INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D

Current *Step 2b* version

dated 26 July 2013

At Step 2 of the ICH Process, a consensus draft text or Guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

Q3D
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Draft ICH Consensus Guideline

Released for Consultation on 26 July 2013, at *Step 2b* of the ICH Process

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Q3D

1. INTRODUCTION

Elemental impurities in drug products may arise from several sources; they may be added intentionally in synthesis, or may be present as contaminants (e.g., through interactions with processing equipment or by being present in components of the drug product) and are consequently detectable in the drug product. Since elemental impurities do not provide any therapeutic benefit to the patient, element impurity levels should be controlled within acceptable limits in the drug product. There are three components of this guideline: the evaluation of the toxicity data for potential elemental impurities, the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern, and development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE. It is not expected that an applicant tightens the limits based on process capability provided that the elemental impurities in drug products are held at or below the PDE. The PDEs established in this guideline are considered to be protective of public health for all patient populations, including pediatric patients. In some cases, lower levels of elemental impurities may be needed when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, in the case of high PDEs, other limits may have to be considered from a pharmaceutical quality perspective; other guidelines should be consulted.

Developing a strategy to limit elemental impurities in the drug product is consistent with risk management processes identified in ICH Q9. The process is described in this guideline as a four step process to assess and control elemental impurities in the drug product: identify, analyse, evaluate, and control.

The PDE of the elements may change if new safety data become available. The guideline may be updated to include other elemental impurities or other routes of administration as new data become available. Any interested party can make a request and submit the relevant safety data to be considered.

2. SCOPE

The PDEs in this guideline have been established based on acceptable safety limits of potentially toxic elemental impurities. The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products employing existing drug substances. The drug products containing: proteins and polypeptides (produced from recombinant or non-recombinant cell-culture expression systems), their derivatives, and products of which they are components (e.g., conjugates) are in the scope of this guideline. In addition, drug products containing synthetically produced polypeptides, polynucleotides, and oligosaccharides are within scope of this guideline.

This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components, crude products of animal or plant origin, dialysate solutions not intended for systemic circulation or drug products containing elements that are intentionally included for therapeutic benefit.

This guideline does not apply to drug products used during clinical research stages of development. In the later stages of development, the principles contained in this

guideline can be useful in evaluating elemental impurities that may be present in new drug product prepared by the proposed commercial process.

The application of this guideline to existing marketed drug products will be addressed by regional regulatory processes.

3. SAFETY ASSESSMENT OF POTENTIAL ELEMENTAL IMPURITIES

3.1 Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration

The method used for establishing the PDE for each element impurity is discussed in detail in Appendix 1. Elements evaluated in this guideline were assessed by reviewing the publicly available data contained in scientific journals, government research reports and studies, international regulatory standards (applicable to drug products) and guidance, and regulatory authority research and assessment reports. This process follows the principles employed in ICH Q3C: Residual Solvents. The available information was reviewed to establish the oral, parenteral and inhalation PDEs provided in the guideline.

A summary safety assessment identifying the critical study for setting a PDE for each element is included in Appendix 3. There are insufficient data to set PDEs by any route of administration for osmium, rhodium, ruthenium and iridium. The PDEs for these elements were established on the basis of their similarity to platinum. The PDEs for each element included in the guideline are summarized in Appendix 2, Table A.2.1.

The factors considered in the safety assessment for establishing the PDE were:

- The oxidation state of the element likely to be present in the drug product;
- Human exposure and safety data when it provided applicable information;
- The most relevant animal study;
- Route of administration;
- Selection of the relevant endpoints or designations (e.g., International Agency for Research on Cancer [IARC] classification, animal carcinogenicity, reproductive toxicology, target organ toxicity, etc);
- The longest duration animal study was generally used to establish the PDE. In some instances, a shorter duration animal study was considered the most relevant study. The rationale for using the shorter duration study is provided in the individual PDE assessment;
- In the absence of data and/or where data were available but were not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, default factors (see below) were used to derive the PDE from the oral PDE;
- In inhalation drug products, soluble salts are more relevant than particulates to assess elemental impurity toxicity. Therefore, inhalation studies using soluble salts (when available) were preferred over studies using particulates for inhalation assessment and derivation of inhalation PDEs.

In some cases, standards for daily intake for some of the elemental impurities discussed in this guideline exist for food, water, air, and occupational exposure. These standards have developed over time with different regional processes and may use different modifying factors or other estimates (e.g., body weight for an individual). In some cases, these standards are not only safety based, rather, based on practical considerations or analytical capability. Where appropriate, these standards were considered in the assessment and establishment of the PDEs using the approach as outlined in Appendix 1.

For PDEs established for inhalation (oral or parenteral routes as applicable), doses were normalized to a 24 hour, 7 day exposure. If data were available for local toxicity to the lung, those data were considered in establishing the inhalation PDE.

Where data were available but were not considered sufficient for a safety assessment for the parenteral route of administration, modifying factors were employed as follows:

Oral bioavailability <1% divide by a modifying factor of 100
Oral bioavailability < 50% divide by a modifying factor of 10
Oral bioavailability between 50% and 90% divide by a modifying factor of 2
Oral bioavailability > 90% divide by a modifying factor of 1

Where inhalation and/or parenteral data were available but were not considered sufficient for a safety assessment or Threshold Limit Value (TLV)/Time Weighted Average (TWA) values were not available for the inhalation route of administration, a calculated PDE was used based on the oral PDE divided by a modifying factor of 100 (Ball *et al.* 2007). In cases where the TLV/TWA or a nonclinical inhalation study was used, the dose levels were normalized to a 24 hour, 7 day week.

PDEs for elements of low risk to human health as impurities in drug products were not established. The elements in this category include: Fe, B, Al, W, Zn, K, Ca, Na, Mn, and Mg.

For elements not included in this guideline for which there is limited or insufficient data, the concepts used in this guideline can be used to determine appropriate PDEs.

3.2 Other Routes of Administration

PDEs were only established for oral, parenteral and inhalation routes of administration. Sufficient data to permit the establishment of a PDE for other routes of administration were generally unavailable. However, the concepts applied and described in this guideline can be used to determine appropriate PDEs for other routes of administration. Application of the parenteral PDE can provide the basis of a route-specific safety assessment.

3.3 Justification for Element Impurity Levels Higher than the PDE

Levels of elemental impurities higher than the PDE may be acceptable in certain cases. These cases could include, but are not limited to the following situations:

- less than daily dosing
- short term exposures (i.e., 30 days or less)
- specific indications (e.g., life-threatening, unmet medical needs, rare diseases)

Justification for increased levels in these situations should be made on a case by case basis justifying the proposed level using a risk based approach. ICH Q3C and this guideline use modifying factors for interspecies (Factor F1) and individual (Factor F2) variability. These modifying factors serve as starting points in extrapolating available data to obtain a PDE. The sub-factor approach (WHO, 2009), may be used to justify a higher PDE, where data are available, using knowledge of the mode of action and pharmacokinetic considerations. A justification may also include but is not limited to a consideration of the duration of the study used to set the PDE relative to the intended clinical use (Factor F3), the nature and severity of the toxicity observed, and whether the toxicity was reversible (Factor F4).

An example of the sub-factor approach can be found elsewhere in a risk assessment for boron (US Environmental Protection Agency [EPA], 2004).

3.4 Parenteral Products

The parenteral PDEs are applied irrespective of dose volume.

4. ELEMENT CLASSIFICATION

The elemental impurities included in this guideline have been placed into categories that are intended to facilitate decisions during the risk assessment.

- Class 1 elemental impurities, As, Cd, Hg, and Pb, are significantly toxic across all routes of administration. Typically they have limited or no use in the manufacture of pharmaceuticals but can be present as impurities in commonly used materials (e.g., mined excipients) and can not be readily removed from the material. Because of their unique nature, these four elemental impurities require consideration during the risk assessment across all potential sources of elemental impurities.
- Class 2 elemental impurities are toxic to a greater or lesser extent based on route of administration. In addition, some of the elements present in this category are infrequently observed as impurities in materials used to produce drug products and as such, unless intentionally added have a low probability of inclusion in the drug product and do not present a significant risk. Class 2 elemental impurities are further categorized to establish when they should be considered in the risk assessment and when their contribution can be judged to be negligible.
    - Class 2A: The following elemental impurities require assessment across all potential sources and routes of administration: V, Mo, Se, and Co due to their higher relative natural abundance (US Geological Survey, 2005).
    - Class 2B: The following elemental impurities require assessment across potential elemental impurity sources only if they are intentionally added to the processes used to generate the material under evaluation: Au, Tl, Pd, Pt, Ir, Os, Rh, Ag and Ru.
- Class 3 elemental impurities are impurities with relatively low toxicity (high PDEs) by the oral route administration but require consideration in the risk assessment for other routes of administration (e.g., inhalation and parenteral routes). For oral routes of administration, unless these elements are intentionally added as part of the process generating the material, they do not need to be considered during the risk assessment. For parenteral and inhalation products, the potential for inclusion of these elemental impurities should be evaluated during the risk assessment. The elemental impurities in this class include: Sb, Ba, Li, Cr, Cu, Sn, and Ni.
- Class 4 elemental impurities are elemental impurities that have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations. If these elemental impurities are present or included in the drug product they are addressed following the practices defined by other guidelines and regional regulation. The elements in this class include: Al, B, Fe, Zn, K, Ca, Na, Mn, Mg, and W.

The classification system is summarized in Table 4.1.

Table 4.1: Elemental Impurity Classification

	Included Elemental Impurities	Include in Risk Assessment?
Class 1	As, Pb, Cd, Hg	Yes
Class 2A	V, Mo, Se, and Co	Yes
Class 2B	Ag, Au, Tl, Pd, Pt, Ir, Os, Rh, and Ru	Yes only if intentionally added
Class 3	Sb, Ba, Li, Cr, Cu, Sn, Ni	Dependent upon route of administration – see Class 3 description
Class 4	B, Fe, Zn, K, Ca, Na, Mn, Mg, W, Al	No

5. ASSESSMENT AND CONTROL OF ELEMENTAL IMPURITIES

In developing the control strategy for elemental impurities in drug products, the principles of quality risk management, described in ICH Q9, should be considered. The risk assessment should be based on scientific knowledge and principles. It should link patient safety considerations with an understanding of the product and its manufacturing process (ICH Q8 and Q11). In the case of elemental impurities, the product risk assessment would therefore be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs presented in this guidance. Information for this assessment includes but is not limited to: data generated by the applicant, information supplied by drug substance, reagent and/or excipient manufacturers or data available in published literature.

The applicant should document the assessment and control approaches in an appropriate manner. The level of effort and formality of the assessment should be proportional to the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or formal procedures, e.g., standard operating procedures.) The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Tools to assist in the risk assessment are described in ICH Q9 and will not be presented in this guideline.

5.1 General Principles

For the purposes of this guideline, the assessment process can be described in four steps: identify, analyse, evaluate and control. In many cases, the steps are considered simultaneously. For example, the analyse and evaluate steps may be iterative steps that initiate adjustments to control elements. The outcome of the assessment may be the result of iterations to develop a final approach to ensure the potential elemental impurities do not exceed the PDE.

Identify: Identify known and potential sources of elemental impurities that may find their way into the drug product.

Analyze: Determine the probability of observance of a particular elemental impurity in the drug product.

Evaluate: Compare the observed or predicted levels of elemental impurities with the established PDE.

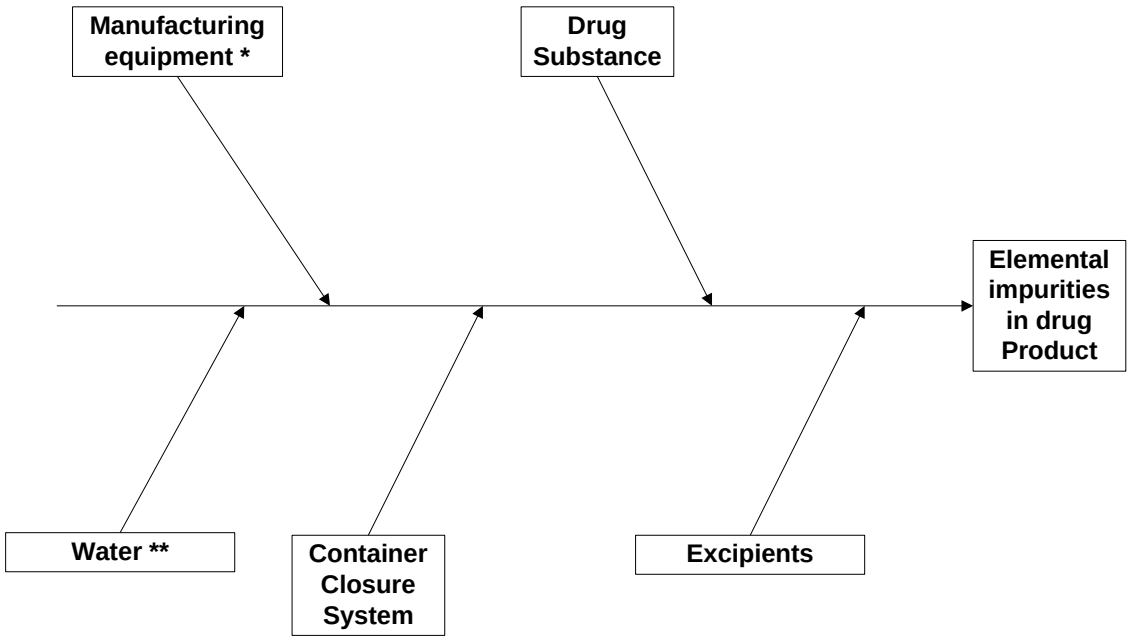
Control: Document and implement a control strategy to limit elemental impurities in the drug product.

