European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA	Belgium
2	NAGARJUNA PH.D	India
3	LEEM – Les Entreprises du Medicament	France
4	Merck Sharp & Dohme Inc.	EU
5	IPEC Europe	UK

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GENERAL COMMENTS - OVERVIEW	
Comment and Rationale	**Outcome**
EFPIA: We welcome this draft document, which is much improved over previous versions and provides clear guidance to industry and regulators, which reflects a common understanding among the E.U health authorities. To the best of our knowledge, there is no public U.S draft regarding this topic. This document, in the draft or final state, could be a starting point for further discussions with other ICH regions with the aim of being extended / implemented to the ICH members. We have no major concerns, but would like to present a number of comments which we believe, it taken into account, would clarify aspects of the final guideline, facilitate implementation and take into account future developments.	We thank EFPIA for their recommendations. However it is currently not considered realistic to bring this subject to ICH level. Therefore no action will be undertaken at this moment
Whilst it is helpful to see a transition period of 5 years proposed for the implementation of this and any guideline to existing marketed drug products, retrospective application is viewed as less than optimal. It would be helpful to also include advice for existing products with European Pharmacopeia monographs with different limits and what would be legally binding. How to eliminate any conflict with existing European Pharmacopeia monographs (including general chapters). In order to facilitate compliance with the final guideline and reduce any unnecessary regulatory activity, we would recommend that the CHMP consider adopting a similar process to that for compliance with the ICH/CHMP guideline on residual solvents that was introduced in 1999. If variations were only required for medicinal products with active substances containing Class 1 metals i.e. those metals of significant safety concern, this would reduce the regulatory burden significantly. The MAH would then take responsibility for updating specifications for active substance containing Class 2 and 3 metals within the 5 year implementation period.	Metal catalysts and reagents can impose risks to public health. From a patients' perspective, this risk is not related to the intake of a new or existing medicinal product. Thus, there is no reason to differentiate in the requirements for metal catalysts in new and existing products and thus this guideline should also be applicable to existing products. However, it is acknowledged that direct retrospective application of the guideline to existing products may cause problems for industry and therewith also for patients as it may impact on the availability of medicines. A five years transition period for industry has been chosen to make their existing products comply with the guideline. This period is considered an acceptable balance between the time necessary to take appropriate actions and the need to avoid any known risks to public health.
It is creditable that the guideline includes a specific exclusion for the clinical research stages of development of a medicinal product: this will prevent unreasonable expectations in the development phase, but may not prevent inconsistent standards being requested by regulators for investigational products. Some text should be added to clarify that higher limits can be acceptable during	This comment has been included in the final Guideline.

the clinical research phases.	
The title of this draft guideline addresses metal catalysts but in the scope metal reagents are also included. On the other hand the executive summary and the introduction only applies to drug substances and excipients. For a better understanding the title should be adapted to metal reagents and the metal reagents should be added to the keywords. In addition the whole text should reflect this extended scope. For very low dose drugs, e.g., less than 100 microgram doses, 1) the general pharmacopoeia test should provide the necessary level of assurance 2) as the amount of a catalyst present could never achieve the calculated PDE/MDD without affecting other parameters, the related requirements within this guideline should not be needed. GMP would control this situation.	This comment has been taken into consideration. The title, scope and executive summary of the final Guideline now contain consistent information making it applicable to metal catalysts and reagents.
We support the concept of controlling these residues in pharmaceutical substances (API and excipients) rather than in drug products. If it can be shown that a metal catalyst used in the synthesis is absent in the API, then routing testing in the API specification can be omitted. Absent should be defined: This could be done similarly as for residual solvents i.e. below 10% of ICH limit is considered absent.	The comment has been taken into consideration. The final Guideline now includes guidance on the need to set a specification, the need to routinely test according the specification and the value of the Ph. Eur. test on heavy metals.
The document defines specifications for a limited number of 14 metals. In the future will other commonly used metal catalysts such as Pb, Hg, Ag, Co be included and what will be the process that is followed?	For revisions or updates of the guideline EFPIA should make proposals including toxicological evaluation of metals to be included.
For Class 3 metals it should be more clearly stated that it is not necessary to test each metal since a general method, as Heavy Metals according to European Pharmacopeia, should suffice.	The comment has been taken into consideration. The final Guideline has been clarified on this issue.
In principle, the limits provided by the guideline are reasonable and we applaud EMEA CHMP's use of risk assessment to provide safety limits for residual metal catalysts.	

