and catalysts are usually not covered by the test of related substances they have to be monitored by specific tests. It has to be considered that metals known to be used in the manufacturing process can either be present in the original form of the metal or as form of the metallic element changed by downstream chemical processing.

Another group of impurities is generated during the process in forms of side products or insufficiently converted intermediates. These are usually controlled by the test on related substances. In general impurities should be removed by the purification of the material to an acceptable level.

Degradation products are likely to be discovered by stress testing of the product. Identification of the degradation products helps to establish the degradation pathways and

the intrinsic stability of the molecule and validate the stability indicating power of the applied analytical methods.[15] The impurities arising from degradation can be monitored by stability studies under long term or accelerated conditions. Impurities can especially arise from oxidation or hydrolytic reactions. Oxidation reactions have an important meaning among the degradation processes. The acceptance criteria for the degradation products have to be met even at the end of the shelf life. So the stability of the substance has to be assured until the end of the shelf life. Accordingly this may be supported by providing appropriate packaging materials and storage conditions.

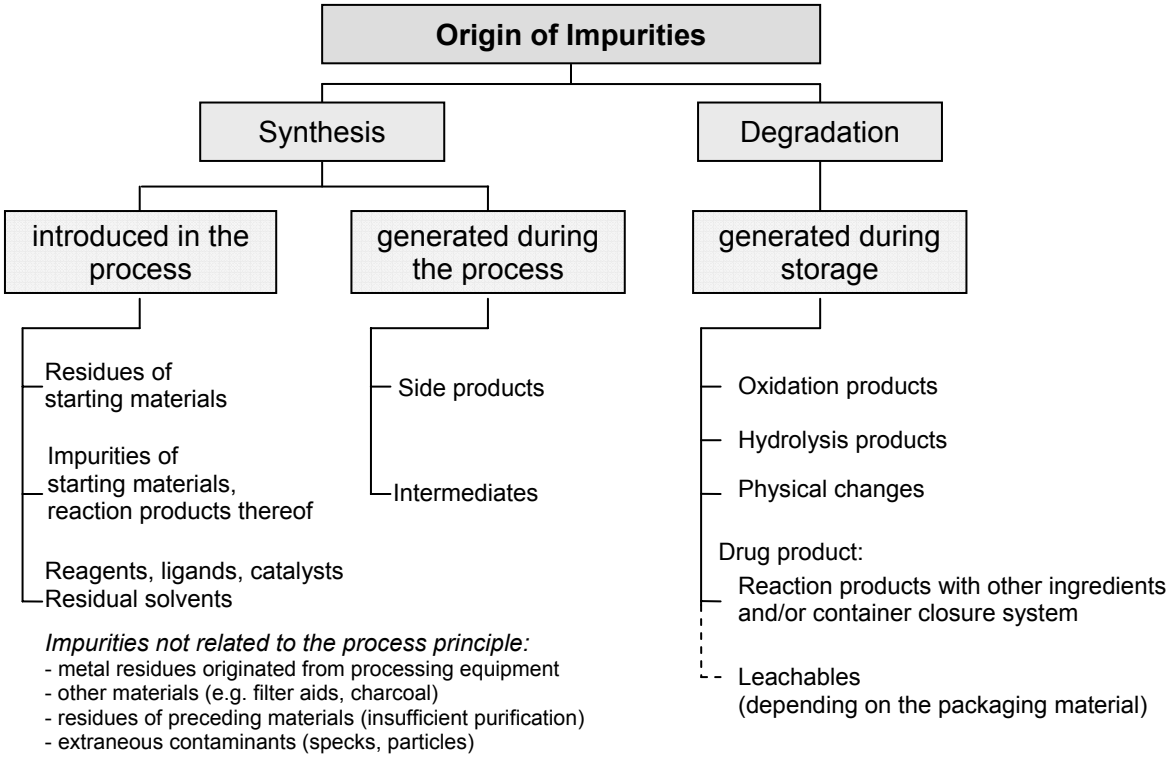


Figure 2: Origin of impurities in chemical substances

Polymorphism is one of the most important reasons for physical changes of APIs. Changes in the crystalline form may result in reduced solubility. This may result in a reduced dissolution and/or bioavailability. Special attention to such aspects has to be paid to excipients like fatty acids and glycerids which may exist in different polymorph forms. Physical changes may also become obvious with slight changes of the appearance of the material.

2.1.1.1 Impurities not related to the principles of the manufacturing process

Impurities not related to the principles of the manufacturing process are likely to appear irregular and not systematically. They may be caused by undiscovered failures in the process or by the equipment applied to run the process. Another reason may be insufficient protection against extraneous contaminants getting into the product or insufficient cleaning of multipurpose equipment and/or failures of cleaning validation so that remaining substances of the preceding production will pollute the following material. Foreign contaminants (small

particles, black specks) or contamination on account of the processing equipment (metals originated from vessels, gaskets, pipes or filter aids, charcoal) are again not directly linked with the synthesis route. Foreign contaminants are more appropriately addressed as Good Manufacturing Practice (GMP) issues.

If these contaminants are of different structure or if they are totally unknown then it will potentially be not possible to detect them with the typically applied analytical procedures. They are not covered by the guidelines on impurities of ICH Q3X series. The process has to be controlled in a way that all these impurities are excluded. Thus, the compliance with the GMP regulations (or "*production within a framework of a suitable quality system*"[16]) is an essential part of the quality assurance for pharmaceutical starting materials. The concept of process validation is a key element in ensuring that these quality assurance goals are met. Process validation is mandatory for the manufacturing of APIs.[17] For excipients the consistent operation of each manufacturing process should be demonstrated.[18]

2.1.1.2 Classification and definition

According to the definition of ICH Q3A(R2) an impurity profile is a description of the identified and unidentified impurities present in a new drug substance. However, a pure qualitative listing of all possible impurities alone would be not sufficient for a proper description of the purity of a substance. To assess the relevance of impurities quantitative information is necessary and required for the application of a marketing authorisation.

"A summary should be given on the nature and levels of the actual impurities detected in the batch samples of the material" and "Justification should be provided for selecting the limits based on safety and toxicity data, as well as on the methods used for the control of impurities." (CPMP/QWP/130/96 (Rev 1) Dec. 2003)[19]

2.1.1.3 Identified – not identified impurities

For identified impurities a structural characterisation has been achieved. Not identified impurities – usually organic compounds – are unknown in regard to their chemical structure but they are characterised by analytical descriptors, e.g. retention time/HPLC.

Considering identification of metals, differences in speciation and form are likely to occur which are dependent, e.g., on oxidation state, co-ordinating ligands and solvation. So far the differences in speciation are usually not considered to be separately characterised. Metal residues of all speciation and forms of a specific metal are typically measured as the total metal content. An exemption is provided in the guideline[6] with the explicit PDE for chromium(VI) for inhalation exposure. Nevertheless, toxicity can vary greatly on speciation and form.

2.1.1.4 Specified – unspecified impurities

A specified impurity is individually listed in the specification and limited with a defined individual acceptance criterion based on respective toxicological data. A specified impurity can be either identified or unidentified. If due to the applied manufacturing process a specified impurity is likely to be present it will be presumed to appear regularly from batch to batch. Unspecified impurities are not explicitly included into the list of impurities of the specification. If unspecified impurities are detectable by the applied analytical method they are limited by an unspecific acceptance criterion, e.g. any other impurity not more than 0.10% (identification threshold Q3A(R2), daily dose ≤ 2 g).

Individually unspecified metal residues are controlled by the test on sulphated ash or the general heavy metal test (see page 13).

2.1.1.5 Genotoxic impurities

The synthesis of pharmaceutical products frequently involves the use of reactive reagents possibly producing reactive intermediates and by-products with the potential for unwanted toxicities including genotoxicity and carcinogenicity and hence can have an impact on product risk assessment. The determination of acceptable limits is not addressed in sufficient detail in the existing ICH Q3X guidelines. Thus, additional guidelines describe a general framework and practical approaches on how to deal with genotoxic impurities in new active substances.[20,21]

Certain metals are known to have genotoxic or carcinogenic potential at least in a particular form, e.g. class 1 metals assessed in the guideline on metal residues like chromium, nickel and platinum

2.2 Metals in the control of pharmaceutical substances

2.2.1 General tests on heavy metals

The classical test for the non-specific control of heavy metals is based on the precipitation of metal sulphides from weak acid media. The intensity of the black or brown colloidal precipitate formed in the test solution is compared with a reference solution: it must not exceed that of the reference solution at the limiting concentration obtained from a standard solution of lead nitrate. The aim of the test is to control metal contaminants potentially coming from reagents, solvents, electrodes, reaction vessels and gaskets or rubber seals. These metal contaminants may be highly toxic or may catalyse decomposition of the substance (for example by oxidation). For the test on heavy metals there are currently seven procedures described in the general method 2.4.8 of Ph. Eur. The procedures differ in the preparation of the sample to obtain a test solution with the possibly containing metals. The

applied procedure depends on the properties of the substance to be examined. If there are water soluble, non coloured and non chelating substances a very simple prepared solution may be used for the test. In the case of coloured, chelating or insoluble substances mineralization methods are applied to obtain the test preparation. For the open mineralization techniques such as methods C and D substantial loss of lead was reported.[22] For this reason it is recommendable to prepare a monitor solution in which the sample is spiked with lead nitrate at the limiting concentration and treated in the same way as the test solution. Thus, an adequate recovery, at least for lead, is monitored directly.