5.2 Potential Sources of Elemental Impurities

In considering the production of a drug product, there are several broad categories of potential sources of elemental impurities.

- Residual elemental impurities resulting from elements intentionally added to reactions or processes leading up to the preparation of the drug substance, reagents, starting materials or excipients (e.g., metal catalysts).
- Elemental impurities known or suspected of being present in the drug substance, reagents, water, starting materials or excipients used in the preparation of the drug product.
- Elemental impurities known or suspected of being introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that are known or suspected of being leached into the drug substance and drug product from container closure systems.

The following diagram shows an example of typical materials or components used in the production of a drug product. Each of these materials or components may contribute elemental impurities to the drug product, through any individual or any combination of the potential sources listed above. During the assessment, the potential contributions from each of these materials or components should be considered to determine the overall contribution of elemental impurities to the drug product.



* The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

** The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US

Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the process(es).

5.3 Assessment – Identification of Potential Elemental Impurities

Class 1 elemental impurities: Due to their inherent toxicity, the risk assessment should include an assessment of the Class 1 elemental impurities. All potential sources of elemental impurities should be evaluated for the potential to transfer the Class 1 elemental impurities to the drug product.

Potential elemental impurities derived from intentionally added catalysts or reagents: For this category, the identity of the potential impurities is known and techniques for controlling the elemental impurities are easily characterized and defined. The predominant elemental impurities that comprise this group are the Class 2 and 3 elemental impurities. Table 5.1 shows the suggested consideration in the risk assessment for each of the elemental impurities covered in this guideline. As identified, if any (Class 1, 2, or 3) elemental impurity is added, it should be considered in the risk assessment.

Potential elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents: Elemental impurities known or suspected of being present in the drug substance, reagents, starting materials or excipients used in the preparation of the drug product should be considered. These elemental impurities are often associated with mined materials and excipients. The presence of these impurities can be variable, especially with respect to mined excipients, which can complicate the risk assessment. The variation should be considered when establishing the probability for inclusion in the drug product. The elemental impurities that are of most significant to this potential source include the Class 1 and Class 2A elemental impurities (see Table 4.1). For parenteral and inhalation routes of administration, the risk assessment should evaluate the probability for inclusion of the Class 1 and most 3 elemental impurities as shown in Table 5.1.

Potential elemental impurities derived from manufacturing equipment: The contribution of elemental impurities may be limited and the subset of elemental impurities that should be considered in the risk assessment is relatively small and is dependent on the equipment involved. Application of process knowledge, selection of equipment, equipment qualification and GMP controls ensure a low contribution from manufacturing equipment. The specific elemental impurities of concern should be assessed based on knowledge of the composition of the components of the manufacturing equipment. The assessment of this source of elemental impurities is one that can be utilized potentially for many drug products using similar process trains and processes.

Elemental impurities leached from container closure systems: Identifying the potential elemental impurities extracted from container closure systems should be based on a scientific understanding of likely interactions between a particular drug product type and its packaging. When a review of the materials of construction demonstrates that the container closure system does not contain elemental impurities, no additional assessment needs to be performed. It is recognized that the probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the assessment. For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system into the drug product during the shelf-life of the product. Studies to understand potential extractables and leachables from the final/actual container closure system (after washing sterilization, irradiation) should be performed.

Factors that should be considered (for liquid and semi-solid dosage forms) include but are not limited to:

- Hydrophilicity/hydrophobicity
- Ionic content
- pH
- Temperature (cold chain *vs* room temperature and processing conditions)
- Contact surface area
- Container/component composition
- Terminal sterilization
- Packaging process
- Component sterilization
- Migration potential
- Duration of storage
- Inclusion of metal chelating agents in the formulation (e.g., Ethylenediamine Tetraacetic Acid [EDTA]).

Table 5.1: Recommendation for Consideration During Risk Assessment

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

5.4 Assessment – Analysis and Evaluation

As the potential elemental impurity identification process is concluded, there are several possible outcomes: the process and product review does not identify any potential elemental impurities or the process identifies a list of one or more potential elements. When present, the elemental impurities may have a single source or multiple sources. In addition, a number of elemental impurities will be excluded from consideration based on the assessment of their probability of occurrence and their potential to exceed the PDE. In order to accurately complete the assessment, data regarding potential elemental impurity levels may be needed. The data for this assessment can come from a number of sources that include, but are not limited to:

- Prior knowledge
- Published literature
- Data generated from similar processes
- Supplier information or data
- Analysis of the components of the drug product
- Analysis of the drug product

The applicant's risk assessment can be facilitated with information about the potential elemental impurities provided by suppliers of drug substances, excipients, starting materials, reagents, container closure systems, and manufacturing equipment.

Since the PDE is established on the drug product, it is necessary to compare the predicted or known levels of the elemental impurities identified with the established PDE in order to define the appropriate steps to take in developing an approach to control potential elemental impurities in the drug product. This may be done in several different ways and the applicant should consider which option is most appropriate for their use given the elemental impurities identified in combination with the source of the elemental impurity.

5.5 Converting Between PDEs and Concentration Limits

The PDEs, reported in micrograms per day (μg/day) provided in this document give the maximum permitted quantity of each element that may be contained in the maximum daily intake of a drug product. Because the PDE reflects only total exposure from the drug product, it is useful to convert the PDE, into concentrations as a tool in evaluating elemental impurities in drug products or their components. The following options describe some acceptable approaches to establishing concentrations of elemental impurities in drug products or components that would assure that the drug product meets the PDEs. The applicant may select any of these options as long as the resulting permitted concentrations assure that the drug product meets the PDEs for elemental impurities. In the choice of a specific option the applicant must have knowledge of, or make assumptions about, the daily intake of the drug product. In all cases, the PDE should be met. The permitted concentration limits may be used:

- As a tool in the risk assessment to compare the observed or predicted levels to the PDE;
- In discussions with suppliers to help establish upstream controls that would assure that the product meets the PDE;
- To establish concentration targets when developing in-process controls on elemental impurities;
- To convey information regarding the controls on elemental impurities in regulatory submissions.

As discussed in Section 5.2, there are multiple sources for elemental impurities in drug products. When applying any of the options described below, elemental impurities from container closure systems and manufacturing equipment should be taken into account prior to calculating the maximum permitted concentration in the remaining components (excipients and drug substance). If it is determined during the risk assessment that the container closure systems and manufacturing equipment do not contribute to the elemental impurity level in the drug product, they do not need to be considered. Where contributions from container closure systems and manufacturing equipment exist, these contributions may be accounted for by subtracting the estimated daily intake from these sources from the PDE prior to calculation of the allowed concentration in the excipients and drug substance.

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than 10 grams:

This option is not intended to imply that all elements are present at the same concentration, but rather provides a simplified approach to the calculations.

The option assumes the daily intake (amount) of the drug product is 10 grams or less, and that elemental impurities identified in the risk assessment (the target elements) are present in all components of the drug product. Using equation (1) below, and a daily intake of 10 grams of drug product, this option calculates a common permissible target elemental concentration for each component in the drug. This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component. The calculated values are provided in Appendix 2 Table A.2.2.

$$Concentration(\mu g/g) = \frac{PDE(\mu g/day)}{daily\ \ amount\ of\ drug\ \ product(g/day)} \qquad (1)$$

If all the components in a drug product meet the Option 1 concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product. An example of this calculation is shown in Appendix 4 Table A.4.1. If the permitted concentrations in Appendix 2 Table A.2.2 are not applied, Options 2a, 2b, or 3 must be followed.

Option 2a: Common permitted concentration limits across drug product components for a drug product with a specified daily intake:

This option is similar to Option 1, except that the drug daily intake is not assumed to be 10 grams. The common permitted concentration of each element is determined using Equation 1 and the actual maximum daily intake.

This approach, for each target element, allows determination of a fixed common maximum concentration in micrograms per gram in each component based on the actual daily intake provided. An example of this calculation is provided in Appendix 4 Table A.4.2.

If all components in a drug product meet the Option 2a concentrations for all target elements identified in the risk assessment, then all these components may be used in any proportion in the drug product.

Option 2b: Permitted concentration limits of elements across drug product component materials for a product with a specified daily intake:

This option requires additional information that the applicant may assemble regarding the potential for specific elemental impurities to be present in specific drug product components. The applicant may set permitted concentrations based on the distribution of elements in the components (e.g., higher concentrations in components with the presence of an element in question). For each element identified as potentially present in the components of the drug product, the total mass of the elemental impurity in the final drug product can be calculated as the sum of the product of the component material masses at the maximum permitted concentrations established by the applicant. The total mass of the elemental impurity in the drug product cannot exceed the PDEs given in Appendix 2 Table A.2.1., as shown in equation 2. If the risk assessment has identified that a specific element is not a potential impurity in a specific component, there is no need to establish a quantitative result for that element in that component. This approach allows that the maximum permitted concentration of an element in certain components of the drug product may be higher than the Option 1 or Option 2a limit, but this should then be compensated by lower allowable concentrations in the other components of the drug product. Equation 2 may be used to set component-specific limits for each element in each component of a drug product.

$$\mathrm{PDE}(\mu\mathrm{g/day}) \geq \sum_{k=1}^{N} C_k \cdot M_k \qquad (2)$$

k = an index for each of N components in the drug product
C_k = concentration of the elemental impurity in component k (µg/g)
M_k = mass of component k in the maximum daily intake of the drug product (g)

An example of this calculation is provided in Appendix 4 Tables A.4.3 – A.4.5.

Option 3: Finished Product Analysis:

The concentration of each element may be measured in the final drug product. Equation 1 may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity. An example of this option is provided in Appendix 4 Table A.4.6.

5.6 Assessment Summary

The process described above is intended to enable the applicant to focus on those elements that require additional control elements. The process permits the applicant to utilize information and knowledge gained across products to establish the particular elemental impurities of concern in the specific drug product.

A number of factors can influence the level of the potential impurity in the drug product and should also be considered in the assessment. These include but are not limited to:

- Efficiency of removal of elemental impurities during further processing;
- Natural abundance of elements (especially important for the categories of elements which are not intentionally added);
- Prior knowledge of elemental impurity concentration factors from specific sources.

For elements that are added or are known to be potentially present in excipients or raw materials, the analysis should consider the percentage of the excipient or raw material in the drug product. Assessment of probable concentrations based on this percent of the total composition of the drug product is an additional tool to determine if the contribution is relevant. The analysis may include an assessment of the levels or concentrations that are identified either in each component (including contributions from the container closure system) or in the drug product.

The initial design of the facility and qualification of utilities and equipment, as part of process qualification, would be expected to identify potential elemental impurities and anticipated potential contributions to the drug product. In general, the contribution of elemental impurities from manufacturing equipment and utilities is likely to be negligible and would normally be addressed by implementing appropriate GMP procedures. However, if the assessment demonstrated that the contribution was significant, the anticipated levels of the identified elements should be reviewed as part of the risk evaluation process.

Finally the applicant should consider the significance of the observed level relative to the PDE of the element. As a measure of the significance of the observed elemental impurity level, a control threshold is defined as a level that is 30% of the established PDE in the drug product. This threshold is used to determine if additional controls may be required. If the total elemental impurity level from all sources in the drug product is consistently less than 30% of the PDE, applying appropriate assessment of the data and demonstrating an adequate control strategy, then additional controls are not required.

If the assessment fails to demonstrate that an elemental impurity level is below the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product.

In order to apply the control threshold, sources of variability should be understood. Important factors include:

- Variability of the analytical method
- Variability of the elemental impurity level in the specific sources
- Variability of the elemental impurity level in the drug product

There are many acceptable approaches to document the assessment and may include: tables, written summaries of considerations and conclusions of the assessment. The summary should identify the elemental impurities, their sources, and the controls and acceptance criteria as needed.

5.7 Control of Elemental Impurities

Control of elemental impurities includes decision making steps designed to reduce or accept the presence of elemental impurities and their respective concentrations that were identified and evaluated through the assessment process. When the assessment determines that the levels of elemental impurities are below the control threshold, no further control is required but periodic verification testing may be used to confirm that the expected levels are consistent and predictive of future (see Section 5.8). The applicant should provide a justification for the application of periodic verification testing.

When the control threshold is exceeded, the controls established should ensure that the PDE is not exceeded. There are a number of control elements or approaches that an applicant can pursue to control the elemental impurities in drug products. These include but are not limited to:

- Identification of the steps in the manufacturing process that result in the reduction of elemental impurities through specific or non-specific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity in the drug product;
- Establishment of material (e.g., synthetic intermediates and raw materials) or excipient specifications to limit the level of elemental impurity contributions from those sources;

- Establishment of specification limits for the drug substance;
- Establishment of specification limits for the drug product;
- Reliance on the compliance with compendial standards for materials used in drug product processes;
- Selection of appropriate container closure systems.