We agree with the two-option approach to setting limits. In most cases, the defined maximum therapeutic dose for a pharmaceutical is much lower than 10 g/day. The document correctly recognizes that safety is ultimately governed by the PDE, and Option 2 provides an appropriate approach for determining safety.	
NAGARJUNA PH.D: Stanus Chloride uses as catalyst in sartan molecules manufacturing process (Valsartan, Candesartan, Irbesartan etc.). Why shouldn`t include limit for Sn? If so what is limit and under which class it will cover? Your response on above questions is appreciable. Please find below JECFA proposed PTDI. JECFA (Joint <FTO/ WHO> Expert Committee on Food Additives) recommended the Provisional Tolerable Daily Intake(PTDI) as 2 mg/kg/day).	For updates of the guideline proposals can be made including toxicological evaluation of metals to be included. For setting limits for Sn please use the principles for limit setting as outlined in the guideline.
LEEM: LEEM welcomes this draft document which reflects a common understanding among the E.U health authorities. To the best of our knowledge, there is no public U.S draft regarding this topic. This document, in the draft or final state, could be a starting point for further discussions with other ICH regions with the aim of being extended / implemented to the ICH members. LEEM would be very grateful to collaborate in such discussions, concerning either API's or excipients.	We acknowledge that Guidelines which would be harmonised within the USA, Europe and Japan would be favourable to industry. However, under the current circumstances this is currently not considered a feasible option. Therefore no action will be undertaken at this moment.
IPEC: In general we welcome the revision of the guideline, the format and style is very helpful in establishing how to extend the principles in the guide to other metals and catalysts. The following comments are specific to excipients which are specifically mentioned in the executive summary. Feedback on this topic from the IPEC Europe membership has been very limited, possibly due to the attention which excipient producers are giving to the REACH initiative.	Please note that the final Guideline is not limited to active substances only.

There remain issues regarding the confidentiality of catalyst identity within the chemical industry, especially as there is no provision for a secure central repository for proprietary information.	

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Page 1 & 2	The title of this draft guideline addresses metal catalysts but in the scope metal reagents are also included. For a better understanding the title should also include "metal reagents". "GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS ***/ REAGENTS"***	The title has been revised in agreement with this comment.
Section Executive Summary Line 2	The title and executive summary refer to residues of metal catalysts, whereas the introduction refers to residual metals from catalysts and reagents (which we assume is correct). We recommend that, for clarity, these inconsistencies should be addressed. Suggest the following correction in the executive summary. "… Residual metals used as process calalysts ***/ reagents*** do not provide any …"	The wording of the guideline has been clarified.

1 INTRODUCTION

Line no. + para no.	Comment and Rationale	Outcome

[1] Where applicable

1-3.2.4	Merck agrees with the determination of the metals but questions the arbitrary 5 year limitation, in testing existing products and excipients. Why was 5 years decided?	See response in general comments section
Section 1. 2d paragraph Lines 4-5	Line 4-5, the option to include other sources of metal residues is introduced. Such new sources mean an extreme extension of the scope. This could lead to a complete new guideline that should be discussed properly before implementation. Therefore updates for new sources should be excluded for this guideline. Suggest clarify this 2d paragraph to exclude "residues from other sources"	We do not agree; see response in general comments section.
Section 1. 2d paragraph Line 5-6	The following sentence in the introduction directly affects the scope of the guideline "The guideline does not apply to metals that are deliberate components of the drug substance (such as a counter ion of salt) or are an excipient in the drug product (e.g. an iron oxide pigment)." Therefore, we recommend to shift it to section 2. Suggest shift sentence "The guideline does not apply to metals that are deliberate components of the drug substance (such as a counter ion of salt) or are an excipient in the drug product (e.g. an iron oxide pigment)." from section 1. to section 2.	The guideline has been revised accordingly.
1-2.9.4	There needs to be further detail of the reasoning for breaking down the sub-classifications of 1A, 1B, 1C and the rational for this breakdown into these sub-groups.	The subgroups have different limits due the available toxicological data
Section 1. Para. 3	We note that the metals classified in the Guideline do not include several metals commonly used in drug manufacture (e.g. lithium, aluminium, magnesium). It would seem useful and appropriate to extend the coverage of the guideline to these metals at the earliest possible time.	Comment accepted