Nevertheless, this method has several limitations. The test can only control those metals precipitating in the weak acid milieu at pH 3.5 in the presence of hydrogen sulphide. Only black or brown precipitates are readily detected. The sensitivity of the test strongly depends on these properties of the elements and so there is a broad variability in the limit of detection between the elements. In any case the limit of detection with the most sensitive method is not lower than 1 µg.[22] The following metals could not be detected under the conditions of the test: chromium, cobalt, manganese, thallium, titanium, tungsten and zinc.[22]

In the guideline on metal residues[6] it is clearly stated that the pharmacopoeial heavy metal test may only be suitable in some cases under special prerequisites: it should be "adjusted" to analyse the metal in question ("*e.g. by using standard addition methods")*, properly validated including cross validation with an element-specific test (see section 4.4 of the guideline[6]). The Technical Guide of Ph. Eur.[23] still requires the inclusion of the heavy metal test for new developed or revised monographs. This unspecific limit test is considered as a general safety test. The criteria for inclusion of the test into monographs and setting of limits are average dose, route of administration and duration of treatment:

Table 1: Criteria for heavy metal test in substance monographs of Ph. Eur.[23]

Daily intake > 0.5 g/day, treatment < 30 days	heavy metal test, limit 20 ppm
Daily intake > 0.5 g/day, treatment > 30 days	heavy metal test, limit 10 ppm
Daily intake < 0.5 g/day, treatment > 30 days	heavy metal test, limit 10 ppm if the substance is used parenterally, otherwise 20 ppm
Daily intake < 0.5 g/day, treatment < 30 days	no heavy metal test

Specific contaminations with heavy metal species related to the process should be covered by specific tests and are not within the scope of the heavy metal test.[24]

2.2.2 Analytical methods for the control of metallic impurities in Ph. Eur.

The European Pharmacopoeia provides general descriptions of analytical methods which are applicable to determine metals as impurities in pharmaceutical substances (Table 2). Besides these general descriptions of instrumental methods, procedures for certain metals are described as limit tests (Table 3). All tests have to be validated before they are applied to

a substance unless they are provided in the specific monograph of that substance. The influence of the matrix as well as the substance itself has to be considered and monitored, especially for the wet chemical limit tests.

Table 2: Ph. Eur. General Methods for trace analysis of metals

Chapter	Title	Abbreviation
2.2.23	Atomic absorption spectrometry, including flame and graphit furnace AAS	AAS, GF-AAS
2.2.22	Atomic emission spectrometry	AES
2.2.57	Inductively coupled plasma-atomic emission spectrometry	ICP-AES
2.2.58	Inductively coupled plasma-mass spectrometry	ICP-MS

As current methods for metal analysis, e.g., voltammetry and X-ray fluorescence spectrometry are not (yet) described as general methods in Ph. Eur. Nevertheless, these methods may be suitable to determine specific elements simultaneously in pharmaceutical substances.

Table 3: Ph. Eur. limit tests for metals

Chapter	Metal	Method
2.4.17	Aluminium	Fluorimetry
2.4.2	Arsen	Wet chemistry (colour)
2.4.3	Calcium	Wet chemistry (turbidity)
2.4.9	Iron	Wet chemistry (colour)
2.4.10	Lead in sugars	AAS, determination after extraction
2.4.6	Magnesium	Wet chemistry (colour)
2.4.7	Magnesium and alkaline-earth metals	Titration (Na_2EDTA)
2.4.31	Nickel in hydrogenated vegetable oils	AAS, after digestion
2.4.15	Nickel in polyols	AAS, determination after extraction

2.3 EMEA Guideline on Specification Limits for Residues of Metal Catalysts and Metal Reagents

2.3.1 Metals in the scope of the guideline

The guideline recommends maximum acceptable concentrations limits for metal residues arising from the use of metal catalysts or metal reagents in the synthesis of pharmaceutical substances. The term “pharmaceutical substances” is defined as a substance that is either an active pharmaceutical ingredient or an excipient. The guideline refers also to metals used in the synthesis “*of any of the pharmaceutical excipients used during the manufacture of the drug product, but no longer present in the drug product itself*”. There is a short monograph on each element including general information, dietary intake, toxicological data and regulatory assessment to provide a conclusion and rationale for the permitted daily exposure (PDE). The guideline includes 14 metals which are divided in three classes. An update by inclusion of further metals is to be expected.

Class 1 Metals: Metals of significant safety concern. *This group includes metals that are known or suspect human carcinogens, or possible causative agents of other significant toxicity.*

Class 1 is further divided into three subclasses 1A, 1B, and 1C. The subclasses 1A and 1B cover highly toxic or carcinogenic metals. For subclass 1B a group limit is applied, the total amount of listed metals should not exceed the indicated limit.

Class 2 metals: Metals of low safety concern. *This group includes metals with lower toxic potential to man. They are generally well tolerated up to exposures that are typically encountered with administration of medicinal products. They may be trace metals required for nutritional purposes or they are often present in food stuffs or readily available nutritional supplements.*

Class 3 metals: Metals of minimal safety concern. *This group includes metals with no significant toxicity. Their safety profile is well established. They are generally well tolerated up to doses that are well beyond doses typically encountered with the administration of medicinal products. Typically they are ubiquitous in the environment or the plant and animal kingdoms.*

For each of these classes exposure and concentration limits are defined (Table 4). The classification of impurities in three classes was already carried out with the ICH-Guideline on residual solvents (ICH Q3C(R4)). Hence, the approach is known with the manufacturers of pharmaceutical starting materials. The classification is solely driven by the toxicological assessments of the specific metals. Quality aspects, for example the colour or the possibility to interact on other components like inducing oxidation or catalysis of degradations is not considered. Leading dimension for the classification of the metals in the classes is the PDE value (see page 6f). In this guideline the PDE is given in the unit µg/day or ng/day. The maximum exposure is always referred to one day and applies for a chronic, if necessary, lifelong application. The PDE is basis for the recommended maximum acceptable concentration limits.

Table 4: 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 minmal safety concern	13000	1300	1300	130	

** see section 4.4 and the respective monographs of the guideline, Pt as hexachloroplatinic acid*

*** Subclass limit: the total amount of listed metals should not exceed the indicated limit*

According to the guideline, limits should be provided for metals which are likely to be present due to introduction into the manufacturing process as metal catalyst or metal reagent:

If synthetic processes of pharmaceutical substances are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal reagent, a concentration limit and validated test for residues of each specific metal should be set.

Thus, it becomes clear that only process-related metal residues are in the scope of the guideline to control the sufficient removal of the pharmaceutical substance. A screening on other metals is not planned, only the metals used in the synthesis are considered. Metals as deliberate components of the pharmaceutical substance are not addressed by the guideline (such as a counter ion of a salt or metals in desired metal organic compounds).

In summary there are four conditions for a metal to be in the scope of this guideline:

- The metal has to be used in the manufacturing process as catalyst or reagent (regardless of the speciation or form of the element)
- It is likely to be present in the pharmaceutical substance
- It is not a deliberate component of the pharmaceutical substance
- It is among the metals of the guideline (14 metals in the current version)

2.3.2 Principles for limit setting

For determination of the concentration limits two options are described. Option 1 assumes that not more than 10 g of the drug product per day is administered. It is to be considered that the daily dose of 10 g refers to the drug product including all drug substances and excipients. If all drug substances and excipients in a formulation meet the limits given in

Option 1, these can be used in the final drug product in any proportion. Then further calculation of limit values is not necessary.

$$Concentration\ (ppm) = \frac{PDE\ (\mu g / day)}{daily\ dose\ (g / day)}$$

Equation 1: Calculation of limit concentration for metallic residues

With Option 2 the opportunity exists to determine the limits with regard to individual cases. This has to be applied, if the given option 1 limit is not accessible, or if the daily dose of the drug product exceeds 10 g and therefore the requirement for application of the option 1 limit is not fulfilled.

With Option 2a the concentration limit can be calculated by use of the daily dose of the pharmaceutical substance in the drug product. By calculating the concentration limit with a daily dose of the pharmaceutical substance smaller than 10 g, higher acceptable concentration limits are obtained than the option 1 limit. The justification for the higher limit is that finally the administered amount of the metal is vital for the toxic effect. The lower the maximum amount of drug product ingested, the higher the permitted concentration of the metallic impurity. If the option 2a limit is applied for the same metal in several pharmaceutical starting materials the complete amount of metal in the drug product will be considered.

Option 2b considers the actual amount of the metal in the drug product and the known maximum daily dose. Thus, even the option 2a limit for a certain metal can be exceeded in a pharmaceutical substance if the total daily amount of the metal in the sum of all starting materials does not exceed the permitted daily exposure. Excess of the option 1 or option 2a limit will then be compensated by lower maximum levels in the other substances. If Option 2b is applied it must be shown that the metal residues were reduced to the practical minimum in all starting materials.