Where testing and acceptance criteria are established, periodic verification testing may be appropriate in some cases (see Section 5.8).

An illustration of the risk assessment process described above can be found in Appendix 4.

5.8 Periodic Verification Testing

In situations where a test is recommended to be included in the specification to provide suitable control of elemental impurities, but where routine measurement for release of every batch may not be necessary, it may be possible to apply periodic verification testing (periodic or skip lot testing as described in ICH Q6A). It should be noted that allowance of periodic verification testing is considered to be helpful to provide periodic confirmation that the controls contained within a process perform consistently over the lifecycle of the product. Periodic testing is a means to ensure that the risk assessment assumptions are valid and ensure that unintended or unknown process or material attributes have not changed over time. Application of periodic verification testing should be applied to processes or materials that are under a state of control (i.e., consistently meets specifications and conforms to an appropriately established facility, equipment, processing, and operational control regimen). If upon testing, the elemental impurity level exceeds the PDE, the applicant should investigate the cause of the failure, reassess the controls that are in place and determine if additional controls may be required. Failures observed in periodic verification testing should be reported to the appropriate regulatory authorities following the established procedures.

5.9 Special Considerations for Biotechnologically-Derived Products

For biotechnology-derived products, the risks associated with elemental impurities being present at levels of safety concerns at the drug substance stage are considered low. This is largely due to the following factors: a) elements are not typically used as catalysts or reagents in the manufacturing of biotech products; b) elements are added at trace levels in media feeds during cell culture processes, without accumulation and with significant dilution/removal during further processing; c) typical purification schemes used in biotech manufacturing such as chromatography steps and dialysis or Ultrafiltration-Diafiltration (UF/DF) have the capacity to clear elements introduced in cell culture/fermentation steps or from contact with manufacturing equipment to negligible levels. As such, a specific control strategy that relates to the control of elements up to the biotech drug substance is not generally needed. In cases where the biotechnology derived drug substance contains synthetic elements (such as antibody-drug conjugates), appropriate controls on the small molecule element for elemental impurities should be performed.

However, potential elemental impurity sources included in drug product manufacturing (e.g., excipients) and other environmental sources should be considered for biotechnologically derived drug products. The contribution of these sources to the finished product should be assessed as typically they are introduced in the drug product manufacture at a step in the process where subsequent elemental impurity removal is not generally performed. Risk factors that should be considered in this assessment should include the type of excipients used, the processing conditions and their

susceptibility to contamination by environmental factors (e.g., controlled areas for sterile manufacturing and use of purified water), as well as the overall dosing frequency.

6. SPECIATION

Speciation is defined as the separation of elemental impurities based on oxidation state, organic combination or complexation state. The PDE has been established using the toxicity information on the species expected to be in the drug product.

The applicant is not expected to provide speciation information; however, such information could be used to justify higher levels for the more relevant or less toxic species.

7. ANALYTICAL PROCEDURES

The determination of elemental impurities should be conducted using appropriate procedures suitable for their intended purposes. Unless otherwise justified, the test should be specific for each elemental impurity identified for control during the risk assessment. Pharmacopoeial procedures or suitable validated alternative procedures for determining levels of elemental impurities should be used.

8. LIFE-CYCLE MANAGEMENT OF THE CONTROL STRATEGY FOR ELEMENTAL IMPURITIES

The quality system elements and management responsibilities described in ICH Q10 are intended to encourage the use of science-based and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle. Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.

The effectiveness of the control strategy should be periodically evaluated throughout the product lifecycle. Knowledge gained from development combined with commercial manufacturing experience and data can be used to further improve process understanding and process performance which can be used to make improvements to the control strategy. It is recognized that the elemental impurity data available for some components is somewhat limited at this time which may direct the applicant to a specific series of control elements. Additional data, if developed, may lead to modifications of the control strategy.

If changes to the drug product process(es) have the potential to change the elemental impurity content of the drug product, the established control elements for elemental impurities should be re-evaluated. Such changes could include but are not limited to: changes in synthetic route, excipient supplier, raw materials, processes, equipment, or facilities. All changes are subject to internal change management process (ICH Q10) and if needed appropriate regional regulatory requirements.

9. RECOMMENDATIONS FOR SUBMISSION OF ELEMENTAL IMPURITIES CONTROL STRATEGY

The information on the control strategy that is provided in a regulatory submission should include the outcome of the risk assessment and a description of the controls established to limit elemental impurities. A good location for the description of the control strategy is Section 3.2.P.5.6. This summary should include appropriate references to the locations of controls on elemental impurities defined in the control strategy (e.g., 3.2.S and 3.2.P). A summary of the approach used to develop the control strategy may be included in the Quality Overall Summary.

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GLOSSARY

ATSDR:
Agency for Toxic Substances and Disease Registry.

CEC:
Commission of the European Community.

CFR:
Code of Federal Regulations (USA).

Change Management:
A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Container Closure System:
The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system. (ICH Q1A)

Control Strategy:
A planned set of controls, derived from current product and process understanding, which assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Control Threshold:
A limit that is applied during the assessment of elemental impurities to determine if additional control elements may be required to ensure that the PDE is not exceeded in the drug product. The limit is defined as 30% of the PDE of the specific elemental impurity under consideration.

Daily Dose:
The total mass of drug product that is consumed by a patient on a daily basis.

EFSA:
European Food Safety Agency.

EHC:
Environmental Health Criteria. (WHO)

EU SCOEL:
European Scientific Committee on Occupational Exposure Limits.

IARC:
International Agency for Research on Cancer.

Inhalation Unit Risk:
The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10-6 per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000

people if exposed daily for a lifetime to 1 μg of the chemical in 1 liter of drinking water. (US EPA)

IPCS:

International Programme for Chemical Safety.

IUPAC:

International Union of Pure and Applied Chemistry.

IRIS:

Integrated Risk Identification System, United States Environmental Protection Agency.

Lowest-Observed-Adverse-Effect Level (LOAEL):

Lowest concentration or amount of a substance *(*dose*)*, found by experiment or observation, which causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure. (IUPAC)

Limit of Detection (LOD):

The limit of detection of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. (ICH Q2)

Lowest-Observed-Effect Level (LOEL):

The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Modifying Factor:

A factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data to human safety. (Q3C) (See related term Safety Factor)

MRL:

Minimal Risk Level.

No-Observed-Adverse-Effect Level (NOAEL):

Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

No-Observed-Effect Level (NOEL):

The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

NTP:

National Toxicology Program.

OELV:

Occupational Exposure Limit Value.

OSHA:

Occupational Safety and Health Administration (USA).

PEL:

Permitted Exposure Limit.

Permitted Daily Exposure:

The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

Product Lifecycle:

All phases in the life of the product from the initial development through marketing until the product's discontinuation. (ICH Q9)

Quality:

The degree to which a set of inherent properties of a product, system, or process fulfills requirements (see ICH Q6A definition specifically for *quality* of drug substance and drug products). (ICH Q9)

Quality Risk Management:

A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle. (ICH Q9)

Quality System:

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met. (ICH Q10)

Raw Material:

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or Active Pharmaceutical Ingredients (APIs). (ICH Q7)

Risk:

The combination of the probability of occurrence of harm and the severity of that harm. (ISO/IEC Guide 51, ICH Q9)

Risk Acceptance:

The decision to accept risk. (ISO Guide 73)

Risk Analysis:

The estimation of the risk associated with the identified hazards. (ICH Q9)

Risk Assessment:

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (ICH Q9)

Risk Control:

Actions implementing risk management decisions. (ISO Guide 73)

Risk Identification:

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. (ICH Q9)

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk. (ICH Q9)

Safety:

Practical certainty that adverse effects will not result from exposure to an agent under defined circumstances. (EHC 240)

Safety Assessment:

An approach that focuses on the scientific understanding and measurement of chemical hazards as well as chemical exposures, and ultimately the risks associated with them. Often (and in this guideline) used synonymously with risk assessment. *Related term*: Risk assessment. (EHC 340)

Safety Factor:

A composite (reductive) factor applied by the risk assessment experts to the No-Observed-Adverse-Effect Level (NOAEL) or other reference point, such as the benchmark dose or benchmark dose lower confidence limit, to derive a reference dose that is considered safe or without appreciable risk, such as an acceptable daily intake or tolerable daily intake (the NOAEL or other reference point is divided by the safety factor to calculate the reference dose). The value of the safety factor depends on the nature of the toxic effect, the size and type of population to be protected, and the quality of the toxicological information available. Related terms: Assessment factor, Uncertainty factor. (EHC 240)

Severity:

A measure of the possible consequences of a hazard. (ICH Q9)

Starting Material:

A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure. (ICH Q3A)

Threshold Limit Value (TLV):

The concentration in air to which it is believed that most workers can be exposed daily without an adverse effect (i.e., effectively, the threshold between safe and dangerous concentrations). The values were established (and are revised annually) by the ACGIH and are time-weighted concentrations (TWA) for a 7- or 8-hour workday and 40-hour workweek, and thus are related to chronic effects. (IUPAC)

Time Weighted Average (TWA):

As defined by ACGIH, time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek. (IUPAC)

URF:

Unit Risk Factor.

US DoL:

United States Department of Labor.

US EPA:

United States Environmental Protection Agency.

WHO:

World Health Organization.

Appendix 1: Method for Establishing Exposure Limits

The Gaylor-Kodell method of risk assessment (Gaylor DW, Kodell RL. Linear Interpolation algorithm for low dose assessment of toxic substance. J Environ Pathol Toxicol 1980;4:305) is appropriate for carcinogenic elemental impurities. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for carcinogenic elemental impurities could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the No-Observed-Effect Level (NOEL).

Acceptable exposure levels for elemental impurities in this guideline were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (Pharmacopeial Forum, Nov-Dec 1989), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria [EHC] 170, WHO, 1994). These methods are similar to those used by the US EPA (IRIS) and the US FDA (Red Book) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values tabulated in Appendix 2 of this document.

PDE is derived from the NOEL, or the Lowest-Observed-Effect Level (LOEL) in the most relevant animal study as follows:

PDE = NOEL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5] *(1)*

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (EHC 170, World Health Organization [WHO], Geneva, 1994), and "modifying factors" or "safety factors" in Pharmacopeial Forum. The assumption of 100% systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species

F1 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 3 for extrapolation from monkeys to humans

F1 = 10 for extrapolation from other animals to humans

F1 takes into account the comparative surface area: body mass ratios for the species concerned and for man. Surface area (S) is calculated as:

$S = kM^{0.67}$ (2)

in which M = body mass, and the constant k has been taken to be 10. The body masses used in the equation are those shown below in Table A.1.1

F2 = A factor of 10 to account for variability between individuals

A factor of 10 is generally given for all elemental impurities, and 10 is used consistently in this guideline

F3 = A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys)

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents

F3 = 10 for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study.

F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity

F4 = 5 for fetal toxicity without maternal toxicity

F4 = 5 for a teratogenic effect with maternal toxicity

F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The mass adjustment assumes an arbitrary adult human body mass for either sex of 50 kg. This relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE.

As an example of the application of this equation, consider a toxicity study of cobalt in human volunteers is summarized in Agency for Toxic Substances and Disease Registry (ATSDR, 2004, op/. cit., Davis JE and Fields JP. Proc Soc Exp Biol Med 1958;99:493-5). The Lowest-Observed-Adverse-Effect Level (LOAEL) for polycythemia is 1 mg/kg/day. The PDE for cobalt in this study is calculated as follows:

PDE = 1 mg/kg/day x 50 kg/[1 x 10 x 10 x 1 x 10] = 0.05 mg/day = 50 µg/day

In this example,

F1 = 1 study in humans

F2 = 10 to account for differences between individual humans

F3 = 10 because the duration of the study was only 3 weeks

F4 = 1 because no severe toxicity was encountered

F5 = 10 because a LOAEL was used

Table A.1.1: Values Used in the Calculations in this Document

Rat body weight	425 g	Mouse respiratory volume	43 L/day
Pregnant rat body weight	330 g	Rabbit respiratory volume	1440 L/day
Mouse body weight	28 g	Guinea pig respiratory volume	430 L/day
Pregnant mouse body weight	30 g	Human respiratory volume	28,800 L/day
Guinea pig body weight	500 g	Dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5 kg	Monkey respiratory volume	1,150 L/day
Rabbit body weight (pregnant or not)	4 kg	Mouse water consumption	5 mL/day
Beagle dog body weight	11.5 kg	Rat water consumption	30 mL/day
Rat respiratory volume	290 L/day	Rat food consumption	30 g/day

Appendix 2: Established PDEs for Elemental Impurities

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
As	1	15	15	1.9
Cd	1	5.0	6.0	3.4
Hg	1	40	4.0	1.2
Pb	1	5.0	5.0	5.0
Co	2A	50	5.0	2.9
Mo	2A	180	180	7.6
Se	2A	170	85	140
V	2A	120	12	1.2
Ag	2B	170	35	6.9
Au	2B	130	130	1.3
Ir[3]	2B	1000	10	1.4
Os[3]	2B	1000	10	1.4
Pd	2B	100	10	1.0
Pt	2B	1000	10	1.4
Rh[3]	2B	1000	10	1.4
Ru[3]	2B	1000	10	1.4
Tl	2B	8.0	8.0	69
Ba	3	13000	1300	340
Cr	3	11000	1100	2.9
Cu	3	1300	130	13
Li	3	780	390	25
Ni	3	600	60	6.0
Sb	3	1200	600	22
Sn	3	6400	640	64

[1] PDEs reported in this table are rounded to 2 significant figures (µg/day).
[2] Classification as defined in Section 4.
[3] Insufficient data to establish an appropriate PDE; the PDE was established based on platinum PDE.

Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1

The values presented in this table represent permitted concentrations in micrograms per gram for elemental impurities in drug products, drug substances and excipients. These concentration limits are intended to be used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses of not more than 10 grams per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
As	1	1.5	1.5	0.29
Cd	1	0.50	0.60	0.34
Hg	1	4.0	0.40	0.12
Pb	1	0.50	0.50	0.50
Co	2A	5.0	0.50	0.29

Mo	2A	18	18	0.76
Se	2A	17	8.5	14
V	2A	12	1.2	0.12
Ag	2B	17	3.5	0.69
Au	2B	13	13	0.13
Ir**	2B	100	1.0	0.14
Os**	2B	100	1.0	0.14
Pd	2B	10	1.0	0.10
Pt	2B	100	1.0	0.14
Rh**	2B	100	1.0	0.14
Ru**	2B	100	1.0	0.14
Tl	2B	0.80	0.80	6.9
Ba	3	1300	130	34
Cr	3	1100	110	0.29
Cu	3	130	13	1.3
Li	3	78	39	2.5
Ni	3	60	6.0	0.60
Sb	3	120	60	2.2
Sn	3	640	64	6.4

** Insufficient data to establish an appropriate PDE; the PDE was established based on platinum PDE

Appendix 3: Individual Safety Assessments

ANTIMONY

Summary of PDE for Antimony

Antimony (Sb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1200	600	22

Introduction

Antimony (Sb) is a silvery white naturally occurring metalloid element that is used in various manufacturing processes. Small amounts of Sb are found in the earth's crust. It exists in valence states of 3 and 5. Metallic Sb and a few trivalent Sb compounds are the most significant regarding exposure potential and toxicity. Some antimonials, such as Sb potassium tartrate, have been used medicinally as parasiticides. Antimony trioxide is being used as a catalyst (e.g., in the manufacturing of PolyEthylene Terephthalate [PET] used for container closure system components). Antimony is nutritionally not essential and no metabolic function is known (ATSDR, 1992).

Safety Limiting Toxicity

Because of the limited *in vitro* genotoxicity data and the lack of *in vivo* tests, the genotoxicity of Sb cannot be determined (ATSDR, 1992). In humans and animals, the gastrointestinal tract (irritation, diarrhea, vomiting) appears to be the primary target organ after oral exposure. In subchronic studies in rats lower mean body weights and adverse liver findings were the most sensitive endpoints. Inhalation of high levels of Sb over a long period can cause adverse respiratory effects in both humans and animals.

PDE – Oral Exposure

Limited oral data on Sb exposure is available in mice and rats (Schroeder *et al.* 1968; Schroeder *et al.* 1970; Poon *et al.* 1998). The WHO evaluated Sb in drinking water (WHO, 2003). Lynch *et al.* concluded that a NOAEL from a 90 day drinking water rat study using antimony potassium tartrate was 6 mg/kg/day based on lower mean body weight and reduced food consumption (Lynch, 1999). This finding is consistent with the earlier reports from Schroeder *et al.* Thus, the Permitted Daily Exposure (PDE) for oral exposure was determined on the basis of the lowest NOAEL, i.e., 50 mg/L (equivalent to 6.0 mg Sb/kg/day).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below:

PDE = 6000 µg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 1200 µg/day.

PDE – Parenteral Exposure

Adverse liver findings were the most sensitive endpoint in rats after repeated intraperitoneal administration. Thus, the PDE for intraperitoneal exposure was determined on the basis of the lowest NOAEL, i.e., 3.0 mg Sb/kg/day. This value was obtained from a 90-day study in rats (based on adverse liver findings at 6 mg/kg in male rats exposed to Sb potassium tartrate *via* intraperitoneal injection) (NTP, 1992).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the human intraperitoneal PDE is calculated as below:

PDE = 3000 µg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 600 µg/day.

PDE – Inhalation Exposure

Sub chronic and chronic inhalation rat studies have been conducted. The lung effects observed across these studies were consistent. Using the data from a 13 week inhalation rat study using antimony trioxide dust, (Newton *et al.* 1994), a NOAEL of 1.08 mg/m^3 was used to determine the inhalation PDE (~83% Sb). At higher dose levels an increase in mean absolute and relative lung weights were observed, a finding not seen in the one year oncogenicity study.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

$$\text{For continuous dosing} = \frac{0.9 \text{ mg/m}^3 \times 6 \text{ h} \times 5 \text{ d}}{24 \text{ h} \times 7 \text{ d}} = \frac{0.16 \text{ mg/m}^3}{1000 \text{ L/m}^3} = 0.00016 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.00016 \text{ mg/L} \times 290 \text{ L/d}}{.425 \text{ kg bw}} = 0.11 \text{ mg/kg/d}$$

PDE = 0.11 mg/kg/d x 50 kg / 5 x 10 x 5 x 1 x 1 = 22 µg/d.

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ARSENIC

Summary of PDE for Arsenic

Arsenic (As)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	15	15	1.9

Introduction

Arsenic (As) is ubiquitous in the environment and present in food, soil, drinking water and in air. Inorganic As occurs in trivalent (e.g., arsenic trioxide, sodium arsenite) or pentavalent forms (e.g., sodium arsenate, arsenic pentoxide, arsenic acid). Arsenic has no known useful biological function in human or mammalian organisms. This assessment focuses on inorganic As, since this is most relevant for drug products.

Safety Limiting Toxicity

Inorganic arsenic has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen (Group 1; IARC, 2012).

Due to its ubiquitous nature and toxicity profile, there have been many risk assessments conducted of arsenic and arsenic compounds, which utilize non-threshold, linear dose response approaches (Meharg and Raab, 2010).

The effects of arsenic in humans for the most part have not been reproduced in animals, so the risk assessments have to rely heavily upon epidemiology data in populations with high exposure concentrations (Schuhmacher-Wolz *et al.* 2009). In humans, both cancer and non-cancer effects have been linked to arsenic exposure. Oral exposure has been linked to cancers of the skin, liver, lung, kidney and bladder. Following inhalation exposure there is evidence for an increased risk of lung cancer (ATSDR, 2007; IARC, 2012; EU EFSA, 2009; WHO, 2011; US EPA, 2010).

The skin (dyspigmentation, palmoplantar keratosis) and gastrointestinal tract (e.g., nausea) appear to be the most sensitive targets for non-cancer adverse effects after oral ingestion while vascular disease, reproductive effects and neurological effects are also reported as non-cancer endpoints (IARC, 2012; Schuhmacher-Wolz *et al.* 2009; US EPA, 2007). Oral exposure studies suggest that skin lesions may appear at levels above 0.02 mg As/kg/day; no effects were generally seen at levels from 0.0004 to 0.01 mg As/kg/day (ATSDR, 2007). There are insufficient epidemiological data to set a LOEL or NOEL for other endpoints. The regions of hyperkeratosis may evolve into skin cancers (ATSDR, 2007) and can possibly be considered predictive of skin and internal cancers and the non-cancer long-term adverse health effects (Chen *et al.* 2005; Hsu *et al.* 2013; Ahsan and Steinmaus, 2013).

Studies of large populations (~40,000) exposed to arsenic concentrations in well water at 1000 µg/L and higher in southwestern Chinese Taipei have been the basis of risk assessments of skin cancer, and more recently of bladder and lung cancer (US EPA, 2010). Recent meta-analyses of cancer risk have indicated no additional bladder cancer risk at low dose exposure (<100–200 µg/L) (Chu and Crawford-Brown, 2006, 2007; Mink *et al.* 2008). This is consistent with the work of Schuhmacher-Wolz *et al.* (2009).

The inhalation unit risk for cancer is 0.0043 per µg/m^3 has been established by the US EPA based on data from two US smelters (US EPA, 2007). The Texas Commission on Environmental Quality provided an update to the US EPA Unit Risk Factor (URF), incorporating additional years of follow-up to the US EPA data and additional data on

workers from the United Kingdom and Sweden, and calculated a URF of 0.0015 per μg/m^3. This URF translates to an air concentration of 0.067 μg/m^3 at a risk of 1 in 100,000 excess lung cancer mortality (Erraguntla *et al.* 2012).

PDE – Oral Exposure

The oral PDE is based on the chronic effects of As to skin and sets the limit at 15 μg/day based on ATSDR Minimal Risk Level (MRL) and US EPA limit of 0.0003 mg/kg/day (ATSDR, 2007; US EPA 2007; EU EFSA, 2009). The PDE calculated based on the ATSDR MRL is consistent with drinking water standards (WHO, 2011).

0.0003 mg/kg/day x 50 kg human = 0.015 mg/day = 15 μg/day.

No modifying factors were applied because they are incorporated into the derivation of the MRL.

PDE – Parenteral Exposure

The oral bioavailability of As is ~95%. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng *et al.* 2002). Therefore the PDE is identical to the oral PDE.

PDE = 15 μg/day.

PDE – Inhalation Exposure

Increased risk of lung cancer and other respiratory disorders have been reported following inhalation exposure to workers in the occupational setting. The rationale for using a cancer endpoint for inhalation to set the PDE is the relative lack of information on linear-dose extrapolation, as compared to the oral route. No modifying factors are needed as the URF were determined for the protection of the general public. Based on the assessment conducted by Erraguntla *et al.* (2012), based on the risk of 1:100.000, the inhalation PDE is:

0.067 μg/m^3 ÷ 1000 L/m^3 x 28800 L/d = 1.9 μg/d.

No modifying factors were applied because the PDE is based on the multiplicate relative risk model described by Erraguntla *et al.* (2012).

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BARIUM

Summary of PDE for Barium

Barium (Ba)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	13000	1300	340

Introduction

Barium (Ba) is a dense, silver-white, soft alkaline earth metal that oxidizes readily in moist air and reacts with water. The Ba^{2+} ion and the water soluble compounds of Ba (chloride, nitrate, hydroxide) are toxic. The insoluble compounds of barium, such as barium sulfate, do not generate free Ba^{2+} ions in the gastrointestinal tract and therefore are generally nontoxic to humans. Ba is nutritionally not essential and no metabolic function is known. Barium sulfate is used as a support for catalyst (e.g., Pd).

Safety Limiting Toxicity

In animals and humans, the kidney appears to be the most sensitive target of toxicity resulting from repeated ingestion of soluble Ba salts. Chronic rodent studies support the evidence for an association between Ba exposure and renal toxicity. In humans, repeated exposure to Ba oxide *via* inhalation may cause bronchitis, including cough, phlegm, and/or shortness of breath.

PDE – Oral Exposure

Mice and rat Ba drinking water studies have been conducted (NTP, 1994). Based on the review of these data, the mouse was determined to be the more sensitive species. The 2-year drinking water study in mice with barium chloride dihydrate was selected as the principal study and compound-related nephropathy was identified as the critical effect for deriving a PDE for Ba and its soluble salts. The lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. These changes were characterized as morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice.

The oral PDE was determined on the basis of the NOAEL of 500 mg/L (equivalent to 30 mg Ba/kg/day), using the modifying factors (F1-F5 as discussed in Appendix 1).

PDE = 30 mg/kg/day x 50 kg / 12 x 10 x 1 x 1 x 1 = 12.5 mg/day ~13.000 µg/day.

PDE – Parenteral Exposure

No relevant data on parenteral exposure to barium compounds were found. The bioavailability of Ba is estimated to be 20 – 60% in adults and infants, respectively (ATSDR, 2007). Thus, a modifying factor of 10 of the oral PDE was used.

PDE = 13.000 µg/day/ 10 = 1300 µg/day.

PDE – Inhalation Exposure

No relevant data on inhalation exposure to barium compounds were found. US DoL (2013) has a reported TWA of 0.5 mg/m^3 based on soluble Ba salts.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

For continuous dosing = $\frac{500\ \mu g/\ m^3 \times 8\ hr/day \times 5\ days/week}{24\ hr/day \times 7\ days/week \times 1000\ L/m^3}$

= 0.119 µg/L

Daily dose = $\frac{0.119\ \mu g/L \times 28800\ L}{50\ kg}$ = 68.6 µg/kg

PDE = $\frac{68.6\ \mu g/kg \times 50\ kg}{1 \times 10 \times 1 \times 1 \times 1}$ = 343 µg/day ~340 µg/day.

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CADMIUM

Summary of PDE for Cadmium

Cadmium (Cd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	6.0	3.4

Introduction

Cadmium (Cd) is a transition metal whose most abundant naturally-occurring isotope is non-radioactive. It is found in nature in mineral forms and is obtained for commercial uses principally from cadmium ore (ATSDR, 2012). Cadmium exists as a salt form in the +2 oxidation state only. Some cadmium salts are water soluble such as cadmium chloride, cadmium sulfate and cadmium nitrate; other insoluble salts can become more soluble by interaction with acids, light or oxygen. Cadmium, cadmium oxide, cadmium salts on borosilicate carrier are used as catalysts in organic synthesis. Silver cadmium alloy is used in the selective hydrogenation of carbonyl compounds.