Section 1. Para. 5	This statement should be reconsidered, since it acts counter to the philosophy of a science and risk-management based approach: if a limit is both safe and assures adequate quality of the product, the applicant should not be required to establish a lower limit simply on the basis of process capability. We request this statement be omitted from the text of the guideline as revised. Suggest removal of the following statement: "~~limits set based on safety criteria may therefore be higher than limits set on the basis of GMP, process capabilities or other suitable quality criteria~~".	The paragraph has been changed accordingly.
1-9.7.7	Merck agrees with the statement "If the synthetic processes do lead to potential residues: routine testing with a suitable, validated method is necessary 2)." However, Merck does not agree with the statement "This testing cannot replace the requirements of relevant monographs of the European Pharmacopoeia." Instead, Merck feels that after the analysis of the metal residues as a result of the synthetic processes with a suitable and validated method, the likelihood of finding other metals is almost nothing. Further test requirements using relevant monographs of the European Pharmacopoeia are redundant and unnecessary. This testing can replace the requirements of relevant monographs of the European Pharmacopoeia.	The guideline has been clarified towards the applicability of the Ph. Eur. Test for heavy metals.
1.2.8	Merck agrees that those Metallic residues should be determined using techniques such as atomic absorption or ICP. But, ICP-MS is becoming more and more popular, and should be mentioned and added in the above sentence. Merck would also encourage validated methodologies for metals determination using AA, ICP, and ICP-MS are included in individual substance monographs. It should read: Metallic residues are typically determined using techniques such as atomic absorption, ICP, and ICP-MS.	The guideline will be open for any appropriate validated method.

GUIDELINE SECTION TITLE – 2. SCOPE		
Section 2. General	The scope should clearly define for which kind of substances the guideline should be applicable. This guideline may be applicable for e.g. new and existing drug substances, synthetic peptides etc. Suggest to revise accordingly	The scope has been clarified.
Section 2. First paragraph Last sentence.	As written in the Introduction, Paragraph 2, we agree that "the safety data in this guideline can also be used for specific metal residues in pharmaceutical products which are residues from other sources". Section 2. Paragraph 1 contradicts this statement. Changes in the wording would support use of the listed PDEs as stand-alone safety-based limits. "Excluded from this document are ~~extraneous metal contaminants that should not occur in drug substances or excipients and are more appropriately addressed as Good Manufacturing Practice (GMP) issues~~ ***the Good Manufacturing Practice (GMP) and quality ramifications associated with issues such as extraneous metal contaminants that should not occur in drug substances or excipients."***	The statement has been clarified and is now worded as: *"the guideline does normally not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any other relevant quality provision."*
Section 2. First paragraph Lines 1-3	The introduction of the guideline states: *The objective of this guideline is to recommend, for the safety of the patient, maximum acceptable metal residues arising from the use of metals as catalysts or reagents in the synthesis of drug substances and excipients.* For already marketed products, which have not undergone major changes to the process, product safety is already implicit. Suggest revise wording as follows: This guideline applies to all new drug products ***and to existing marketed products where major changes have been made to the manufacturing process***. ~~In the latter case, a time limit of 5 years is set for the implementation of the guideline in case an earlier implementation is not feasible.~~	This is not considered appropriate.

Section 2. First paragraph Lines 5-7	As the source of the metal may be unknown, the intent of the statement is better suited for the INTRODUCTION rather than the SCOPE. Suggest move this statement from Section 2. SCOPE to Section 1. INTRODUCTION "Excluded from this document are extraneous metal contaminants that should not occur in drug substances or excipients and are more appropriately addressed as Good Manufacturing Practice (GMP) issues."	The guideline has been revised accordingly.
Section 2. 2nd paragraph	The guideline advises that, "… for existing marketed products a time limit of 5 years is set for the implementation of the guideline in cases an earlier implementation is not feasible." Whilst we support a 5-year implementation period for existing marketed products, we believe that this requires qualification by taking into account the QP release of the medicinal product onto the market. Suggest the follow text after the second sentence as follows: "***Following 5 years implementation, the QP can only release medicinal product manufactured using drug substance which complies with the guideline."***	The statement has been clarified and is now worded as: *"Following this 5 years transitional period only drug products which have been manufactured using pharmaceutical substances which comply with the guideline can be released to the market"*
2.0	The five year interval for compliance in existing marketed drug products is appropriate. This will ensure continuity of supply of drug products.	The comment is appreciated; no response needed.
GUIDELINE SECTION TITLE – 3. LEGAL BASIS		
Section 3.	We recommend adding the ICH Guidance *Q2(R1): Validation of Analytical Procedures: Text and Methodology* to the list of relevant Guidance documents.	ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology The guideline has been revised accordingly