The acceptable daily exposure of metals should not only be exhausted by drug products. With the definition of concentration limits to metals it is considered that also foodstuffs may contain metals. The PDE values in the guideline are set in consideration of additional dietary metal intake.

2.3.3 Concentration limits – depending on the route of administration

With the EMEA guideline on metal residues[6] the route of administration has an influence on the acceptance criteria for impurities. This in contrast to other ICH Q3X guidelines where the route of administration is not considered for the concentration limits for impurities. Different values of the permitted daily exposure of metals (PDE) for the oral and parenteral application are indicated and connected to different concentration limits for the allowed residues in pharmaceutical substances. Since an incomplete absorption of metals through the

gastrointestinal tract is assumed, higher concentration limits for the oral intake than for parenteral administration are justified. While with the two first drafts of the guideline, dated January, 2001 and June, 2002 still calculated with different bioavailabilities for the individual metals, a simplistic assumption has been laid down for the final version: as there are very limited non-oral data the bioavailability was assumed in general with 10% to estimate the parenteral PDEs compared with oral PDEs, taking into account a 10% absorption of the metals from the gastrointestinal tract. For the oral intake the concentration limits are therefore by the factor 10 higher than for the parenteral administration. Nevertheless, these higher concentration limits apply only to the oral exposure or to other dosage forms with absorption probably not higher compared to with the oral administration, e.g. local administration on the skin. The concentration limits for parenteral exposure are to be applied without further justification for all the other forms of administration, e.g. inhalation exposure.

For pharmaceutical substances intended for the production of inhalatives again clearly lower limit values are demanded for platinum nickel and chromium(VI), because these metals are associated with the development of allergy, sensitations, skin reaction or cancer after intake about the lung. With regard to the requirement for the inhalation therapy the PDE value is mentioned only. A figure for a concentration limit according to Option 1 is not provided. This is due to the fact that the option 1 limit is based on a daily dose of 10 g of drug product which will not be ingested by inhalation.

3 Results

3.1 Information about metal residues in purchased pharmaceutical substances

3.1.1 Purchased starting materials

Many pharmaceutical substances are not produced at the drug product manufacturer, but are purchased. The available information about the production of purchased pharmaceutical substances is not necessarily complete concerning the use of metal catalysts or metal reagents. The choice of a suitable metal catalyst may be specialist knowledge of the substance manufacturer and may be liable to patent protection, e.g. catalysts used in stereo selective syntheses. For excipients still little or no information about the production may be available because this is not necessarily needed for the marketing authorisation application (MAA).

For purchased pharmaceutical substances a questionnaire and a supplier audit of the manufacturing process are suitable procedures to obtain the necessary information.

With a questionnaire the information can be received fast and with comparably little effort. However, by use of questionnaires misunderstandings can occur and thereby may result in

misleading information. Misunderstandings may appear by wrong understanding with regard to meaning and background of the questions. Some companies, in particular the bigger ones, often use standard information sheets on certain subjects instead of completing the individual questionnaire. In consideration of the numerous different subjects this is a suitable action to cope with the many different enquiries at all. However, from the enquiring company's point of view it is not guaranteed that all desired information is provided. Hence, with the receipt of written information of a manufacturer or supplier the completeness and the plausibility of the answers have always to be checked thoroughly, the effectiveness of which is muss less than having a direct response to the enquiring company's questionnaire. Ideally the information from the questionnaire should be confirmed by an audit.

The questionnaire should be developed in a way that it is possible to provide the necessary information for all intended uses completely. Therefore, it must be structured clearly and formed as simple as possible to allow a quick response and to generate no unnecessary extra work for the supplier. The questionnaire should be completed by a change control agreement with regard to the given information. This is to make sure that significant changes in regard to the given information are notified. Irrespective of that a general change control agreement to the manufacturing process of the substance should be arranged. The questionnaire on metal residues on basis of the guideline[6] should cover the following points:

- Are metal catalysts or metal reagents used in the final manufacturing step or used in an earlier manufacturing step without being removed consistently by the manufacturing process?
  If the answer is "no", all the following questions need not to be answered.
- If the answer is "yes": are metals used among the 14 metals of the guideline?
- Are residues of these metals within the concentration limits of the guideline? Thereby the option 1 limit for the parenteral exposure will be applied to allow an applicability of the statements for all possible purposes.
- Are further metals used? This question is to put the user of the substance into the position to analyse a possible impurity. On the other hand this can be seen as a preparation on a possible amendment of the guideline with further metals.
- Are there several process variants?
  If a supplier has several sources from which the pharmaceutical substance is purchased, the possibility should be given to provide information to different manufacturing processes. This is also possible for a manufacturer of pharmaceutical substances who applies different procedures which require different statements for the use of metals.
- In the sense of the guideline, has adequate removal of metal residues from the product been proven?
- Are the analytical methods which are used to determine metal residues in the substance validated?
- Space for comments on the answers given.

Figure 3 shows the questionnaire developed recently by Merck KGaA[25] to receive information about metal residues from suppliers and manufacturers of pharmaceutical substances:

GMP-Questionnaire for Suppliers
– Residues of Metal Catalysts or Metal Reagents –

Dear Sir or Madam,

MERCK requires binding information on the residues of metal catalysts or metal reagents used in order to check the concentrations of these in the products delivered. This procurement of information is based on the EMEA **GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS, Ref. No. EMEA/CHMP/SWP/4446/2000**.

Information on the use of metal catalysts and/or reagents in a standard process

Any **metal catalyst and/or metal reagent** is used in the final manufacturing step or used in an earlier manufacturing step without removing consistently by the manufacturing process.

Yes ☐ No ☐

If so, please fill in table 1. If other than the listed metals are used, please specify:

Table1: Information on metals used in the standard process

Class	Metals	Presence		Typical measurement values	Limit of Quantitation	Acceptance limit, for information (option 1)
		Yes	No			
1A	Pt			ppm	ppm	1 ppm
	Pd			ppm	ppm	1 ppm
1B	Ir			ppm	ppm	∑ 1 ppm
	Rh			ppm	ppm	
	Ru			ppm	ppm	
	Os			ppm	ppm	
1C	Mo			ppm	ppm	2.5 ppm
	Ni			ppm	ppm	2.5 ppm
	Cr			ppm	ppm	2.5 ppm
	V			ppm	ppm	2.5 ppm
2	Cu			ppm	ppm	25 ppm
	Mn			ppm	ppm	25 ppm
3	Fe			ppm	ppm	130 ppm
	Zn			ppm	ppm	130 ppm
Other Metals				ppm	ppm	ppm
				ppm	ppm	ppm

GMP-Questionnaire for Suppliers
– Residues of Metal Catalysts or Metal Reagents –

Information on the use of metal catalysts and/or reagents in several process variants

There is a reasonable variation in the manufacturing process. Metal compounds vary in relation to this.
Yes ☐ No ☐

If so, please fill in table 2:

Table 2: Information on metals in process variants.

Variants	Metals according to Table 1	Typical measurement values
Variant A		
Variant B		

Proof of adequate removal of metal residues from the product
For all contained metals it is demonstrated that they have been adequately removed from the product. Adequate removal is demonstrated if in 3 consecutive industrial scale batches a metal residue <30% of the appropriate concentration limit according to EMEA Guideline EMEA/CHMP/SWP/4446/2000 was found.

Yes ☐ (please enclose the relevant evaluations) No ☐

Validation data
For determination of each metal residue an appropriated and validated method according to ICH is used.
Yes ☐ No ☐

Methods and method validations are available on request.
Yes ☐ No ☐

Comments

In future, Merck KGaA will be informed of any changes to the manufacturing process which may lead to changes in these data. The information will be given before changes are established.

Name: Date: Signature:

Figure 3: Content of the questionnaire for starting materials regarding metal residues currently used by Merck KGaA, Darmstadt

3.1.2 Experience with provided information from suppliers

To receive information about metal residues, Merck KGaA sent out the questionnaire for several starting materials to suppliers and manufacturers. About 75 % of the enquired questionnaires were answered, representing more than 100 substances (status June, 2009).[26] However, the enquiries are ongoing and the missing questionnaires are going to be requested repeatedly. The information is necessary for the maintenance of supplier qualification. If the answer, even after repeated reminder, is considered to be insufficient or is not provided at all it will have a negative impact on supplier evaluation and a written product-related risk assessment will be necessary. This may be based on multi elemental screening test on metals connected with an assessment of the manufacturing process including the relevant purification steps. Nevertheless it may result in stop of supply and qualification of an alternative manufacturer/supplier. The available information can be divided as follows:

- The provided questionnaire was answered. The information is sufficient and plausible. Further enquiries are not necessary. (Case A)
- The provided questionnaire was answered. Nevertheless, the information is not yet sufficient or plausible, so that complementary information is needed. This additional information can be already existent or must be separately requested. (Case B)
- The enquiry was answered not using the provided questionnaire, e.g. by a standard information sheet of the supplier/manufacturer on that topic. The information is sufficient and plausible. Further enquiries are not necessary. (Case C)
- The enquiry was answered not using the provided questionnaire, e.g. by a standard information sheet of the supplier/manufacturer on that topic. However, the requested information is not provided completely by the information sheet. Complementary information is necessary which may already be available or must be separately requested. (Case D)

Table 5: Results of answered questionnaires on metal residues

Case	Case description	Percentage	Percentage of sufficient answers
A	Questionnaire answered, information is sufficient	64%	94%
B	Questionnaire answered, additional information required	4%	
C	Enquiry was answered not using the provided questionnaire, information is sufficient	19%	59%
D	Enquiry was answered not using the provided questionnaire, additional information is required	13%	

Due to the experience with the enquiry on residues on metal catalysts or metal reagents the percentage of sufficient answers is clearly higher if the provided questionnaire is used. If the enquiry is answered e.g. by a standard information sheet, additional information is comparatively required more often.