Safety Limiting Toxicity

Cadmium has shown to be genotoxic, but not mutagenic and has been acknowledged as a human carcinogen (Group 1; IARC, 2012). Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al.* 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012).

Evidence from numerous epidemiologic studies assessing inhalation exposures to cadmium *via* both occupational and environmental routes has demonstrated an increased risk of developing cancer (primarily lung) that correlates with inhalation exposure to cadmium (IARC, 2012; NTP, 2004).

PDE – Oral Exposure

A sensitive endpoint for oral exposure to cadmium and cadmium salts is renal toxicity (Buchet *et al.* 1990). Skeletal and renal effects are observed at similar exposure levels and are a sensitive marker of cadmium exposure (ATSDR, 2012). A number of oral exposure studies of cadmium in rats and mice showed no evidence of carcinogenicity. Therefore the renal toxicity endpoint was used to establish the oral PDE for cadmium, following the recommendations of ATSDR, a level of 0.1 µg/kg for chronic exposure is used to set the oral PDE. This is in line with the WHO drinking water limit of 0.003 mg/L/day (WHO 2011).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 0.1 µg/kg/day x 50 kg = 5.0 µg/day.

PDE – Parenteral Exposure

12 week study in rats given daily subcutaneous injections of 0.6 mg/kg Cd, 5 days per week showed renal damage at week 7 and later (Prozialeck, 2009). The LOAEL of this study is 0.6 mg/kg.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the parenteral PDE is calculated as:

PDE = 0.6 mg/kg/day x 50 kg / 5 x 10 x 5 x 10 x 2 = 6.0 µg/day.

F4 was chosen as 10 because cadmium is carcinogenic by the inhalation route. F5 was set at 2, since no NOAEL was identified in this study.

PDE – Inhalation Exposure

The use of 5 µg/m^3 as the PEL (US DoL, 2013) was considered acceptable as cadmium is non-mutagenic. This PDE is similar to the quantitative estimate of carcinogenic risk from inhalation exposure to cadmium (1:10·000 risk, US EPA, 1992; EU SCOEL, 2010).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

For continuous dosing = 5 µg/m^3 ÷1000 L/m^3 = 0.005 µg/L

0.005 µg/L x 8 hours x 5 days ÷ 24 hours x 7 days = 0.0012 µg/L

Daily Dose = 0.0012 µg/L x 28800 L/day ÷ 50 kg = 0.69 µg/kg

PDE = 0.69 µg/kg x 50 kg / 1 x 10 x 1 x 1 x 1 = 3.4 µg/day.

A modifying factor F2 of 10 was applied to cover the full population with the data coming from the worker population.

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CHROMIUM

Summary of PDE for Chromium

Chromium (Cr III)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	11000	1100	2.9

Introduction

Chromium (Cr) is found in a variety of oxidation states, the most important being Cr 0 (in stainless steel) Cr II, III and VI. Cr II is readily oxidized and is used as a reducing agent in chemical synthesis. Cr VI is a powerful oxidant, chromate, CrO_4^{2-}, and dichromate, $Cr_2O_7^{2-}$, being the best known oxyanions. Cr III, the most abundant environmental form, is an essential element that plays a role in glucose metabolism. Chromium deficiency causes changes in the metabolism of glucose and lipids and may be associated with maturity-onset diabetes, cardiovascular diseases, and nervous system disorders (Anderson, 1993, 1995). Sources of chromium in pharmaceuticals may include colorants, leaching from equipment or container closure systems, and catalysts. With the exception of use as a catalyst, intake of chromium from pharmaceuticals will be in the form of metallic chromium (Cr 0) or Cr III rather than the more toxic Cr VI; therefore, for drug products, this safety assessment is based on the known toxicity of Cr III and Cr VI is excluded from this assessment. Chromium present as a colorant (e.g., chromium oxide green, chromium hydroxide green; see 21 CFR 72) is intentionally added and thus beyond the scope of this guidance.

Safety Limiting Toxicity

The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

No specific target organ toxicities have been identified for the oral intake of chromium. Generally oral intake of 5 mg/kg/day Cr III (US EPA, 1998) is not expected to be associated with adverse health.

The 2 year NTP studies (2010) on the carcinogenicity of Cr (III) picolinate administered in feed to rats and mice provided the most relevant safety information for Cr as present in drug products. The NOAEL was 90 mg/kg Cr (III) picolinate (11.9 weight %; 10.7 mg/kg/day CrIII) in rats based on increase in the incidence of preputial gland adenoma in male rats at 460 mg/kg. This finding was not dose-dependent and was considered an equivocal finding by the study authors. This finding was not observed male mice or in the female counterpart in either species (clitoral gland). In the absence of a treatment-related carcinogenic finding, F4 was set at 1.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 10.7 mg/kg/day x 50 kg/ 5 x 10 x 1 x 1 x 1 = 10.7 mg/day ~11000 µg/day.

PDE – Parenteral Exposure

Recommendation for the nutritional intravenous administration of Chromium (III) vary per age group between 0.05 µg/kg/day in preterm infants and 15 µg/kg in adults (Moukazel, 2009). There is insufficient information to assess if exceeding these

recommended daily doses may lead to adverse responses e.g., for the kidney especially in newborns and preterm infants.

The safety review for Cr was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an oral bioavailability of about 10% for chromium and inorganic chromium compounds (ATSDR, 2012), the recommended PDE for chromium for a parenteral exposure is:

PDE = 11000 µg/day/10 = 1100 µg/day.

PDE – Inhalation Exposure

The study by Deralenko (1999) used inhalation of Cr (III) sulfate particles during 13 weeks (6h/day and 5 days per week) causing predominantly chronic inflammation of the airways (mononuclear infiltrate, particular material) and locally thickening of alveolar walls. The effect was observed at all doses. The LOAEL is 17 mg/m^3 (3 mg CrIII/m^3). A lack of systemic toxicity was noted in a 13 week inhalation study in rats administered soluble or insoluble Cr (III). Based on these data the on these data, the inhalation MRL of 0. 1µg/m^3 was used to set the PDE (ATSDR, 2012).

PDE =0.0001 mg/ m^3 /1000 m^3/L x 28800 L/day = 2.9 µg/day.

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COBALT

Summary of PDE for Cobalt

Cobalt (Co)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	50	5.0	2.9

Introduction

Cobalt (Co) is a naturally-occurring element, often combined with other elements such as oxygen, sulfur, and arsenic. Co is essential in the human body because it is an integral component of Vitamin B-12 and functions as a co-enzyme for several enzymes critical in the synthesis of hemoglobin and the prevention of pernicious anemia. The Recommended Dietary Allowance of vitamin B12 is 2.4 µg/day, which corresponds to 0.1 µg of Co. No essential biological function of inorganic Co in the human body has been identified. Cobalt compounds (e.g., cobalt octoate) are being used as catalysts in selective hydrogenation.

Safety Limiting Toxicity

The IARC (2006) concluded that Co sulphate and other soluble Co (II) salts are possible human carcinogens (Group 2B). The data indicate the location of tumors is limited to the lung in rats and humans.

Polycythemia is considered to be the most sensitive finding after repeated oral exposure to humans. Inhalation exposure of humans to Co has been associated with a severe and progressive respiratory disease known as hard-metal pneumoconiosis, as well as asthma and contact dermatitis.

PDE – Oral Exposure

The oral PDE is based on the available human data. Polycythemia was the most sensitive finding in humans after repeated oral exposure to 150 mg of cobalt chloride (~1 mg Co /kg/day). The oral PDE was determined on the basis of the LOAEL of 1 mg/kg/day in male human volunteers after oral exposure over a period of 22 days (WHO, 2006).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below:

PDE = 1 mg/kg/day x 50 kg / 1 x 10 x 10 x 1 x 10 = 0.05 mg/day = 50 µg/day.

PDE – Parenteral Exposure

No relevant data on parenteral exposure to cobalt compounds were found. On the basis of the oral bioavailability ranging largely from 18-97% for cobalt and inorganic cobalt compounds (ATSDR, 2004). Using a safety factor of 10 to account for low bioavailability, the PDE for cobalt for parenteral exposure is:

PDE = 50 µg/day / 10 = 5.0 µg/day.

PDE – Inhalation Exposure

Co sulphate and other soluble Co (II) salts are possible human carcinogens (Group 2B) which can induce lung tumors.

Pneumoconiosis, asthma and contact dermatitis were the principal non-carcinogenic effects in humans after chronic inhalation. For the calculation of the inhalation PDE, the chronic inhalation MRL of 0.1 microgram / m^3 was used (ATSDR, 2010).

0.0001 mg/ m^3 /1000 m^3/L x 28800 L/day = 2.9 µg/day.

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COPPER

Summary of PDE for Copper

Copper (Cu)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1300	130	13

Introduction

Copper (Cu) is a Group 11 element of the first transition series and has two main oxidation states, Cu I and Cu II. It is an essential trace element in both animals and humans. Copper plays a vital role in a number of critical enzyme systems and is closely linked with normal hematopoiesis and cellular metabolism. Copper compounds (e.g., copper chromite) are being used as catalysts in hydrogenolysis and decarboxylation reactions

Safety Limiting Toxicity

A general review of relevant safety data for animals and humans indicates that copper can produce adverse effects to the gastrointestinal tract, liver, and kidney upon ingestion of toxic doses (Araya *et al.* 2003).

PDE – Oral Exposure

Studies on cupric sulfate and copper 8-quinolinolate have been conducted in mice and rats and dogs (EHC, 1998). Rats were determined to be the more sensitive species to effects on liver and kidney. In a 13 week study in rats the NOAEL was 17 mg/kg/day for copper sulfate, equivalent to 6.7 mg Cu/kg/day (Hebert, 1993).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 6.7 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 1.34 mg/day = 1340 µg/day ~1300 µg/day.

PDE – Parenteral Exposure

The safety review for copper was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. The human gastrointestinal system can absorb 30-40% of ingested copper from the typical diets consumed in industrialised countries (Wapnir, 1998). On the basis of limited oral bioavailability of 30%-40% for copper and inorganic copper salts, the recommended PDE for copper for parenteral exposure is:
PDE = 1340 µg/day / 10 = 134 µg/day ~130 µg/day.

PDE – Inhalation Exposure

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs (ATSDR, 2004).

The inhalation PDE was calculated by dividing the oral PDE by 100 (as described in Section 3.1).

1340/100 = 13.4 µg/day ~13 µg/day.

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GOLD

Summary of PDE for Gold

Gold (Au)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	130	130	1.3

Introduction

Gold (Au) exists in metallic form and in oxidation states of +1 to +5, the monovalent and trivalent forms being the most common. Elemental gold is poorly absorbed and consequently is not considered biologically active. Gold is being used on a carrier or in complexes like gold chloride and $L–Au^+$ (where L is a phosphane, phosphite, or an arsine; Telles, 1998), as catalysts in organic synthesis. The only source for gold in drug products comes from the use as catalyst. Gold (I) salts are used therapeutically.

Safety Limiting Toxicity

Most knowledge of gold toxicity is based on therapeutic uses of gold. Currently available therapies are gold salts of monovalent gold (I) with a sulfur ligand (Au-S), but metallic gold has also been studied. No toxicity was seen in 10 patients administered colloidal metallic gold (monoatomic gold) at 30 mg/day for one week followed by 60 mg/day the second week or the reverse schedule. The patients were continued on trial for an additional 2 years at 30 mg/day. There was no evidence of hematologic, renal or hepatic cytotoxicity but some improvement in clinical symptoms of rheumatoid arthritis and in cytokine parameters were noted (Abraham and Himmel, 1997).

Long term animal data are available with Au compounds. However, these studies have been performed with monovalent gold Au I and are not considered sufficiently relevant to assess the potential toxicity of Au in pharmaceutical products.

Au (III) is thought to be the more toxic form and is used in catalysis, e.g., as gold trichloride. There is only limited data on gold (III) complexes. In one study, the gold (III) compound $[Au(en)Cl_2]Cl$ (dichloro(ethylenediamine-aurate(III) ion) caused minimal histological changes in the kidney and liver of rats, and no renal tubular necrosis, at a dose of 32.2 mg/kg in mice administered the compound intraperitoneally for 14 days (Ahmed *et al.* 2012).

PDE – Oral Exposure

The toxicologically significant endpoint for gold exposures is renal toxicity.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

PDE = 32.2 mg/kg x 50 kg / 12 x 10 x 10 x 1 x 10 = 134 µg/day ~130 µg/day.

F5 was put at 10 because the NOAEL was not established and the toxicological assessment was not complete.

PDE – Parenteral Exposure

In humans, 50 mg intramuscular (IM) injections of gold sodium thiomalate resulted in >95% bioavailability (Blocka, 1986). In rabbits, ~70 % of the gold sodium thiomalate was absorbed after an IM injection of 2/mg/kg (Melethil, 1987).

Based on high bioavailability, the parenteral PDE is equivalent to the oral PDE.