GUIDELINE SECTION TITLE – 4. MAIN GUIDELINE TEXT		
Section 4.2 Table 1	Even though ICH Q3C guidance is cited as the basis for calculation of the PDE, this does not appear to have been applied to the metals. "Pragmatic reasons" seem to have been applied with no explanation. It still appears that a level was preceded and data made to fit the level.	The comment has not been accepted. The principles for PDE calculation as outlined in ICH Q3C have been applied in general and exceptions are noted in the monographs.
Section 4.2 Table 1 Footnote *	It is noted that a footnote to Table 1 refers the reader to Section 4.4 for specific inhalation exposure limits for certain metals. Furthermore, we are concerned that the limits proposed for inhalation exposure to nickel, chromium VI and platinum (as hexachloroplatinic acid) will present significant challenges in terms of analytical methodology, i.e. severe sample preparation problems, and equipment operating at the limit of its capability. It is considered more useful to list these limits in Table 1, on page 6. We wish to highlight this significant concern for further discussion among interested parties.	The comment is not accepted. The limits are clearly stated in 4.3.3.
Section 4.3 p. 6	What is meant by maximum daily dose (MDD) - is it the maximum daily product mass (as in the ICH guideline for residual solvents Q3C (R3)) or is it the actual daily intake of the particular excipient or drug substance (as in the previous draft of this guideline)? Explain if product mass or daily dose of each excipient and each drug substance is meant by maximum daily dose. In case drug product mass is meant it should be considered to modify the wording in the executive summary and also mention "drug product". Currently it is stated "This guideline recommends maximum acceptable limits of metal residues in drug substances and excipients." In case the maximum daily dose of each excipient and each drug substance is meant it should be explained more detailed how to deal with cases where the same metal is a residual metal in several ingredients of one drug product. Furthermore in the sentence under option 2 "… to determine the concentration of residual metal allowed in the drug product." "drug	

	product" should be replaced by "drug substance or excipient". Suggest to revise accordingly	The guideline has been revised accordingly (consistently drug product)
Section 4.3 Option 1	In Option 1 the limits are discussed in relation to drug substance, excipients and the drug product, while in option 2 the limits are discussed only in relation to the drug product. The pharmaceutical term "maximum daily dose" is normally used for the quantification of drug substances medical application. This confuses the setting of the limits. We recommend defining the calculation of the concentration limit referring clearly on the daily dose of the particular ingredient. The term MDD should be adapted respectively. Suggest replace second sentence in Option 1 by *"They were calculated ~~using equation (1) below by assuming a maximum daily dose (MDD) of 10 grams (g) administered daily~~* ***~~by assuming a maximum of 10 grams (g) of any ingredient (drug substance or excipient) administered daily.~~"***	The guideline has been revised accordingly.
Section 4.3 Option 1	We remain disappointed that only the option 1 limit can be considered when making a case for adequate removal of a metal in the 'Testing Strategy'. As this option 1 limit does not allow for consideration of the specific dose regimen of the drug product (and is constructed for the arbitrary – and high-dose of 10g per day) this requirement to use the Option 1 limit in the consideration of the 'Testing Strategy' seems arbitrary and non-scientific. We would suggest that the option 2 limit should be also allowed for consideration of what testing strategy is appropriate for a specific material. Not to do so reduces the scientific value of the guideline considerably.	This comment has been addressed (see paragraph 4.5).
Section 4.3 Option 1	Modify as per the underlined section. The term "pharmaceutical substances" is preferred over the listing for consistency. The sentence should be revised as follows. "These limits are considered acceptable for all listed metal residues present in ~~drug~~ ***pharmaceutical*** substances, ~~excipients, or products~~ and can be applied for each individual metal."	The guideline has been revised accordingly.

Section 4.3 Option 2	This statement "…and equation (1) above to determine the concentration of residual metal allowed in the drug product." Is in conflict with the statement in paragraph 1 of the INTRODUCTION, which says this is applied to APIs and excipients, not the final drug product. Suggest revise as follows "…and equation (1) above to determine the concentration of residual metal allowed in the ~~drug product~~ ***pharmaceutical substance."***	The guideline has been revised accordingly.
Section 4.4	As Pharmacopoeias usually distinguish in their requirements on oral and parenteral medical applications, there should be no general statement to use the lowest applicable limit for substances that may be administered by several routes Suggest delete the third paragraph in this section ("The lowest applicable …") Suggest add as follows ***"Limits should be set in consideration of the route of administration."***	The guideline has been revised accordingly.
Section 4.4 1st paragraph	This states that, "… oral concentration limits should be applied for cutaneous administration." We believe that this should read "…., concentration limits or PDE " as in the previous section (i.e. concentration when a dose is unknown or fixed, and PDE when it is known)." Suggest amend text as follows. "For example, ***for cutaneous administration*** oral concentration limits should be applied ~~for cutaneous administration~~ ***when a dose is unknown or PDE should be applied when a dose is known***.	The comment is not accepted as it would change the meaning of the paragraph.
Section 4.4 2nd paragraph	This implies that <5ppm is a safe level, yet in the first paragraph it suggests using oral limits for dermal products (i.e. 10 - 1300 ppm). This needs clarification. Suggest clarify this statement.	The statement has been deleted.