The most frequent cause for case D is missing information on whether any metal catalyst and/or metal reagent was used in the final manufacturing step or used in an earlier manufacturing step without having been removed consistently by the manufacturing process.

The typical content of certain metal impurities is often provided instead. With this information a contribution to an impurity profile is given. However, it has not been sufficiently answered if metals were used during the manufacturing process or not. An analytically ascertained value cannot solely answer this question. In this case further information about the manufacturing process is necessary to make transparent whether metal catalysts or metal reagents are used.

3.1.3 CEP

With a “European certificate of Suitability to the Monograph of the European Pharmacopoeia” (CEP)[27] the manufacturer of a substance will be able to provide proof that the quality of the substance is suitably controlled by the relevant monographs of the Ph. Eur. The CEP certifies that by applying the relevant monographs of the Ph. Eur., if necessary, with an annex appended to the certificate, it is possible to check whether or not the quality of the substance is suitable for use in medicinal products. It ensures that all possible impurities and contamination from this particular route of manufacture (including source materials) can be fully controlled by the requirements of the monographs. If the monograph is not able fully to control the quality of the substance in the certificate, including the annex, *is given the full text of the additional test and the full list of named impurities including their limits controlled by that test*.[27] This may also apply to metal impurities which are likely to be present in a substance due to the current manufacturing process. A restriction consists in the fact that the CEP procedure is intended only for substances for which a monograph has been adopted by the European Pharmacopoeia Commission.

A CEP is a reliable source of information for all possible impurities from the production process. Of course this applies also for possible residues of metal catalysts or metal reagents. Moreover, with a CEP suitable analytical methods and concentration limits are given to control the relevant metals. They are either already included in the monograph, or the limit values and methods are described in the CEP and the annex. The limit values mentioned in it are basically valid. Nevertheless, incompliance may arise in that, the option 1 limit for the respective metal of the guideline is lower than the declared concentration limit in the CEP or monograph. Moreover, it is also possible that the respective option 1 limit for the oral exposure is fulfilled, whereas the limit for the parenteral exposure is not compliant. Thus, an individual case to case decision will be necessary. It has to be taken into account that the option 1 limit is based on a maximal daily intake of the drug product of 10 g, a dose of which is in many cases unrealistic high.

3.2 Information about metal residues in pharmaceutical substances produced within the corporate company

Even if the pharmaceutical substance is produced within the corporation, it is usually manufactured at different sites than the operational unit for drug product manufacturing. The one who is responsible to submit the data about metal residues therefore depends always on correct information, no matter whether these come from internal colleagues of the company or from external. The pharmaceutical substances originating from in-house production and with regard to the production steps carried out at the local production site, the metals used as reagents or catalysts, should be easily to identify. Reliable information for that can be taken from the lists of materials and the manufacturing instructions. However, there is still no information given whether metal reagents or metal catalysts were used in the production of starting materials introduced in this manufacturing process. This is in particular relevant when the use of metals in the production of the raw materials is possible and the carried out manufacturing steps are not or not significantly able to remove metals from the substance. This is the case, for example, for purely physical operations like mixing or milling. But also following other processes the raw materials are basically to be evaluated with regard to metal residues.

3.2.1 Use of metals in the production of raw materials

Raw materials used for the manufacturing of pharmaceutical substances may contribute to metal residues in the pharmaceutical substance.

Thus, the question turns up to what extent the possible use of metals are to be traced back and how far preceding steps of the production are to be considered. Impurities with metals can be preserved about several manufacturing steps and may not be removed completely by purification processes. Provided that a risk consists in carryover of impurities of the last manufacturing steps, it should be evaluated with the help of a risk analysis. ICH Q9[28] provides guidance to perform a quality risk management. Basically supposable procedures for removal of metal residues are, e.g., filtration, crystallisation, chromatography as well as distillation. The effectiveness with regard to the removal of the metals might increase generally in this order. On the one hand the effectiveness of the purification process has to be considered to which extent metal residues are removed. On the other hand the current amount and monitoring of metal residues in the raw material used has to be taken into account. If the relevant metal on the stage of a raw material is controlled by a validated test and with limits according to the guideline the test need not to be repeated for the pharmaceutical substance unless this metal is used again in the following manufacturing steps.

The carryover of impurities about several manufacturing steps could be of greater relevance with metal residues than with residual solvents. The solvent applied in a final step will displace the residual solvent of the preceding step, assumed both solvents are entirely soluble. Such a displacement will not occur with metal residues. Nevertheless, residual solvents of a preliminary stage are still to be expected or even enriched in the product when these are harder to be removed by distillation (e.g. higher boiling point) than the solvent used. ICH Q3C(R4) recommends a validated process to demonstrate consistent removal of solvent residues. It is noteworthy that the corresponding text in the guideline on metal residues[6] is nearly identical (Table 6). Nevertheless, the concept of a validated process is found only in ICH Q3C(R4), not in the guideline to metal residues.

Table 6: Comparison of the term „likely to be present“ in different guidelines

ICH Q3C(R4)	EMEA/CHMP/SWP/4446/2000
"Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process.	*"Likely to be present" refers to the metal used in the final manufacturing step and to metals that are used in earlier manufacturing steps and not removed consistently by the manufacturing process.*

It is to be considered that a validated process is not required for the manufacturing of excipients. Since both guidelines are valid not only for active substances, the formulation in EMEA/CHMP/SWP/4446/2000 seems to be more appropriate. With both guidelines, as well ICH Q3C(R4) as CHMP/SWP/4446/2000, the term "removed consistently" is used to describe the entire removal of impurities from the last as well as from preceding manufacturing steps.

3.2.2 Use of metals in the process – consistently removed

Certain manufacturing processes using metals as catalysts or reagents result in products without detectable amounts of the respective metal/s. In this context the guideline states:

Manufacturers of medicinal products need information about the content of metallic residues in pharmaceutical substances in order to meet the criteria of this guideline. Thus, it is necessary that the manufacturers of pharmaceutical substances provide a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers. (Section 4.6 "Reporting Levels of Metallic residues")

It is therefore necessary that the manufacturer of pharmaceutical substances clearly provides information to the drug product manufacturer on all possible metal residues which are likely to be present due to the manufacturing process, the knowledge of which enables the drug product manufacturer to decide whether the metals are still likely to be present in the product. A metal is assumed as likely to be present unless it is consistently removed. But when is a metal considered to be consistently removed, even when it was used in the manufacturing process?

To reliably determine whether a metal is still present, a validated analytical method is necessary. The validation parameters LOD and LOQ describing the sensitivity of the method are of special interest whether a metal residue is still in the product or is consistently removed. A limit for the highest acceptable LOD or LOQ is not directly given in the guideline. However, the concentration limits are in several cases quite low and challenging. In an analytical sense "consistently removed" may have the meaning of "not detectable". This means that with the chosen method no signal is obtained which would show the presence of the respective metal with an acceptable error. The risk that the analyte is not detected when it is in fact present has to be defined (false negative result, β error). According to ICH Q2(R1)[29] the risk for false negative assumption (β error) is not explicitly indicated. The LOD is defined, e.g., as 3.3 times the standard deviation divided through the slope of a calibration curve at low concentrations. With this concept the false negative error (β error) as well as the false positive error (α error) is reported to be 5%.[30] This is a comparably low risk not to detect an analyte although it is in fact present.

A process validation approach could be suitable to demonstrate that a metal used in the production is not carried over in the product. However, a process validation is demanded for active substances (ICH Q7[31]), but not for excipients.[32] If a validation for the complete process is not performed, it should be shown for the relevant manufacturing step that metal residues do not carry over in the product or that an effective purification is carried out. Batches are selected as it is described in section 4.5 of the guideline: six consecutive pilot scale batches or three consecutive industrial scale batches are to be analysed. Adequate removal of a metal residue is considered if less than 30% of the appropriate concentration limit was found. This would allow skip testing but does not mean that the test may also be deleted from the specification. In contrast “removed consistently” is not defined in terms of certain percentages of the appropriate concentration limit.

In regard to residual solvents a routine test for a class 1 solvent present in another solvent is not required when “*it is demonstrated with a validated method that the class 1 solvent is not detected (i.e. below the limit of detection) in a suitable intermediate or in the final active substance. Supporting data should be presented on 6 pilot scale batches or 3 industrial scale batches.*”[34] However, a comparable approach is not (yet) described in regard to residues of metal catalysts or reagents.