PDE = 130 µg/day.

PDE – Inhalation Exposure

In the absence of relevant inhalation and parenteral data, a modifying factor of 100 was applied to the oral PDE as described in Section 3.1.

PDE = 134 /100 = 1.34 µg/day ~1.3 µg/day.

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LEAD

Summary of PDE for Lead

Lead (Pb)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	5.0	5.0	5.0

Introduction

Lead (Pb) is the most common heavy element. It occurs in organic and inorganic forms. The generally bivalent Pb compounds include water-soluble salts such as Pb acetate as well as insoluble salts such as Pb oxides. Organic Pb compounds include the gasoline additives tetramethyl- and tetraethyl-lead. Organic Pb compounds undergo fairly rapid degradation in the atmosphere and form persistent inorganic Pb compounds in water and soil. Pb has no known useful biological function in human or mammalian organisms (ATSDR, 2007).

Safety Limiting Toxicity

In humans and animals, exposure to Pb may cause neurological, reproductive, developmental, immune, cardiovascular and renal health effects. In general, sensitivity to Pb toxicity is greater when there is exposure *in utero* and in children compared to adults. A target blood level of 1-2 µg/dL was set, and using modelling programs (US EPA, 2009) that assumed 100% bioavailability and no other exposure, a PDE was obtained. For this reason, the PDEs are the same regardless of the route of administration.

PDE – Oral Exposure

Adverse neurobehavioral effects are considered to be the most sensitive and most relevant endpoint in humans after oral exposure. Data from epidemiological studies show that blood Pb levels <5 µg/dL may be associated with neurobehavioral deficits in children (NTP, 2011).

According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) Model, 1994) (100% absorption, no other sources of lead), oral intake of 5 µg/day translates into a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months).

PDE = 5.0 µg/day.

PDE – Parenteral Exposure

The oral effects of Pb are based on blood levels. Therefore, the parenteral PDE is equal to the oral PDE of 5.0 µg/day.

PDE – Inhalation Exposure

The oral effects of Pb are based on blood levels. Therefore, the inhalation PDE is equal to the oral PDE of 5.0 µg/day.

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LITHIUM

Summary of PDE for Lithium

Lithium (Li)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	780	390	25

Introduction

Lithium (Li) is a common metal that is present in plant and animal tissues. Lithium is used as a therapeutic agent to treat bipolar disease. Lithium is being used alone or in combination with other metals as catalyst. Lithium compounds (e.g., lithium aluminum hydride) are being used as reagents in organic synthesis.

Lithium exists commonly as a salt in the +1 form oxidation state only.

Safety Limiting Toxicity

The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

There is a minimal amount of data on the effects of lithium carbonate on the immune system. A 14 day mouse study was conducted to assess the effects of lithium carbonate on the immune system (NTP, 1986). Doses were modified to 100, 300 and 400 mg/kg in repeat and later studies because of a lack of effect at 50 and 200 mg/kg. Findings included dose-dependent effects on decreased in liver and thymus weight, and changes in leukocytes and red blood cells and associated parameters.

Using 200 mg/kg/day (18.7 mg Li/kg/day) as the NOAEL and modifying factors (F1-F5 as discussed in Appendix 1), the PDE is:

PDE = 18.7 mg/kg/day x 50 kg/ 12 x 10 x 10 x 1 x 1 = 0.78 mg/day = 780 µg/day.

PDE – Parenteral Exposure

There are no adequate data to develop a parenteral PDE. However, based on oral bioavailability of 85% (Grandjean, 2009) and using a modifying factor of 2, the parenteral PDE is calculated as:

PDE = 0.77 mg/day / 2 = 0.39 mg/day =390 µg/day.

PDE – Inhalation Exposure

Rabbits were exposed to lithium chloride at 0.6 and1.9 mg/m^3 for 4-8 weeks, 5 days/week for 6 hours/d (Johansson *et al.* 1988). Lungs were studied by light and electron microscopy with focus on inflammatory changes. No significant effects were reported, so the highest dose was used to set the PDE.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as:

For continuous dosing: PDE = 1.9 mg/m^3 /1000 L/m^3 = .0019 mg/L

0.0019 mg/L x 6 h/day x 5 days / 24h/day x 7days = 0.000339 mg/L

Daily dose: 0.339 µg/L x 1440 L/day/4 kg = 122.04 µg/kg/day

PDE = 122.04 µg/kg/day x 50kg /2.5x10x10x1x1 = 25 µg/day.

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MERCURY

Summary of PDE for Mercury

Mercury (Hg)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	40	4.0	1.2

Introduction

Mercury (Hg) is an element widely existing in the global environment. Hg exists in three forms: elemental mercury, inorganic mercury and organic mercury. The most likely form of residual mercury in drug products is the inorganic form. Therefore, this safety assessment is based on the relevant toxicological data of elemental or inorganic Hg. This safety assessment and derived PDEs do not apply to organic mercury.

Safety Limiting Toxicity

There is no data to indicate that inorganic mercury is carcinogenic in human. There is limited evidence in experimental animals for the carcinogenicity of mercuric chloride. IARC concluded that inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3; IARC, 1997).

Inorganic mercury compounds show significantly lower oral bioavailability compared to organic mercury and induce different toxicological effects including neurological, corrosive, hematopoietic, renal effects and cutaneous disease (acrodynia). The safety limiting toxicity for inorganic mercury and salts is renal toxicity.

PDE – Oral Exposure

There were well organized NTP studies of $HgCl_2$ up to 2 years. The 6 month gavage study in rats was selected because it had more detailed clinical pathology assessment and wider range of doses than the 2 year study. Based on adverse renal effects from the 6-months rat study (NTP, 1993), the LOAEL was 0.23 mg/kg/day for mercury (0.16 mg/kg day for mercury when corrected for 7 days of exposure/week).

Using the modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is calculated as:

PDE = 0.16 mg/kg /day x 50 kg / 5 x 10 x 2 x 1 x 2 = 0.04 mg/day = 40 µg/day.

F5 was set to 2, because no NOAEL was identified in the study and the effect at the LOAEL was a slight increase in incidence of an effect also present in the control animals.

PDE – Parenteral Exposure

Animal studies indicate that the oral bioavailability of inorganic mercury is in the 10-30% range (ATSDR, 1999). Therefore, the oral PDE is divided by a factor of 10 (as described in Section 3.1).

PDE = 40/10 = 4.0 µg/day.

PDE – Inhalation Exposure

Neurobehavioral effects are considered to be the most sensitive endpoint following inhalation exposure in humans as shown in occupational studies at the range of air TWA levels between 14 and 20 $\mu g/m^3$ (US EPA, 1995; EU SCOEL, 2007).

The presence of neurobehavioral effects at low-level mercury exposures (14 µg/m^3) in dentists (Ngim *et al.* 1992) indicates that the TWA needs to be considered as a LOAEL.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated based on the long-term inhalation exposure to elemental mercury vapor:

For continuous dosing = $\frac{14\ \mu g/m^3 \times 8\ hr/day \times 6\ days/week}{24\ hr/day \times 7\ days/week \times 1000\ L/m^3}$

= 0.004 µg/L

Daily dose = $\frac{0.004\ \mu g/L \times 28800\ L}{50\ kg}$ = 2.30 µg/kg

PDE = $\frac{2.30\ \mu g/kg \times 50\ kg}{1 \times 10 \times 1 \times 1 \times 10}$ = 1.2 µg/day.

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MOLYBDENUM

Summary of PDE for Molybdenum

Molybdenum (Mo)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	180	180	7.6

Introduction

The main oxidation states for Mo are IV and VI, the most common forms of which are oxyanions. The predominant form of Mo occurring in soils and natural waters is the molybdate ion, MoO_4^{2-} which forms soluble compounds with a variety of cations including K^+, NH_4^+ and Ca^{2+}. Mo exists in soil in various forms at concentration of 0.1-10 mg/kg. MoO_2 and MoS_2 are insoluble in water. It is widely present in vegetables, dairy products and meats. Mo combinations (e.g., Bi-Mo, Fe-Mo, molybdenum oxide and Mo-complexes) are being used as catalysts in organic synthesis.

Mo deficiency is characterized by night blindness, nausea, disorientation, coma, tachycardia, tachypnea and associated with various biochemical abnormalities including high plasma methionine. In addition an almost undetectable serum uric acid concentration has been reported in a patient receiving total parenteral nutrition (Abumrad et *al.* 1981).

Safety Limiting Toxicity

Molybdenum as the trioxide was not mutagenic (NTP, 1997). Carcinogenicity has not been evaluated by IARC or US EPA.

Alteration of estrus cycle is the most sensitive effect observed in the various rat studies. Absorption and retention of Mo is markedly influenced by interactions with dietary Cu and sulfate and the typical symptoms from excessive Mo intake were similar to those of copper deficiency including weight loss, growth retardation, anorexia, anemia, diarrhea, achromotrichia, testicular degeneration, poor conception, deficient lactation, dyspnea, incoordination and irritation of mucous membranes (Engel *et al.* 1956).

PDE – Oral Exposure

Fungwe *et al.* (1990) examined the effects on fertility and reproductive performance of sodium molybdenate in female rats given drinking water containing 0, 5, 10, 50 or 100 mg Mo/L. After 6 weeks the effect of Mo on the estrous cycle (3 cycles) and vaginal cytology was determined, and some animals then mated to untreated males. Pregnant dams continued to be dosed to day 21 of gestation with Mo and fetal effects determined. Effects on the estrous cycle, gestational weight gain, and the fetus were observed at 10 mg/L and higher; thus, a dose level of 5 mg/L can be considered a NOAEL. Vyskocil and Viau (1999) calculated this NOAEL to be 0.9 mg Mo/kg/day.

Using modifying factors (F1-F5 as discussed in Appendix 1) the oral PDE is:

PDE = 0.9 mg/kg/day x 50 kg / 5 x 10 x 1 x 5 x 1 = 0.180 mg/day = 180 µg/day.

F4 was selected to be 5 based on the presence of fetal effects.

PDE – Parenteral Exposure

In Vyskocil and Viau (1999), it was reported that oral bioavailability in humans ranged from 28-77%. Turnland *et al.* (2005) report that molybdenum absorption was about 90% in healthy men. Therefore, the parenteral PDE is the same as the oral PDE.

PDE= 180 µg/day.

PDE – Inhalation Exposure

Chronic inflammation in the alveoli was seen in rat and mouse. In addition, a slight trend for bronchiolar alveolar adenoma and carcinoma was observed in male rats exposed to molybdenum trioxide in a 2-year inhalation study (NTP, 1997). Lung neoplasms were not seen in female rats. In mice, bronchiolar alveolar adenoma and carcinoma were observed at the lowest dose of 10 mg/m^3 (6.7 mg/m^3 of Mo).

The inhalation PDE was calculated based on the low dose in the mouse carcinogenicity study, where findings of alveolar and bronchiolar carcinoma were observed, using the modifying factors (F1-F5 as discussed in Appendix 1).

6.7 mg/m^3 ÷1000 m^3/L = 0.0067 mg/L

$$\text{For continuous dosing} = \frac{0.0067 \text{ mg/L} \times 6 \text{ hr} \times 5 \text{ d}}{24 \text{ hr} \times 7 \text{ d}} = 0.0012 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.0012 \text{ mg/L} \times 43 \text{ L/d}}{0.028 \text{ kg}} = 1.83 \text{mg/kg}$$

$$\text{PDE} = \frac{1.83 \text{ mg/kg} \times 50 \text{ kg}}{12 \times 10 \times 1 \times 10 \times 10} = 7.6 \text{ µg/day.}$$

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NICKEL

Summary of PDE for Nickel

Nickel (Ni)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	600	60	6.0

Introduction

Nickel (Ni) is a Group 10 element of the first transition series. Although Ni may have valences of 0, I, II and III, its main oxidation state is +2. Ni is a naturally occurring metal existing in various mineral forms. In general, the more soluble Ni compounds, including Ni chloride, Ni sulfate, and Ni nitrate, tend to be more toxic than less soluble forms, such as Ni oxide and Ni subsulfide. Ni is nutritionally not essential for humans, but Ni deficiency may cause adverse effects in animals. Nickel as Ni-Al alloys is being used as catalyst in hydrogenation reactions.

Safety Limiting Toxicity

Nickel is genotoxic, but not mutagenic (IARC 2012). There is no indication of carcinogenicity of Ni salts after oral administration. Depending on the type of salt there was an increase in tumors in some rodent inhalation studies (ATSDR, 2005; EU EFSA, 2005). Combining all forms of Ni, IARC (2012) classified Ni as a human carcinogen (Group 1).

In humans and animals, ingestion of large amounts of Ni may cause stomach pain, depression of body weight and adverse effects on blood and kidneys. Humans generally become sensitised to Ni after prolonged contact with the skin. Chronic inhalation may produce adverse changes in lung and nasal cavity in both humans and animals.

PDE – Oral Exposure

Human sensitisation to Ni was used to establish the oral PDE, because it is the most sensitive endpoint. Human data show that an oral challenge dose of 0.012 mg Ni/kg can induce dermatitis in nickel-sensitized individuals. Exposure to these nickel concentrations did not result in dermatitis in non-sensitized individuals (Nielsen 1999). Similar data were presented for 0.02 mg/kg by ATSDR (2005).