Section 4.4 3rd paragraph	This states: "The lowest applicable limits should be used for a pharmaceutical substance that may be administered by several routes." We strongly disagree with this requirement as it would mean that a MAH would have to apply the tighter (parenteral) limit for a residual metal catalyst in a drug substance used in the manufacture of an oral dosage form, if it produced the two dosage forms types. There is no scientific justification for applying a tighter limit to an oral dosage form in this way. A manufacturer should be able to manage two (or more) active substances with different specifications through its stock control procedures. Please clarify.	The guideline has been revised accordingly.
Section 4.4 3rd paragraph	Safety is dependent on route of exposure, so separate specifications for a drug substance with multiple routes of administration should be allowed for each route. Requiring the lowest applicable limit to be used could have a significant impact on manufacturing. For example, the limits for platinum, chromium VI, and nickel are justifiably low for the inhalation route of exposure. This may not be a hardship for an inhaled drug that has a low therapeutic dose, but it would be a hardship for an oral drug that has a significantly higher therapeutic dose. If a drug substance is administered by multiple routes, then limits must be derived for each route.	The guideline has been revised accordingly.
Section 4.5	Generally the considerations in this section are not limited to drug substances. They are as well applicable for excipients. Suggest rename the title to "*Short-term use*".	The guideline has been revised accordingly.
Section 4.5	Compounds used for life-saving indications should be discussed separately from short-term use indications. Suggest separate the last sentence of this section into a section on its own.	The guideline has been revised accordingly.
Section 4.6	Class 1 specifications for parenteral exposure according to Option 1 are 1ppm (classes 1A/1B) or 3 ppm (class 1C).	

Line 7	A skip-test should be justified if results from at least 3 batches are not more than 30% of the specifications. Hence the limits of quantification should be lower than 0.3 and 1ppm respectively. Some techniques such as Atomic Spectrometry (AS) or ICP-Optical Emission Spectrometry or ICP-MS are used to quantify metal catalysts. ICP-MS is the most sensitive but also the most expensive technique; for this reason ICP-MS is not be accessible by all little/medium-sized pharmaceutical companies. For poorly soluble API's, AS and ICP-OES show quantitation limits sometimes higher than skip-test limits, whilst ICP-MS techniques show that catalyst contents in batches are lower than skip-test specifications. A proposal is in the opposite column. (As a reminder Class 1B LODs are not lower than 0.5ppm for individual values) (As a reminder Class 1B LODs are not lower than 0.5ppm for individual values) Suggest, after "Routine testing may be replaced by skip testing", add the following sentence: "***Skip testing may be replaced for a formal validation in the application providing results from 3 consecutive production batches for prospective validation, or ten to thirty batches for retrospective validation as proposed in the ICH Q7A document (§12.50).***	The paragraph has been revised and this point is now addressed in section 4.5
Section 4.6 Line 7	Analogous to the CPMP Annex I to Guideline on Impurities: Residual Solvents it should be possible to omit routine testing if it could be shown that the content of class 2 and 3 catalyst is below 30 % of the acceptable concentration limit. The sentence "If the synthetic processes are shown to result in the removal of potential residues (A catalyst can be considered adequately removed if, in an appropriate number (minimum 3) of representative batches of the final substance or an intermediate less than 30% of the option 1 limit could be found) of this particular metal, routine testing may be replaced by skip testing" should be supplemented by "***In case of class 2 and 3 metals routine testing may be exempted from routine control if it could be shown that the content is below 30 % of the***	The paragraph has been revised and this point is now addressed in section 4.5