3.2.3 Requirements on LOQ in metal impurity determination

To analyse metal impurities quantitatively the limit of quantitation (LOQ) has to be determined.[29] The LOQ should be validated to a lower value than the specification limit. In pharmaceutical analysis fixed specification limits for impurities are required, and the analytical procedure needs to be able to reliably quantify the analyte. A long-term application

of the analytical method should be considered and even the use of different equipment or a method transfer to other laboratories should run without difficulties. Thus, there is a need for a safety margin between an experimentally determined LOQ and the acceptance limit. The required level of the LOQ has to be fixed prior to performing the analytical method validation. This question is important to choose the appropriate analytical method which is able to achieve the necessary quantification limit.

As a starting point the acceptance limits for the metals of the guideline can be used. In regard to APIs the ICH guidelines define reporting thresholds for unknown related substances.[7,8] Usually the acceptance limit is twice the reporting threshold, e.g. 0.10% (identification threshold) corresponding to the reporting threshold 0.05% (ICH Q3A(R2) ,daily dose ≤ 2 g). The identification threshold is used as an acceptance criterion for all unspecified impurities.

A general acceptance criterion of not more than (≤) the identification threshold for any unspecified impurity … should be included. (ICH Q3A(R2)[7], page 4)

The reporting threshold should be higher than or at least equal to the quantitation limit:

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold. (ICH Q3A(R2)[7], page 3)

As a pragmatic approach the LOQ should be targeted to be 50% of the respective specification acceptance limit. This is in compliance with the "Technical Guide for the Elaboration of Ph. Eur. Monographs"[23] recommending the range for determination of an impurity to be from LOQ or "*from 50% of the specification of each impurity, whichever is greater, to 120% of the specification*".

At low concentration levels the performance of the analytical method should be considered. With a lower analytical precision it may be necessary to obtain a LOQ smaller than half the specification limit. *Ermer and Burgess* described a calculation for an acceptable 'general' LOQ by using the actual precision of the analytical procedure at the concentration level of the LOQ.[30] This equation provides a possible approach to confirm and justify the necessary level for the LOQ in the applied analytical method validation.

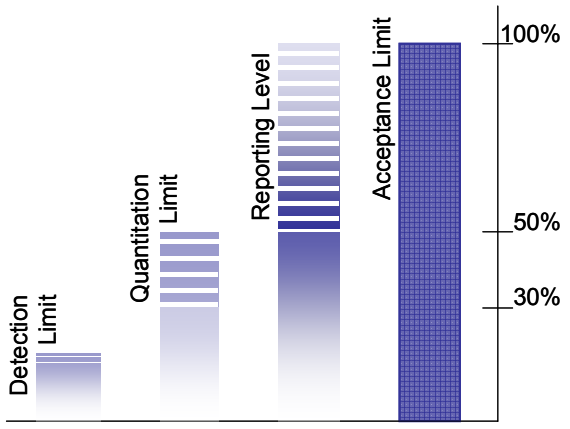
$$LOQ_{general} = AL - \frac{(s\, t_{df,\,95\%})_{validation}}{\sqrt{n_{assay}}}$$

$LOQ_{general}$	Upper limit of the distribution of all individual LOQs of several studies
AL	Acceptance limit of the specification of the impurity
S	Precision standard deviation at LOQ
n_{assay}	Number of repeated, independent determination in routine analyses, as far as the mean is the reportable result
t_{df}	Student t-factor for the degrees of freedom during determination the precision, usually at 95% level of statistical confidence

Equation 2: Calculation of a required general LOQ in dependence of the acceptance limit and the precision of the method. Acc. to[30]

The capability of the manufacturing process to remove potential residues should not be justified by investigations that are only based on the limit of Option 1. With a maximum daily dose higher than 10 g the limit of Option 2 could be lower than the option 1 limit. In general the appropriate concentration limit has to be applied to estimate the necessary levels of LOQ and LOD.

For the metals of class 2 and 3 significant lower LOQs than 50% of the acceptance criteria will usually be easily achievable. For the metals of class 1, typically 50% of the applied concentration limit (parenteral exposure) may be challenging and should be usually sufficient as an acceptable LOQ, depending on the precision of the method.



The reported level of metal concentrations may reach the acceptance limit (for class 2 and 3 metals). The LOQ should not be higher than 50% of the acceptance limit. The LOD is usually around one third of the LOQ, but is not necessarily to be determined for quantitative testing of impurities.
To demonstrate a metal to be adequately removed the LOQ has to be not more than 30% of acceptance limit.

Figure 4: Orientation for the target of LOD and LOQ dependent on the acceptance limit

Semi-quantitative methods result in assessment like "corresponds" or “failed“, in this case the LOD is validated instead of the LOQ. The determination of the LOQ is not possible with a method where a limit value is the only reportable result. (ICH Q2(R1)[29], page 3)

Interestingly, the guideline gives evidence for acceptable LOD limits for the platinoids of the class 1B, because analytically difficulties are to be expected:

Specifically with respect to platinoid Class 1B, where a group limits applies, it is accepted that due to technical limitations, the lower limit of detection may not be below 0.5 ppm for individual platinoids. *(Page 8/34)*

Considering the group limit of 1 ppm (parenteral exposure) a limit of detection of 0.5 ppm may be not sufficient if more than one metal class 1B is concerned. With a LOD of 0.5 ppm the LOQ can be estimated to be at least 1 ppm. Thus, the statement < 1 ppm (without a decimal place) can be derived for every platinoid individually. Nevertheless, for the calculation of a sum solely analytic values above the LOQ should be used. By use of different platinoids of the group 1B the result < 1 ppm can therefore be met by any platinoid individually. The statement that the sum of the platinoids of class 1B is also not more than 1 ppm cannot be met definitely with an individual LOD of 0.5 ppm and more than one platinoid to be considered. Hence, from an analytical point of view, the "group limit" concept for the metals of class 1B is challenging, if more than one metal of class 1B is likely to be present. The introduction of individual limits would therefore be desirable as outlined for the metals of all other classes. From a safety point view a group limit is suitable if the metals among the group act by the same mode of action and have the same molecular target and thus might exert effects in an additive manner.

3.2.4 Consistently removed versus information about the use of metals in the manufacturing process

The question is raised if the guideline poses a requirement for the manufacturer of pharmaceutical substances to inform the drug product manufacturer about the use of metals used as catalysts or reagents, even if they are considered to be consistently removed from the product.

The objective of the guideline is to assure the safety of patients by the recommendation of maximum acceptable concentration limits. Hence, information is demanded about the metals which are likely to be present as residues in pharmaceutical substances. Nevertheless, if it is shown that a metal in spite of its application during the production cannot be contained in the product any more, no potential risk exists for the patients. For this purpose it must be proven that the metals are removed completely by the purification process or that it is not possible to get them into the product at all due to technical conditions. Hence, an explicit requirement cannot be derived from the guideline to inform about any metals used as a catalyst or reagent, provided that these are removed consistently from the product.

It is also stated that no detailed tests on metals of all starting materials is expected from the drug product manufacturer, but that they may rely on information of trustworthy suppliers.

Pharmaceutical companies are not supposed to perform extensive tests on metal residue findings of unknown sources to comply with this guideline. They may rely on general information from trustworthy suppliers. (page 3/34)

The use of catalysts may show a special know-how of the manufacturing process, so that the circulation of this information is accompanied by an understandable suspiciousness.

However, Article 51(a) of Directive 2001/83/EC states that the Qualified Person (QP) of the marketing authorisation holder is responsible that *each batch of medicinal products has been manufactured and checked in compliance with the laws in force (...) and in accordance with the requirements of the marketing authorisation*.[33] Thus, the QP has to assure, if applicable, that all pharmaceutical substances used in drug product manufacture are in compliance to the guideline. Consequently, the QP should be able to evaluate the consistent removal of metals used. Ideally disclosure of the metals used can be achieved, if necessary with a confidentiality agreement. If this is can not be agreed a written product-related risk assessment should be conducted. This may be based e.g., on data of multi elemental analyses (ICP-MS) of three industrial batches, on the assessment of the manufacturing process including purification, and on documentation of consistent removal of the metal(s) that may be reviewed e.g. during a supplier audit. Moreover the compliance with the guideline should be certified by the supplier.

3.3 Testing strategies

The guideline clearly states that analytical methods are to be used which are validated for the determination of the respective metal residues, only. The choice of the method is basically free with the provision of the following recommendations:

- The test should be *specific for each element*, unless otherwise justified. With application of an unspecific method, which is suitable to measure several elements together with a general concentration limit, it must be shown that the exposure limit is exceeded for none of the specified metals.
- If only elements of the classes 2 and 3 are present, *a non-specific method may be used*. This concession is probably of low relevance in practice up to now, because the current elements of the class 2 (Mn and Cu) and the class 3 (Fe and Zn) are usually not measured together with a non-specific method.
- Any *harmonised procedures as described in the pharmacopoeias* should be used. The methods of the Ph. Eur. are harmonised in Europe. As a European guideline is concerned, the term „harmonised method“ is appropriate for any method described in the general part of the Ph. Eur.
- For the platinoids of the class 1B a group limit is applied. It is expressly accepted that the *lower limit of detection* of class 1B may not be below 0.5 ppm for individual platinoids.