PDE = 0.012 mg/kg/day x 50 kg = 0.60 mg/day = 600 µg/day.

PDE – Parenteral Exposure

A human study using a stable nickel isotope estimated that 29–40% of the ingested label was absorbed (based on fecal excretion data) (Patriarca *et al.* 1997). On the basis of limited oral bioavailability of Ni and water-soluble Ni compound. Therefore, the oral PDE is divided by a factor of 10 (as described in Section 3.1).

PDE = 600 µg/day / 10 = 60 µg/day.

PDE – Inhalation Exposure

For calculation of the inhalation PDE, a relevant form of Ni was selected from the available data. In 2 year studies with nickel oxide (the form commonly used in stainless steel coatings), no tumors were observed in hamsters (Wehner *et al.* 1984) or mice (NTP, 1996), but there was some evidence of carcinogenicity in rats (NTP, 2006) and no evidence of carcinogenicity with inhalation of metallic nickel (Oller, 2008).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated based on the NOAEL in the rat study of 0.5 mg Ni/m^3/day.

For continuous dosing 0.5 mg/m^3 / 1000L/m^3 = 0.0005 mg/L

0.0005 mg/L x 6 hr x 5 d /24 hr x 7 d = 0.000089 mg/L

Daily dose 0.000089 mg/L x 290 L/d / 0.425 kg = 0.060 mg/kg

PDE = 0.060 mg/kg x 50 kg / 5 x 10 x 1 x 10 x 1 = 6.0 µg/day.

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PALLADIUM

Summary of PDE for Palladium

Palladium (Pd)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	100	10	1.0

Introduction

Palladium (Pd) is a steel-white, ductile metallic element resembling and occurring with the other platinum group metals and nickel. It exists in three states: Pd^0 (metallic), Pd^{2+} and Pd^{4+}. It can form organometallic compounds, only few of which have found industrial uses. Palladium (on various supports) is being used as catalyst in hydrogenation reactions. Palladium metal is stable in air and resistant to attack by most reagents except aqua regia and nitric acid.

Several mutagenicity tests of different palladium compounds with bacterial or mammalian cells (Ames test with *Salmonella typhimurium*; SOS chromotest with *Escherichia coli*; micronucleus test with human lymphocytes) *in vitro* gave negative results.

Safety Limiting Toxicity

The data was reviewed to identify the safety limiting toxicities based on routes of administration.

PDE – Oral Exposure

A number of long-term animal studies have been conducted exploring the toxicity and carcinogenicity of palladium salts. However, none to date have been executed in accordance with current guidelines for toxicological studies. The available data suggest potential NOAELs for palladium in the range of 0.8 – 1.5 mg/kg. A lifetime study with mice given palladium(II) chloride in drinking-water at a dose of about 1.2 mg Pd/kg/day found a significantly higher incidence of amyloidosis in several inner organs of males and females and suppressed growth in males, but not in females (Schroeder and Mitchner, 1971; IPCS, 2002). This study also contained a signal that suggested a possible carcinogenic endpoint; however, the design of the study (single dose level, pooling of the tumor rates from male and female animals, and a significant increase in the age of the treated *vs* control animals) limited the utility of the data to assess the carcinogenic potential.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated based on the LOEL of 1.2 mg/kg/day.

PDE = 1.2 mg/kg/day x 50 kg / 12 x 10 x 1 x 5x 1 = 0.1 mg/day = 100 µg/day.

PDE – Parenteral Exposure

The safety review for Pd was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. Palladium(II) chloride ($PdCl_2$) was poorly absorbed from the digestive tract (<0.5% of the initial oral dose in adult rats or about 5% in suckling rats after 3-4 days). Absorption/retention in adult rats was higher following intratracheal or intravenous exposure, resulting in total body burdens of 5% or 20%, respectively, of the dose administered, 40 days after dosing (IPCS, 2002). On the basis of an oral bioavailability the PDE for palladium for parenteral exposure is:

PDE = 100 µg/day / 10 = 10 µg/day.

PDE – Inhalation Exposure

There are no adequate inhalation data on Pd. Therefore, the inhalation PDE for palladium was derived from the oral PDE by division by a factor of 100 (as described in Section 3.1).

PDE = 100 µg/day / 100 = 1.0 µg/day.

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PLATINUM

Summary of PDE for Platinum

Platinum (Pt)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	1000	10	1.4

Introduction

Platinum (Pt) is a Group VIII element of the third transition series. It is the most important of the six heaviest of the group VIII elements, collectively called the "platinum group metals" or "platinoids", including palladium, osmium, rhodium, ruthenium and iridium. Platinum and Pd are more chemically reactive than the other platinoids. Metallic Pt has been shown to catalyze many oxidation-reduction and decomposition reactions and the major industrial use of Pt is as a catalyst. Pt complexes exhibiting a range of oxidation states are known, although the principal valences are Pt II and IV. Pt II forms a tetra-coordinate aqua ion $[Pt(H_2O)_4]^{2+}$. The most common Pt IV catalysts are chloroplatinate salts such as tetra and hexachloroplatinate ions.

Safety Limiting Toxicity

The data was reviewed to identify the safety limiting toxicities based on routes of administration.

Chlorinated salts of platinum are responsible for platinum related hypersensitivity and are a major occupational health concern (US EPA, 2009). The hypersensitivity appears to be the most sensitive endpoint of chloroplatinate exposure, at least by the inhalation route. Signs include urticaria, contact dermatitis of the skin, and respiratory disorders ranging from sneezing, shortness of breath, and cyanosis to severe asthma (IPCS, 1991). Exposure reduction was effective in resolving symptoms (Merget *et al.* 2001). Neutral complexes and complexes without halogenated ligands do not appear allergenic (US EPA, 2009; EU SCOEL, 2011). The risk of hypersensitivity appears to be related to sensitizing dose and dose and length of exposure (IPCS, 1991; US EPA, 2009; Arts *et al.* 2006) and cigarette smoking (US EPA, 2009; Merget *et al.* 2000; Caverley, 1995).

PDE – Oral Exposure

No experimental data are available on the carcinogenicity of platinum and platinum compounds, and toxicology data are limited (US EPA, 2009). In one study in male rats administered $PtCl_2$ (relatively insoluble) and $PtCl_4$ (soluble) for 4 weeks, the toxicity of the two platinum salts was investigated. No significant effects on body weight gain or food consumption for either compound, and no effects were observed on hematological parameters for $PtCl_2$. Some hematological parameters were influenced by $PtCl_4$; a reduction of about 13% in hematocrit and erythrocyte parameters was reported at the dose of 50 mg Pt/kg in the diet. Platinum concentration increased in tissues in animals dosed with either compound, particularly the kidney. For this reason plasma creatinine was examined, and found to be increased in animals dosed with $PtCl_4$ when added in the diet at 50 mg Pt/kg diet for 4 weeks, but not $PtCl_2$. This dose corresponded to 21 mg Pt/animal (Reichlmayr-Lais *et al.* 1992). This study was used in the determination of the PDE as one endpoint in the study was renal toxicity (plasma creatinine), a target organ of platinum and a site of accumulation. Renal toxicity is an also an adverse effect of treatment with chemotherapeutic agents such as cisplatin.
Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated based on the NOAEL of 10 mg/kg/day.

PDE = 10 mg/kg/day x 50 kg / 5 x 10 x 10 x 1 x 1 = 1 mg/day = 1000 µg/day.

PDE – Parenteral Exposure

The safety review for platinum identified limited assessments of platinum salt toxicity for parenteral routes of administration. The oral absorption of platinum salts is very low (<1%) (US EPA, 2009). Therefore, the oral PDE is divided by a factor of 100 (as described in section 3.1).

PDE = 1000 µg/day / 100 = 10 µg/day.

PDE – Inhalation Exposure

Due to the use of the chloroplatinates in catalytic converters, numerous animal (Biagini *et al.* 1983) and human (Pepys *et al.* 1972; Pickering 1972; Merget *et al.* 2000; Cristaudo *et al.* 2007) studies have been conducted. The US EPA (1977; 2009) and the EU SCOEL (2011) have also examined the safety of chloroplatinates based on sensitization. The EU SCOEL concluded that the database does not allow for setting an occupational limit for soluble platinum salts. The US DoL (2013) has established an occupational limit for soluble Pt salts at 2 µg/m^3; however, whether this exposure level is completely protective of workers has been questioned (Merget and Rosner, 2001).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

2 µg/m^3 ÷1000 m^3/L = 0.002 µg/L

For continuous dosing = $0.002\ \mu g/L \times \frac{8\ hr \times 5\ d}{24\ hr \times 7\ d} = 0.00048\ \mu g/L$

Daily dose = $\frac{0.00048\ \mu g/L \times 28800 L/d}{50\ kg} = 0.27\ \mu g/kg/d$

PDE = $\frac{0.27\ \mu g/kg/d \times 50\ kg}{1 \times 10 \times 1 \times 1 \times 1} = 1.37\ \mu g/day \sim 1.4\ \mu g/day.$

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SELENIUM

Summary of PDE for Selenium

Selenium (Se)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	170	85	140

Introduction

Selenium is present in the earth's crust, often in association with sulfur-containing minerals. It can assume four oxidation states (-2, 0, +4, +6) and occurs in many forms, including elemental selenium, selenites and selenates. Selenium is an essential trace element for many species, including humans. Selenium is incorporated into proteins *via* a specific selenocysteine tRNA. Selenium is being used as a catalyst in the manufacture of rubber. Ru-Se catalysts are used in oxygen reduction. Aryl- and alkyl-Selenium reagents have various applications in organic synthesis.

Safety Limiting Toxicity

Selenium was listed as a Group 3 compound by IARC (1987), not classifiable for carcinogenesis. The only selenium compound that has been shown to be carcinogenic in animals is selenium sulfide (NTP, 1980). According to the US EPA, selenium sulfide is in Group B2 (probable human carcinogen) (US EPA, 2002). Other selenium compounds are classified as D; not classifiable as to carcinogenicity in humans.

The most significant toxicity observed in these assessments was hepatotoxicity.

PDE – Oral Exposure

In a rat carcinogenicity study of selenium sulfide, the NOAEL for hepatocellular carcinoma was 3 mg/kg/day (1.7 mg Se/kg/day) (NTP, 1980). There is insufficient data to assess carcinogenicity of other forms of selenium, and the human relevance of the rodent liver tumors has been questioned (IARC, 1999). Some human data are available but only in a limited number of subjects (ATSDR, 2003). The PDE is in line with the MRL of 5 µg/kg/day for Se (ATSDR 2003).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 1.7 mg/kg/day x 50 kg / 5 x 10 x 1 x 10 x 1 = 170 µg/day.

PDE – Parenteral Exposure

The safety review for selenium was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. Studies in humans and experimental animals indicate that, when ingested, several selenium compounds including selenite, selenate, and selenomethionine are readily absorbed, often to greater than 80% of the administered dose (ATSDR, 2003). On the basis of oral bioavailability of ~80%, the PDE for selenium for parenteral exposure is (as described in section 3.1).

PDE = 170 µg/day / 2 = 85 µg/day.

PDE – Inhalation Exposure

The safety review for selenium was unable to identify any significant animal models or clinical studies of inhalation toxicity. However, occupational limits have established time weighted averages for selenium exposures of 0.2 mg/m^3 (US DoL, 2013).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as below.

0.2 mg/m^3 /1000 L/m^3= 0.0002 mg/L

For continuous dosing = 0.0002 mg/L x 8 h x 5 d/24 x 7 = 0.0000476 mg/L

Daily dose = 0.0000476 mg/L x 28800 L/50 kg = 0.027 mg/kg

$$\text{PDE} = \frac{0.027 \text{ mg/kg} \times 50 \text{ kg}}{1 \times 10 \times 1 \times 1 \times 1} = 0.135 \text{ mg/day} = 140 \text{ µg/day.}$$

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SILVER

Summary of PDE for Silver

Silver (Ag)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	170	35	6.9

Introduction

Silver (Ag) is present in silver compounds primarily in the oxidation state +1 and less frequently in the oxidation state +2. Ag occurs naturally mainly in the form of very insoluble and immobile oxides, sulfides and some salts. The most important silver compounds in drinking-water are silver nitrate and silver chloride. Most foods contain traces of silver in the 10–100 µg/kg range. Ag is nutritionally not essential and no metabolic function is known. Silver is being used as a catalyst in the oxidation of ethylene to ethyleneoxide. Silver-Cadmium alloy is used in selective hydrogenation of unsaturated carbonyl compounds. Silver oxide is used as a mild oxidizing agent in organic synthesis.

Safety Limiting Toxicity

Silver is not mutagenic. Animal toxicity studies and human occupational studies have not provided sufficient evidence of carcinogenicity. Based on these data Ag is not expected to be carcinogenic in humans (ATSDR, 1990).

Argyria appears to be the most sensitive clinical effect in response to human Ag intake. Silver acetate lozenges are used in smoking cessation (Hymowitz and Eckholdt, 1996). Argyria, a permanent bluish-gray discoloration of the skin, results from the deposition of Ag in the dermis combined with an Ag-induced production of melanin. Inhalation of high levels of silver can result in lung and throat irritation and stomach pains (ATSDR, 1990).