	option 1 limit..”	
Section 4.6 Line 7	We are disappointed that, having shown ‘adequate removal’ of a metal residue through manufacture, the applicant is held to ‘skip testing’. We would consider it appropriate to not establish a test at all once sufficient data to assure adequate removal has been generated (e.g. from a number – 3+ - of representative lots of the final substance or intermediate manufacture at predictive scale). As an alternative proposal, analogous to the CPMP Annex I to Guideline on Impurities: Residual Solvents it should be possible to omit routine testing if it could be shown that the content of class 2 and 3 catalyst is below 30 % of the acceptable concentration limit. That limit should be the limit agreed to be safe, and could be either Option 1 or Option 2. This is important since, for some of the Class 1 metals, the concentration limit is 1ppm; we suggest that testing to less than 30% of this limit will prove challenging in a routine production environment. The sentence “If the synthetic processes are shown to result in the removal of potential residues (A catalyst can be considered adequately removed if, in an appropriate number (minimum 3) of representative batches of the final substance or an intermediate less than 30% of the specification limit could be found) of this particular metal, routine testing may be replaced by skip testing” should be supplemented by “***In case of class 2 and 3 metals routine testing may be exempted from routine control if it could be shown that the content is below 30 % of the specification limit.”***	See response to previous comment.
Section 4.6 Foot note [1])	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 since the limit of Option 2 could be lower than limit Option 1. Otherwise in such cases by skip-lot testing batches may be released which are out of limit Option 2. The term “*Option 1 limit*” should be replaced by ***“set/specified testing limit”.***	This point is now addressed in the section 4.5 and has been changed to “appropriate concentration limit
Section 4.6	Further, we note that, for some of the Class 1 metals, the concentration	

Foot note [1])	limit is 1ppm. We recommend that there should be facility for development data to underwrite “adequate removal” of potential residues of a metal, and that “no test” (or sunset test provision) should be supported as a result.	The need to set a specification and to actually perform a test is now clearly explained in the guideline.
4.6 Testing strategy First Point	Class 1 specifications for parenteral exposure according to Option 1 are 1ppm (classes 1A/1B) or 3 ppm (class 1C). A skip-test should be justified if results from at least 3 batches are not more than 30% of the specifications. Hence the limits of quantification should be lower than 0.3 and 1ppm respectively. Some techniques such as Atomic Spectrometry (AS) or ICP-Optical Emission Spectrometry or ICP-MS are used to quantify metal catalysts. ICP-MS is the most sensitive but also the most expensive technique; for this reason ICP-MS is not be accessible by all little/medium-sized pharmaceutical companies. For poorly soluble API's, AS and ICP-OES show quantitation limits sometimes higher than skip-test limits, whilst ICP-MS techniques show that catalyst contents in batches are lower than skip-test specifications. A proposal of LEEM is in the opposite column. (As a reminder Class 1B LODs are not lower than 0.5ppm for individual values) Add after "Routine testing may be replaced by skip testing": Skip testing may be replaced for a formal validation in the application providing results from 3 consecutive production batches for prospective validation, or ten to thirty batches for retrospective validation as proposed in the ICH Q7A document (§12.50).	The paragraph has been revised and this point is now addressed in section 4.5. The proposal was however not considered relevant here.
Page 7 Section 4.6 Foot note [2])	This testing cannot replace the requirements of relevant monographs of the European Pharmacopoeia (Ph.Eur.) that may, for instance, describe a general test for heavy metals. Having these requirements would provide something to support elimination of the non-specific compendia tests. This also supports our recommendation for this to become an ICH document.	The comment is appreciated.

Section 4.7 2d paragraph Line 1st	In certain pharmacopoeia monographs for the testing on metallic residues ICP or atomic absorption may not be required. In these cases the guideline could be in contradiction. Therefore we recommend to delete the sentence "*Metallic residues are typically determined using techniques such as atomic absorption or ICP.*" "~~*Metallic residues are typically determined using techniques such as atomic absorption or ICP*~~."	Specific method recommendation has now been avoided.
Section 4.7 2d paragraph Lines 4-5	A Colorimetric procedure is mentioned as example for a non-specific method. On the other hand colorimetric procedures could be specific indeed. Suggest to edit the sentence as follows: "*If only Class 2 or class 3 metals are present, a non-specific method* ~~*such as a colorimetric procedure*~~ *may be used.*"	This comment has been addressed (see now in section 4.4).
Section 4.7 4th paragraph	Validation of methods for metallic residues should conform to ICH guidance *Q2(R1): Validation of Analytical Procedures: Text and Methodology*. The cited ICH guidance documents Q2A and Q2B should be replaced by *Q2(R1): Validation of Analytical Procedures: Text and Methodology* Suggest to replace this sentence "~~Q2A Text on Validation of Analytical Procedures (March 1995) and Q2B Validation of Analytical Procedures: Methodology (November 1996)~~" by ***"Q2(R1): Validation of Analytical Procedures: Text and Methodology."***	Most relevant guidelines have been cited.
Section 4.8 Lines 1-3	The use of metals as catalysts is often regarded as being process know-how, which suppliers of excipients do not want to disclose. We therefore propose to add a requirement for disclosure of the identity and quantity of Class 2 and 3 metals for excipients. "Manufacturers of pharmaceutical products need certain information about the content of metallic residues in excipients and drug substances in order to meet the criteria of this guidance. ***Thus, the excipients and drug substance manufacturers are requested to provide a clear statement on the identity and quantity of Class 2 and 3 metals present***	This comment has been addressed in section 4.6.