Thus, the wet chemical test on heavy metal on the basis of precipitation at pH 3.5 of coloured metal sulphides can be used very restrictedly, only due to the fact that a quantitative determination of the current level of a certain metal is not possible with that method. This method is only applicable for the purposes of the guideline if it is adjusted with regard to the respective element and properly validated. A cross-validation with an element-specific test is recommended. This limits the practical applicability of the classical heavy metal test for this

purpose. Thus, the classical heavy metal test for use as a routine test might be left only to very few cases.

There are several analytical techniques for specific trace metal determination. The choice of a suitable method depends mainly on the respective metal(s), number of different metals to be analysed, required sensitivity, available sample amount and substance solubility. Typically applied methods will be

- inductively coupled plasma atomic emission spectroscopy (ICP-AES), also referred to as inductively coupled plasma optical emission spectrometry (ICP-OES),
- inductively coupled plasma mass spectrometry (ICP-MS),
- atomic absorption spectroscopy, with different procedures to atomize the sample (flame, graphite furnace, hydride generator).

Other suitable methods may be, e.g. voltammetry or X-ray fluorescence spectrometry.

3.3.1 Skip testing – adequately removed

Routine testing for the metal can basically be replaced by non-routine (skip) testing, e.g. on statistical basis, if the manufacturing process have shown to result in "adequate" removal of a potential metal residue.

A metal residue can be considered adequately removed if, in 6 consecutive pilot scale batches or 3 consecutive industrial scale batches less than 30% of the appropriate concentration limit was found.

A comparable approach is given for residual solvents. In an EMEA position paper on specifications on class 1 and class 2 residual solvents in active substances[34] a 10% limit for intermediates is introduced to allow replacement of routine testing by skip testing for class 2 solvents.

If it is demonstrated in a suitable intermediate that the content of class 2 solvent(s) is not more than the 10% acceptable concentration limit (…) mentioned in the CPMP/ICH/283/95 Note for Guidance on Impurities: Residual Solvents, a routine test is not required.

The metal should remain within specification during non-routine testing. Only for class 3 metals an option is granted to delete the test from the specification.

Only for class 3 metals, the test may be deleted from the relevant specification if the drug product manufacturer sufficiently demonstrates that the adequate removal of the metal residue from the pharmaceutical substance or the drug product is guaranteed. (EMEA/CHMP/SWP/4446/2000, page 8)

For that purpose the drug product manufacturer has to demonstrate sufficiently that the adequate removal of the metal from the pharmaceutical substance or the drug product is guaranteed. The application of this possibility assumes information of the drug product manufacturer about the potential presence of the metal. For the supplier of a pharmaceutical starting material this means that the specification of the substance must also contain the class 3 metal, unless the potential presence of the metal is pointed out with complementary information. Vice versa this means for the drug product manufacturer that the specification

with regard to class 3 metals is not necessarily enough as a source of information about the "likely to present" metals. On the fact of the absence of class 3 metals in the specification it can not be concluded that a class 3 metal is not likely to be present. Complementary information about the potential presence of metal catalysts or metal reagents is therefore necessary. In any case, the deletion of class 3 metals from the specification is only possible if the metal is "adequately removed" in the sense of the guideline.

3.3.2 Reporting levels of metallic residues

In section 4.6 of the guideline examples for acceptable statements are given to provide sufficient information about the content of metal residues in pharmaceutical substances. This is outlined in detail because the manufacturer of pharmaceutical substances has to provide "*a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers.*" The manufacturer of a drug product needs this information for the marketing authorisation application to meet the criteria of this guideline. Therewith it becomes noticeable that the requirement on the information about analytical data refers to metal residues potentially present. Thus, it can be reasoned that a test on metal residues, at least in routine testing, is not necessary if it is already demonstrated that the metals used during the production were removed reproducible and completely from the substance (consistently removed).

A reporting threshold is not explicitly defined in the guideline on metal residues. For a class 1 metal the LOD and LOQ of the method should be reported "*if the metal is found below the LOD or LOQ of the applied analytical method"*. Thus, the reporting threshold may correspond to the validated LOD or LOQ. An information in the form "< LOQ" would therefore be considered as acceptable. Results larger than the LOQ are to be given as effective values.

Regarding metals of classes 2 and 3 it is considered sufficient if the result is reported as „*not more than the option 1 limit*". Thus, the reporting threshold is not required to be lower than the acceptance limit for class 2 and 3 metals. This is different as recommended in ICH Q3A/B, where the reporting threshold is always underneath the identification threshold and the acceptance level. The option 1 limit has to be defined according to the route of administration of the material (oral/parenteral). For the metals of class 2 and 3, and in contrast to metals of the class 1, it is not necessary to indicate an effective value. Even a reportable result, e.g., "smaller than LOD or LOQ" is not necessary for class 2 and 3 metals based on the example provided in the guideline.

For metals of the class 1 and class 2 the individual name of the respective metal has to be listed, this is not required for class 3 metals (currently Fe and Zn). Table 7 shows a summary to the required indication of analytical results of the metals.

Table 7: Overview about the required reporting levels of metallic residues

Result / Class	≥ 30% of the Limit	< 30 % of the Limit **and "adequately removed"** (determined on 3 consecutive industrial or 6 pilot scale batches)
Class 1	**Effective value**	**Effective value or ≤ LOQ** Skip testing is possible
Class 2	**≤ Limit parenteral/oral**	**≤ Limit parenteral/oral** Skip testing is possible
	if justified, a non specific method is possible, but the metals have to be named individually	
Class 3	**≤ Limit parenteral/oral**	**≤ Limit parenteral/oral** Skip testing is possible *The test may be deleted from the relevant specification if the drug product manufacturer sufficiently demonstrates that the adequate removal of the metal residue from the pharmaceutical substance or the drug product is guaranteed.*
	if justified, a non specific method is possible, no obligation to name the metals individually	

The term "Limit" in this table refers to the option 1 limit

3.4 Approach to find an appropriate medium to provide information about metal residues

3.4.1 General aspects to provide information on metal residues

The information about metal residues according to the EMEA guideline should be made available very simple and clear by the supplier of a pharmaceutical substance to the drug product manufacturer using available media as far as possible. The statement should be as clear as possible to avoid further enquiries. The usage of the specification, and the certificate of analysis (CoA), as a suitable medium of information for that purpose will be examined. It may be appropriate, as the metals which are likely to be present in the product should be included in the specification and as the CoA is provided to the customer anyway.

The possibilities are evaluated on how the information regarding the requirements of the EMEA guideline can be integrated into the specification, the criteria of which are listed and assessed according to importance. Some possibilities for the integration of the desired information in the specification are considered, differing in arrangement and form of the added information: directly at the respective metal parameter, or the respective parameter is marked with a sign and a text is added in a footnote or the parameter remains unchanged and the respective metals are listed with the concerned information in a footnote. With the

help of a decision analysis the most appropriate option is selected and presented for a decision.

3.4.2 Matter of decision

The matter of decision is to find the most suitable way to integrate the information about metals according to the guideline EMEA/CHMP/SWP/4446/2000 in specification and CoA: how to indicate the respective analytical parameter and outline the necessary statements.

3.4.3 Points to consider

When including the information into the specification two basic cases are to be distinguished: *a)* Metals are possibly present due to use as a catalysts or reagents; or *b)* they are not likely to be present, because they have been proven to be completely removed or they have not been used.

a) Metals likely to be present due to their use as metal catalysts or reagents will be necessarily specified. A possible way will be to add information directly at the analytical parameter. The information should demonstrate that this metal parameter refers to the guideline with title and number, either written directly behind the parameter or by using specific indicators and footnotes. Other metals as well can already be included in the specification because they are demanded e.g. by declared pharmacopoeias or other regulations. Nevertheless, these metals are not necessarily used in the manufacturing process or do not belong to the 14 metals of the guideline.

b) Metals of the guideline not likely to be present are referenced by a complementary statement in the specification to provide this information. Again an unambiguous relation to the guideline should be given to make clear that exclusively the mentioned root cause of contamination is referred to and that only the mentioned metals of the guideline are considered. The requirements and the weighted importance of the criteria to integrate the information about metals concerning the guideline in the specification are summarised (Table 8).

Table 8: Criteria to be considered for a decision

Group of criteria	**Criteria**	**Weighting** 4 very important 3 important 2 to consider 1 nice to have
Content:		
	Clarification that only residues of metal catalysts or metal reagents according to the guideline are concerned	4
	Entry must be clearly and well comprehensible arranged	3
Layout:		
	Uniform representation for different substances for all intended uses is possible	3
	Good integration within the list of other, already specified metals	2
	Uniform applicability of the entry even if several metals are concerned (avoidance of auxiliary verbs like "is" or "are")	1
Set up and maintenance:		
	Easy and clear set up in the LIMS	3
	Easy check of correctness with every specification amendment (enable high awareness of the concerned entry in the LIMS)	2
	If further metals in the guideline are added: Adaptation of the entry is easily possible	2
	As low as possible effort for maintenance	1

3.4.4 Results of decision analysis

3.4.4.1 Metals used and likely to be present

According to these criteria an option resulted as most suitable among the ones considered, in which the concerned metal is marked with an asterisk which is explained in the footer of the specification by using the text:

> * specified acc. to EMEA/CHMP/SWP/4446/2000
> (Specification Limits for Residues of Metal Catalysts or Metal Reagents).
> Further metal residues acc. to this guideline are not likely to be present.

By designation with an asterisk a text directly at the parameter is not necessary. Thus, the specification remains clearly arranged. However, it may turn out that in a specification of a pharmaceutical substance registered in several pharmacopoeias, not all metals will be in the specification solely due to the guideline. For some substances even more metals will be included in the specification due to the requirements of the pharmacopoeias if they are used as metal catalysts or metal reagent or not. Therefore certain metals may be marked within a specification, while other metals have no marking. Because of the explicit relation to the guideline it is not possible and necessary to address metals, which are not mentioned in guideline, but used as catalysts or reagents. On the other hand, it is very easy to complement the marking of a metal, if the respective metal will be included into the guideline. The approach therefore allows flexibility with regard to expected revisions of the guideline in the future.

3.4.4.2 Metals not likely to be present

If residues of metal catalyst or metal reagents are not likely to be present, the following statement is mentioned in the footer of the specification as supplementary information:

> Residues of metal catalysts or metal reagents acc. to EMEA/CHMP/SWP/4446/2000 are not likely to be present.

With this text reference to the guideline is made and with it the intended use of the metals is pointed out as the root cause. Other sources or causes for the presence of metals than the use as metal catalysts or metal reagent may lead to detectable traces of metals without infringing the criteria of the guideline. The wording “likely to be present” as used in the guideline is connected with “not”. Therewith it is expressed that the metals of the guideline are either not used in the manufacturing process or were removed consistently from the substance. The provided information is considered to be sufficient to meet the criteria of the guideline for pharmaceutical substances used in the manufacture of drug products.

4 Discussion

4.1 TTC concept

A concept for limit setting for unusually toxic substances is already applied for genotoxic impurities.[35,36] Such compounds can easily react with biological macromolecules as for example the DNA and cause damages. Hence, they exhibit potentially genotoxic properties and thereby closely related also tumour-promoting properties. The respective ICH guidelines (ICH Q3A/B) provide no sufficient answer to this topic. Thus, a new EU guideline was adopted by the CHMP for the definition of limits for genotoxic impurities which has become into force in the beginning of 2007.[20]

Adverse effects of genotoxic impurities might occur even at lowest doses without a safe exposure. Complete elimination of genotoxic impurities from substances is often not achievable, thus, the implementation of a concept of acceptable risk is required. The recommended concept of Threshold of Toxicological Concern (TTC) was established on the basis of the analysis of potencies of hundreds of non-genotoxic and genotoxic carcinogens from rodent long-term studies and estimates a daily human intake value for a high probability of not exceeding a 10^{-6} cancer life time risk.[37] For most genotoxic carcinogens an intake of less than 1.5 µg per day is connected with a theoretical cancer life time risk from less than 1 to 100,000 what is accepted as a satisfactory risk level for drug products. This TTC value is accepted as a general reference value for the definition of tolerable limits of genotoxic impurities in drug products. This concept is not applicable to certain classes of genotoxic impurities (e.g. aflatoxin-like- , N-nitroso-, and azoxy-compounds, “cohort of concern”[36]) as

well as substances with available long-term data for a product-specific assessment which would require control to levels lower than the TTC.

The TTC concept presents a risk-based system to determine limit values for substances with exceptionally high toxicological potential. Thus, it can be seen as a general concept. Hence, the transmission of this TTC concept to metals without assigned PDE might be also applicable. However, as the limit is very low this might be only appropriate if there is well founded concern for a certain metal and higher limits cannot be sufficiently justified.

4.2 Approach of the USP

The USP has published a stimuli article[38] that describes a concept proposal of future dealing with metal residues in pharmaceutical starting materials (API, excipients) and dietary supplements. The purpose is to provide a revision of the chapter <231> Heavy Metals and to invite to comment on the proposed approach.

The concept of the USP aims at a replacement of the current test on heavy metals. This wet chemical test is subjected to several restrictions and should be revised by modern analytical technologies of elemental analysis (ICP-MS, ICP-AES, AAS, etc). Defined concentration limits are indicated for 31 metals and thereby these are distinguished between limit values for oral and parenteral exposure, the limits for parenteral exposure being 10 fold lower than the concentration limit for oral exposure. The method of analysis is not explicitly assigned.

The method selected may include plasma spectrochemistry, atomic absorption spectroscopy, or any other method that displays requisite accuracy (trueness and uncertainty) and established sensitivity and specificity.

In the section "Equipment" ICP-AES and ICP-MS are listed, only. It can be concluded that these are provided as default procedures but not as referee methods.[39] However, the procedure chosen must meet USP accuracy, sensitivity and specificity requirements.

The sample preparation method is based on solubility of the sample, like aqueous solution (dilute acid), organic solvent, or closed-vessel microwave digestion for substances not sufficiently soluble in any solvent. Four working standards and a blank are to be analysed. A spiked sample (monitor) has to be prepared in the same manner as the sample to be tested.

System suitability criteria are proposed regarding sensitivity, accuracy, calibration and drift. They have to be met at any analysis performed and are shortly outlined:

Sensitivity: a „method reporting limit“ (MRL) is defined *as the lowest element concentration of a solution prepared in the working calibration standard matrix that can be determined within ± 30% of the prepared concentration*. The MRL has to be (not more than) 50% of the USP limit for each applicable element.

Accuracy is determined in terms of recovery of the USP reference standard. The method has to demonstrate being capable to obtain results within ± 20% of the certified concentration for each required element. Spike recovery of a spiked test article solution has to be within ± 20% of the spike concentration as well.

Calibration standards are prepared on four concentration levels by which the lowest level is not more than 50% of the indicated concentration limit (MRL). The recovery function is evaluated at five concentration levels, including a blank. Standard curve acceptance criteria must be met according to USP chapter <730> that means e.g. correlation coefficient should be not lower than 0.99.

Instrument drift has to be monitored throughout and following the final test using a working standard solution to be within ± 30% of the prepared concentration for each element.

USP reference standards must be used to perform this determination, of which three types shall be offered (not currently available):

- for test articles soluble in aqueous solutions,
- for test articles soluble in organic solvents,
- for closed-vessel microwave digestions

The concept is to provide a suitable standard material for any kind of substance. According to the current timeline the USP aims to develop the standards at the end of 2009 and to have the new methodology finalised in November, 2010.[40] However, implementation may take several years beyond that.

4.2.1 Comparison of the USP stimuli article with the EMEA guideline

The essential difference to the EMEA guideline consists in the fact that the USP draft includes an analytic screening carried out on 31 metals, whereas, the EMEA guideline restricts the scope to metals which are likely to present as impurities from the process, only. The EMEA guideline is not applicable to unknown sources of metals. EMEA's current thinking is to limit other sources of metallic residues by GMP measures. Thus, the scope of the USP stimuli article is much broader with respect to sources of impurities like not discovered contaminations of starting or raw materials (minerals, herbals), contamination by processing equipment, and pollutions from environment.

The main focus of the USP stimuli article lies therefore on the control of impurities that are not necessarily related to the manufacturing process whereby process-related impurities may be included. The intention of both approaches is therefore different, even if the subject of the control of metal residues is the same. Table 9 summarises the comparison of both approaches.

Table 9: Comparison of the EMEA guideline with the USP stimuli article

	EMEA guideline	USP stimuli article
Restriction on process-related metallic impurities	yes	no
Screening on impurities not related to the process	no	yes
Requirements on the method of analysis	validated	meet SST requirements
Providing of concentration limits (parenteral/oral)	yes	yes
Individual justification for the limit	yes	no
Number of metals	14	31
Valid for starting materials of	drug products	drug products, dietary suppl.

4.2.2 Comments on the USP stimuli article

A "digest of comments received on the stimuli article" was published on the USP-website.[41] In this overview the comments are divided into four categories: general, toxicity limits, methodology, and implementation. To summarise, many comments are concerned to the following points:

4.2.2.1 General

- A risk based approach should be the basis for testing on metals: Testing and reporting should only be required for elements which are reasonably expected to be present or those which have been previously identified. General metal screening might be appropriate when performed on new materials or when evaluating new suppliers. It is not necessary to look for all the metals in all the materials all of the time.[42]
- The elements lead, cadmium, arsenic, and (methyl) mercury are metals of special interest due to known toxic effects and demonstrated potential for contamination in pharmaceutical ingredients.[43]
- Harmonisation is recommended between the approach of the USP General Chapter and the approach of the EMEA guideline on specification limits for metal residues.[44]

4.2.2.2 Toxicity limits

- A rationale behind the proposed limits should be provided
- In the current stimuli article only one option for limit setting is provided, based on an ingestion of 10 g of product per day. A second option is missing taking into account the actual exposure contributed by the individual ingredients and the final product as wells as duration of treatment
- Limits are given for oral and parenteral exposure. For drug products administered via other routes the applicable limits are not clear.

4.2.2.3 Methodology

- For some of the substances the level of specific metals will not be achievable at the limits proposed. Thus, these products will no longer meet USP or NF specifications and consequently could be removed from the market for pharmaceutical purposes.
- The introduction of the required special analytical equipment and performing of the analyses will induce significant costs. Very low element limits for parenteral materials

for some elements will be analytically unachievable with the less expensive analysis technology ICP-OES.