	in their products supplied to Pharma customers. The following statements are given…."	
Section 4.8 Line 6	For Class 3 metals, the statement about the results and the applicability, either oral or parenteral, are missing. Therefore we suggest to add the following sentence. "Only Class 3 metals are likely to be present. ***All are below the Option 1 limit for oral or parenteral exposure (here the supplier would define the applicability, either oral or parenteral of the product)."***	This comment has been addressed in section 4.6.
Section 4.8 Line 7	There is no indication about the applicability, either oral or parenteral, for Option 1 limit. Therefore we suggest to add the following. "Only Class 2 metals X, Y,… are likely to be present. All are below the Option 1 limit ***for oral or parenteral exposure*** (here the supplier would name the Class 2 metals represented by X, Y ***and define the applicability, oral or parenteral of the product)."***	This comment has been addressed in section 4.6.
Section 4.8 Line 9	Metals below the LOQ or LOD cannot be quantified or identified. Therefore we suggest to add the following. "If Class I metals are likely to be present, they should be identified and quantified ***unless below the limit of detection (LOD) or the limit of quantitation (LOQ)."***	This comment has been addressed in section 4.6. **"**If the metal is found below the LOD or LOQ of the applied analytical method, than the LOD and LOQ of this method are given)"
4.3	Option 1 for setting concentration limits, results in a value which is independent of the proportion of the excipient present in the drug product. This could lead to excipients used at a low proportion being prohibited, without any real safety concern	This is covered by the different options provided in the guideline.
4.3	The use of Option 2 by excipient manufacturers will not be viable in most cases as excipients are used in a wide range of products with a huge variation in maximum daily dose.	This comment is not considered relevant in this context.

4.3/4	The excipient manufacturer does not often know the proposed route of administration with any certainty, so may have to assume a 'worst case scenario'	This comment is not considered relevant in this context.
4.7	Validation of test methods is currently not a requirement of excipient GMPs. This new requirement could lead to additional costs	This comment is not considered relevant in this context.
GUIDELINE SECTION TITLE – 5. GLOSSARY		
General	The listing of abbreviations is not convenient for searching purposes. Suggest to re-arrange listing alphabetically	The guideline has been revised accordingly.
General	In section 4.3 the abbreviations "*MDD*", "ppm" are defined. This should be listed here. Suggest to add ***"ppm - parts per million",*** "***MDD - Maximum Daily Dose***" (or modified abbreviation (see. proposed change 4.3)) to the listing.	The guideline has been revised accordingly.
General	The exact interpretation of 'daily dose' should be defined in the Glossary. Suggest to add exact interpretation of 'daily dose'	The guideline has been revised accordingly.
GUIDELINE SECTION TITLE – 6. REFERENCES (Scientific and / or legal)		
Section 6	We recommend to make clear that REFERENCES is a separate section, in adding the number 6 to this section. ***"6.*** REFERENCES (Scientific and / or legal)"	The guideline has been revised accordingly.
Section 6	We recommend to add the ICH Guidance *Q2(R1): Validation of Analytical Procedures: Text and Methodology* to the list of "REFERENCES". ***"ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology"***	The guideline has been revised accordingly.
GUIDELINE SECTION TITLE – APPENDIX 1: RATIONAL FOR PDE SETTING		
Appendix 1	"It should however be appreciated that since metals were not in the database used to define the TTC level…". This is technically	