- Regarding the performance of the analytical test the obligatory use of USP standard material is criticised. Extensive range of system suitability criteria of a quantitative assay is not compliant to the scope of "screening method" to identify the presence of potentially hazardous elements.[44]

The application of modern analytical technologies to the control of heavy metals is generally welcomed since the current methodology for heavy metals testing is inadequate and should be replaced by instrumental methods of higher specificity and sensitivity.[45]

In the USA the regulation to limit metal residues in pharmaceutical products and dietary supplements will be enforced. It is obvious that the revision process of chapter <231> will move on rather quickly. In April 2009 "Metal Impurities" has become one of the "Hot Topics on the USP website[46] and a metal impurities workshop was organised. USP anticipates that the new draft chapter <231> "Heavy Metals" will be published in PF at the end of 2009 with the final revision out in 2010. This will become official at a later date or with a sufficient transition period to allow manufacturers sufficient time to incorporate changes in their processes.[47]

4.3 Where are heavy metals likely to occur and when do they need control?

It will be the goal to set limits for appropriate metal impurities of known toxicity and for metals that are likely to be present. The limits should be based on toxicology data, metal species, daily dose and metal fraction, route of administration, and patient population.

In-depth evaluation should be performed for items of higher risk like certain minerals or herbals. Elevated levels of metal impurities were reported for Ayurvedic herbals or Nigerian herbals.[48] Generally control of impurities should be achieved through process control rather than by testing. It can not be in the scope of a pharmacopoeial monograph to control any impurity that could be in a substance. This is confirmed in the General Notices of the USP:

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. (USP, General Notices, Test and Assays)

Unexpected non-process related metal impurities are therefore not necessarily in the scope of a pharmacopoeial monograph. Monographs should include metals tests only for materials of specific risk. Safety limits should be provided based on toxicological assessment and daily intake. Manufacturers of pharmaceutical substances should be expected to have a control based strategy on their material composition.

The role of Industry should be to assure a reliable and robust control of the supply chain of all starting materials. Traceability and consistent quality from all points in the supply chain should be safeguarded and will belong to the manufacturer responsibilities. Screening for

inorganic impurities might be appropriate for new materials or materials of new suppliers. Thereby the need for inclusion of specific tests into routine testing can be determined. The criteria for inclusion of parameters into routine testing should be risk based. Moreover, control will be necessary for metals which are likely to be present based on natural occurrence in source materials.

5 Conclusion and outlook

The European guideline on specification limits for residues of metal catalysts or metal reagents came into effect on 01 September, 2008 and applies to new and existing marketed products. For existing marketed drug products *a time limit of 5 years is set for implementation of the guideline in case an earlier implementation is not feasible*. It is anticipated that further changes are to be expected with regard to the control of metal residues. In the text of the guideline it is already stated that it may be updated to include other metal residues in due course as the guideline currently includes 14 metals, only. However, the first step is done, the guideline sets standards on how to regulate the presence of metal residues in pharmaceuticals in Europe. An inclusion of the principles of the guideline as a general chapter into the European Pharmacopoeia is conceivable, as it has been done comparably for the guideline on residual solvents.

5.1 Further metals to add

According to the comments on the USP approach the “big four” elements lead, cadmium, arsenic, and mercury, exert well-established safety concerns. Thus, these elements probably will come into consideration for setting acceptable limits for a maximum daily oral and parenteral exposure in drugs and dietary supplements.[46] These “big four” elements may play a leading role during the revision of the USP chapter <231> on heavy metals. Concentration limits for these four metals are already provided in the European council directive 88/388/EC as amended which applies for ‘flavourings' used or intended for use in or on foodstuffs to impart odour and /or taste, and to source materials used for the production of flavourings:[49]

“Member States shall take all measures necessary to ensure that they do not contain more than 3 mg/kg of arsenic, 10 mg/kg of lead, 1 mg/kg of cadmium and 1 mg/kg of mercury

These limits for flavourings might give an orientation; however, flavourings are usually used in only small amounts. So it is questionable if the limits will be appropriate for the EMEA guideline as these are based on a maximum dosage of 10 g per day. The proposed limits for oral exposure in the USP stimuli article are 1.5 µg/g of arsenic, 1 µg/g of lead, 2.5 µg/g of cadmium and 1.5 µg/g of mercury.

5.2 Complexity of safe limits for metal residues

There are various problematic aspects associated with providing recommendations on safe limits for metal residues, e.g., limitations in available toxicological data, duration of exposure, route of administration, speciation and form and others. Some of the difficulties in safety assessment are shown for aluminium, a constituent of the catalyst raney nickel or complex hydrides, however, currently being not included among the 14 metals of the guideline.

Aluminium belongs to the metals for that currently one of the strictest concentration limits is applied among the Ph. Eur. monographs: the aluminium content is limited to not more than 1 ppm, or even 0.2 ppm, if intended for use in the manufacture of dialysis solutions (e.g. sodium chloride, sodium lactate, citric acid, magnesium chloride). For non-parenteral applications such strict limits are not required. FDA has set a limit of not more than 25 µg/l of aluminium in large and small volume parenterals used in total parenteral nutrition.[50] However, the proposed concentration limit for parenteral exposure in the USP stimuli article of 500 µg/g is on a higher level. On the other hand, the limit for oral exposure is proposed to be 5000 µg/g whereas aluminium lake compounds are frequently used as colouring agents in pharmaceuticals.[51] Products containing such ingredients could exceed the suggested amounts.

General setting of safe limits of metals is discussed controversial. Further the question turns up if a single factor of 0.1 is appropriate to set the parenteral PDEs compared with oral PDE for all metals. Intestinal absorption of aluminium is estimated to be less than 0.5%[52] resulting in a factor of lower than 0.01 between oral and parenteral PDE. It becomes obvious that setting of appropriate, harmonised PDE levels to be applied for all intended uses is a complex task which needs lots of data e.g. from toxicological investigations or diet studies.

5.3 Harmonisation approaches

On account of worldwide trade of pharmaceutical substances a harmonisation of the requirements is highly appreciated, e.g. within the scope of an ICH process or via PDG.[39] USP announced recently to target a new general chapter <232> “Elements and Limits” covering the “big four” elements as well as the EMEA metal catalysts, including their scope as outlined in the EMEA guideline (12 metals with EMEA limits, less iron and zinc). This general chapter will be presented to the PDG for harmonisation.[39] It should be the objective to adopt common standards harmonised all over the world so that, for a product manufactured at the same site and marketed in different countries, the manufacturer does not have to repeat testing according to different specifications for the various regions (Europe, United States and Japan). This would allow setting a “global specification” for pharmaceutical substances with agreed safe limits for relevant metal impurities, properly analysed and thereby ensuring the quality and safety of medicines.

6 Summary

Due to the apparent significant impact of impurities on pharmaceutical safety and quality there are regulatory recommendations on impurities in pharmaceutical substances. The guidelines of the International Conference on Harmonisation (ICH) are presumed to be the most important ones. However, metallic impurities are not addressed in sufficient detail in the current ICH Q3X guidelines. The development of the European "Guideline on Specification Limits for Residues of Metal Catalysts or Metal Reagents" intends to fill this gap. The final version of this guideline has been issued by the EMEA after about 10 years of consultation and came into effect on the 1st of September, 2008. For existing marketed drug products a time limit of five years is set for the implementation, if not feasible earlier.

The scope of the EMEA guideline covers metals that are likely to be present due to deliberate addition during the manufacturing process. Maximum acceptable concentration limits for the residues of metal catalysts or metal reagents that may be present in pharmaceutical substances or in drug products are recommended. The applicant for the Marketing Authorisation Application has to compile correct information on this matter. In many cases it will not be sufficient to consider only the last manufacturing step to assess the metals which are "likely to be present". Preceding steps of production and starting materials should also be considered. A metal used as a catalyst or reagent in the manufacturing process is assumed as "likely to be present" unless it is demonstrated to be removed consistently. Requirements on metal analysis and reporting levels are discussed.

A questionnaire for manufacturers and suppliers is presented to obtain information on metal residues in purchased pharmaceutical substances. Besides an audit of the manufacturer, this has been demonstrated to be a suitable tool to obtain the necessary information. The completed questionnaires of more than 100 substances are evaluated with regard to completeness, plausibility and way of providing the information. Moreover, an appropriate option is discussed on how to include information on metal residues in the certificate of analysis of a substance to be in line with the criteria of the guideline.

The development of the EMEA guideline beginning with the first draft up to the currently valid version is reviewed and the current developments in this area are summarised. The guideline is discussed in connection with the existing regulatory framework on impurity control. An overview of the general concepts relating to impurities and their fundamental origins in pharmaceutical substances is provided whereby the existing guidelines are considered particularly to their relation to metallic impurities.

"Metal Impurities" has become one of the "Hot Topics" on the USP website after the USP published a concept for revision of the general test on heavy metals. The proposed USP

approach is compared with that of the finalised EMEA guideline and an outlook for future developments is discussed.

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Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegeben Hilfsmittel verwendet zu haben.

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Datum, Unterschrift