8th paragraph	inaccurate. Metals were included in the carcinogenic potency database but were an exception in the risk assessment decision tree paradigm developed by Kroes et al. 2004. Therefore we suggest to modify the sentence as follows. "It should however be appreciated that since ~~metals were not in the database used to define the TTC level~~ ***metals were specific exceptions in applying the TTC concept,*** metal containing compounds and non essential metals…."	The guideline has been revised accordingly.
GUIDELINE SECTION TITLE – APPENDIX 2: MONOGRAPH ON ELEMENTS		
General	We propose that Appendix 2 should not be part of the guideline similar to ICH Q3C. The data could be published in PharmEuropa as for ICH Q3C. Suggest removal of Appendix 2 from this Guideline.	The comment is not accepted and revision not needed.
Platinum Conclusion, 1st §	Although included in appendix 3, individual safety factors defining total safety factor of 5,000 are not defined in the monograph. Use ICH Q3C methodology. "….5,000 ***(5 x 10 x 10 x 10 x 1)….*** "	The guideline has been revised accordingly.
Molybdenum Conclusion	Several assumptions not defined. Need to specify why RIVM (10 µg/kg/day) was chosen versus other standards. Need to specify why a 0.6 safety factor was chosen. Need to specify why an uncertainty factor of 8 was used for parenteral exposure. Suggest to revise the statement.	The comment is not accepted and revision not needed.
Nickel Regulatory Assessments 2nd §	Several typos. Replace: "…1.8 x 10-4 µg/m3 (range: 0.9 x 10-4 µg/m3 – 3.6 x 10-4 µg/m3)…..cancer risk of 8.6 .10-8 (range 4.3 .10-8 - 17.3 . 10-8). Based on these data a 1 in 105 lifetime risk ..." By the following sentence. "…1.8 x **10^{-4}** µg/m3 (range: 0.9 x **10^{-4}** µg/m3 – 3.6 x **10^{-4}** µg/m3)…..cancer risk of 8.6 in 10^8 (range 4.3 **in 10^8** - 17.3 **in 10^8**). Based on these data a 1 in **10^5** lifetime risk ..."	The guideline has been revised accordingly.
Nickel Regulatory	The cancer risk may be overestimated since the epidemiological study included a population who may also have been exposed to cadmium,	

Assessments 2nd §	benzene, and 1,1-trichloroethane. Suggest to include a description of the Boudet et al. assessment. Suggest revise the statement.	The comment is not accepted: the guideline is not intended to provide detailed abstracts of references (Boudet).
Nickel Conclusion 1st §	Assumptions not defined for safety factor of 800. An alternative approach would be to define the safety factors of 1000 and then disclose rounding to 300 µg/day as was done in Pt monograph conclusion. Suggest define components of safety factor according to ICH Q3C methodology (e.g. Appendix 3).	The comment is not accepted and revision not needed.
Nickel Conclusion, 2nd §	Typos: 0.6 µg Ni/kg/day instead of 0.6 mg Ni/kg/day "…0.6 ~~mg~~ **µg** Ni/kg/day …"	This comment has been addressed.
Chromium Regulatory Assessments, 7th §	Typo: " … 1 in **10^5** …" instead of "… 1 in 105 …" " …For a 1 in ~~105~~ **10^5** lifetime risk…"	This comment has been addressed.
Chromium Conclusion 1st §	Inconsistent assumptions. 60 kg person used when 50 kg person is in glossary and used for other monographs. Suggest use 50 kg person	The guideline has been revised accordingly.
Vanadium Conclusion, 1st §	Safety factor 80 not defined. Suggest define safety factor components according to ICH Q3C methodology (e.g. Appendix 3).	The comment is not accepted and revision not needed.
Copper Conclusion, 1st §	Components of safety factor 100 not defined in monograph but in Appendix 3. Define safety factor components according to ICH Q3C methodology " 100***…(2 x 10 x 5 x 1 x 1)***..".	The guideline has been revised accordingly.
Magnesium Conclusion, 1st §	No rationale for choosing 2.5 mg. Suggest define endpoint, safety factors and assumptions used to develop PDE.	The comment is not accepted and revision not needed.
Zinc	No rationale for safety factor of 4.	

Conclusion 1st §	Suggest define the safety factor using ICH Q3C methodology (e.g. Appendix 3).	The comment is not accepted and revision not needed.
GUIDELINE SECTION TITLE – APPENDIX 3: EXAMPLE CALCULATIONS FOR CONCENTRATION LIMITS		
p. 30 and 31/32	Typo error. Replace "F2 = 10 to account for variability etween individuals" by Replace "F2 = 10 to account for variability between individuals". "F2 = 10 to account for variability ***b***etween individuals	This comment has been addressed.
p. 31/32	Typo error in the last sentence. Replace "… be calculated as describe in point 4.3. option 2:" by " "… be calculated as described in point 4.3. option 2:" "… be calculated as describe***d*** in point 4.3. option 2: …"	This comment has been addressed.