PDE – Oral Exposure

Silver nitrate was added at 0.015% to the drinking water of female mice (0.9 g/mouse; 32.14 mg/kg silver nitrate; 64% silver) for 125 days to examine neurobehavioral activity of the animals based on potential neurotoxicity of silver (Rungby and Danscher, 1984). Treated animals were hypoactive relative to controls; other clinical signs were not noted. In a separate study, silver was shown to be present in the brain after mice were injected with 1 mg/kg ip silver lactate (Rungby and Danscher, 1983). The oral PDE is in line with the reference dose of 5 µg/kg/day (US EPA, 2003).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

20 mg/kg x 50 kg / 12 x 10 x 5 x1 x 10 = 167 µg/d ~170 µg/day.

A factor 10 was chosen for F5 as a NOAEL was not seen in this study and few toxicological endpoints were examined.

PDE – Parenteral Exposure

US EPA (2003) identified a LOAEL of 0.014 mg/kg Ag/d using long-term (2 to 9 years) human iv data based on argyria following colloidal and organic silver medication.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the parenteral PDE is calculated as below.

0.014 mg/kg/d x 50 kg = 700 ug/d/1 x 10 x 1 x 1 x 2 = 35 µg/day.

A factor of 2 was chosen for F5 as the finding of argyria was not considered a serious toxicity and a factor of 10 is used for F2, for a combined modifying factor of 20.

PDE – Inhalation Exposure

Lung and throat irritation and stomach pains were the principal effects in humans after inhalation of high Ag levels.

Using the TLV of 0.01 mg/m^3 for silver metal and soluble compounds (US DoL, 2013), taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

0.01 mg/m^3 /1000 L/m^3= 0.00001 mg/L

For continuous dosing = 0.00001 mg/L x 8 h x 5 d/24 x 7 = 0.00000238 mg/L

$$\text{Daily dose} = \frac{0.00000238 \text{ mg/L} \times 28800 \text{ L/day}}{50 \text{ kg}} = 0.00137 \text{ mg/kg/day}$$

$$\text{PDE} = \frac{0.00137 \text{ mg/kg} \times 50 \text{ kg}}{1 \times 10 \times 1 \times 1 \times 1} = 0.0069 \text{ mg/day} = 6.9 \text{ µg/day.}$$

The factor F2 was set to 10 to extrapolate to the general population.

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THALLIUM

Summary of PDE for Thallium

Thallium (Tl)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	8.0	8.0	69

Introduction

Pure thallium (Tl) is a bluish-white metal. It exists primarily in two valence states: monovalent (thallous) and trivalent (thallic). Monovalent thallium is similar to potassium (K+) in ionic radius and electrical charge, which contribute to its toxic nature. Many of the thallium salts are soluble in water with the exception of the insoluble thallium (III) oxide. Tl sulfate has been used in medicine, primarily as a depilatory agent, but also to treat infections, such as venereal diseases, ringworm of the scalp, typhus, tuberculosis, and malaria. Thallium(III) salts are being used in organic synthesis. Tl is nutritionally not essential and no metabolic function is known (ATSDR, 1992).

Safety Limiting Toxicity

In humans and animals, the skin, especially the hair follicles, appears to be the most sensitive target of toxicity from repeated oral exposure to Tl (US EPA, 2009).

PDE – Oral Exposure

The primary target organ for oral exposure to Tl in humans and animals appears to be the skin, especially the hair follicles, as shown in a 90-day toxicity rat study with Tl sulfate. The NOAEL was defined at 0.04 mg Tl/kg on the basis of an increased incidence of alopecia at the higher doses (Stoltz *et al.* 1986; US EPA, 2009). Thus, the oral PDE was determined on the basis of the NOAEL of 0.04 mg Tl/kg in rat.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 0.04 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 0.008 mg/day = 8.0 µg/day.

PDE – Parenteral Exposure

No relevant data on parenteral exposure to thallium compounds were found. The bioavailability of soluble thallium salts is high (> 80%) (US EPA, 2009). Therefore, the parenteral PDE is the same as the oral PDE.

PDE = 8.0 µg/day.

PDE – Inhalation Exposure

No relevant data on inhalation exposure to thallium compounds were found. Using the TLV of 0.1 mg/m^3 for thallium, soluble compounds (US DoL, 2013; CEC, 2000).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the inhalation PDE is calculated as:

0.1 mg/m^3 /1000 L/m^3= 0.0001 mg/L

For continuous dosing = 0.0001 mg/L x 8 h x 5 d/24 x 7 = 0.0000238 mg/L

$$\text{Daily dose} = \frac{0.0000238 \text{ mg/L} \times 28800 \text{ L/day}}{} = 0.0137 \text{ mg/kg/day}$$

$$PDE = \frac{0.0137 \text{ mg/kg} \times 50 \text{ kg}}{1 \times 10 \times 1 \times 1 \times 1} = 0.069 \text{ mg/day} = 69 \text{ µg/day.}$$

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TIN

Summary of PDE for Tin

Tin (Sn)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	6400	640	64

Introduction

Tin (Sn) is a silvery-white metal that exists in valence states of 2 and 4. The most important inorganic compounds of tin are its oxides, chlorides, fluorides and halogenated sodium stannates and stannites. Tin is present in some multi-vitamin and mineral food supplements (levels up to 10 µg Sn/tablet). Tin is possibly nutritionally essential for some animals, it has not been shown to be essential for humans. Tin(II) chloride is being used as a reducing agent, and as a stabilizer of polyvinylchloride (PVC). This safety assessment focuses on inorganic tin considering that the more frequent occurrence of inorganic tin is more relevant with respect to metal impurities in drug products than organic tin compounds.

Safety Limiting Toxicity

There is no indication of *in vivo* genotoxicity or carcinogenicity for tin and tin salts. In several studies in rats, a decrease in hemoglobin as an early sign for anemia, was the most sensitive endpoint.

PDE – Oral Exposure

Anemia was the most sensitive endpoint in rats after repeated oral administration. Thus, the PDE for oral exposure was determined on the basis of the lowest NOAEL, i.e., 150 ppm (equivalent to 32 mg Sn/kg/day). This value was obtained from a 90-day study in rats based on signs of anemia starting at 500 ppm in rats exposed to stannous chloride *via* diet (De Groot *et al.* 1973).

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 32 mg/kg/day x 50 kg / 5 x 10 x 5 x 1 x 1 = 6.4 mg/day = 6400 µg/day.

PDE – Parenteral Exposure

The safety review for tin was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an oral bioavailability of about 5% for tin and inorganic tin compounds (ATSDR, 2005), and using the default factor of 10, the PDE for tin for a parenteral exposure is (as described in Section 3.1).

PDE = 6400 µg/day / 10 = 640 µg/day.

PDE – Inhalation Exposure

The safety review for tin was unable to identify any significant assessments on inorganic tin upon which to calculate a PDE for inhalation routes of exposure. Although a TLV is available for tin (2 mg/m^3; US DoL, 2013), there is insufficient data to set a MRL (ATSDR 2005; EU SCOEL 2003).

Therefore, the PDE for tin is calculated by using a factor of 100 to convert the oral PDE to the inhalation PDE (as described in Section 3.1).

PDE = 6400 µg/day / 100 = 64 µg/day.

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ATSDR. Toxicological profile for tin and tin compounds. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2005.

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VANADIUM

Summary of PDE for Vanadium

Vanadium (V)			
	Oral	Parenteral	Inhalation
PDE (µg/day)	120	12	1.2

Introduction

Vanadium (V) is present as a trace element in the earth's crust and can exist in a variety of oxidation states (-1, 0, +2, +3, +4 and +5). V is also present in trace quantities in most biological organisms with the principal ions being vanadate, VO_3^- and vanadyl, VO_2^+. Absorption of vanadium from the gastrointestinal tract is poor. Estimates of total dietary intake of vanadium in humans range from 10 to 60 µg/day. Intake from drinking water depends on the water source and estimates are up to 140 µg/day. Human populations have variable serum concentrations of vanadium, with 2 µg/L being the high end of the normal range. Despite its ubiquitous presence in the body, an essential biological role for vanadium in humans has not been established. Vanadium has been reported to have potentially beneficial effects in treatment of osteoporosis, osteopenia, cancer, and diabetes. Oral vanadyl sulfate in amounts up to 20 mg/day is included in some dietary supplements intended to promote muscle growth. Vanadium oxide is used as a catalyst in the manufacturing of sulfuric acid.

Safety Limiting Toxicity

Vanadium is genotoxic, but not mutagenic (ATSDR, 2009). Vanadium pentoxide is classified as a possible human carcinogen (Group 2B; IARC, 2012).

PDE – Oral Exposure

Following oral administration to animals and humans the gastrointestinal tract, cardiovascular, and hematological system are the primary targets of toxicity. The most appropriate study to assess vanadium toxicity through oral administration was conducted in humans exposed to vanadium for 12 weeks. In these studies, no significant alterations in hematological parameters, liver function (as measured by serum enzymes), cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen), body weight, or blood pressure were observed in subjects administered *via* capsule 0.12 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks (ATSDR, 2012). The oral NOAEL of 0.12 mg vanadium/kg/day for hematological and blood pressure effects was used to calculate the oral PDE.

Taking into account the modifying factors (F1-F5 as discussed in Appendix 1), the oral PDE is calculated as below.

PDE = 0.12 mg/kg/day x 50 kg / 1 x 10 x 5 x 1 x 1 = 0.12 mg/day = 120 µg/day.

PDE – Parenteral Exposure

The safety review for vanadium was unable to identify any significant assessments upon which to calculate a PDE for parenteral routes of exposure. On the basis of an approximate oral bioavailability of <1–10% for vanadium and inorganic vanadium compounds (ATSDR, 2012), the oral PDE was divided by 10 (as described in Section 3.1).

PDE = 120 µg/day / 10 = 12 µg/day.

PDE – Inhalation Exposure

A two year chronic inhalation exposure study in rats was considered for use for the inhalation PDE for vanadium. In this study, carcinogenic effects were observed to the lowest dose tested, 0.5 mg/m^3 vanadium pentoxide (Ress *et al.* 2003). Vanadium pentoxide is a caustic agent and is not considered to be present in drug products. Therefore, the inhalation PDE for vanadium was derived from the oral PDE by division by a factor of 100 (as described in Section 3.1).

PDE = 120/100 = 1.2 µg/day.

REFERENCES

ATSDR. Toxicological profile for vanadium. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2012.

IARC. Arsenic, metals, fibres, and dusts: a review of human carcinogens. Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer, World Health Organization, Lyon. 2012;100C.

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Appendix 4: Illustrative Example – Calculation Options for Converting PDEs to Concentrations

Examples for Converting PDEs into Permitted Elemental Impurity Concentrations

Option 1: Permitted common concentration limits of elemental impurities across drug product component materials for products with daily intakes of not more than 10 grams.

For this example, consider a solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1). Because this drug product does not exceed a maximum daily intake of 10 grams, the concentrations in Table A.2.2 may be used. As Option 1 has a common permitted concentration, each of the 9 components can be used at any level in the formulation. The drug substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of the risk assessment. The maximum daily intake of each elemental impurity in the drug product is given in Table A.4.2 assuming that each elemental impurity is present at the concentration given in Table A.2.2. The maximum potential daily intake of an elemental impurity is determined using the actual drug product daily intake and the concentration limit for the elemental impurity in Table A.2.2 (concentration multiplied by the actual daily intake of the drug product of 2.5 grams). The maximum daily intake given for each elemental impurity is not a summation of values found in the individual columns.

This calculation demonstrates that no elemental impurities exceed their PDEs. Thus if these concentrations in each component are not exceeded, the drug product is assured to meet the PDEs for each identified elemental impurity.

Table A.4.1: Maximum Daily Intake of Components of the Drug Product

Component	Daily Intake, g
Drug Substance	0.200
MCC	1.100
Lactose	0.450
Ca Phosphate	0.350
Crospovidone	0.265
Mg Stearate	0.035
HPMC	0.060
Titanium Dioxide	0.025
Iron Oxide	0.015
Drug Product	2.500

Table A.4.2: Permitted Concentrations from Table A.2.2 (assuming uniform concentrations and 10 grams daily intake)

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	4	10	12	60
MCC	0.5	1.5	0.5	4	10	12	60
Lactose	0.5	1.5	0.5	4	10	12	60
Ca Phosphate	0.5	1.5	0.5	4	10	12	60
Crospovidone	0.5	1.5	0.5	4	10	12	60
Mg Stearate	0.5	1.5	0.5	4	10	12	60
HPMC	0.5	1.5	0.5	4	10	12	60
Titanium Dioxide	0.5	1.5	0.5	4	10	12	60
Iron Oxide	0.5	1.5	0.5	4	10	12	60
Maximum Daily intake, µg	**1.25**	**3.75**	**1.25**	**10**	**25**	**30**	**150**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

Option 2a: Permitted common concentration limits across drug product component materials for a product with a specified daily intake:

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1) used in Option 1. As Option 2a has a common permitted concentration, each of the 9 components can be used at any level in the formulation. The drug substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of the risk assessment. The concentration of each elemental impurity identified in the risk assessment can be calculated using the PDEs in Table A.2.1 and equation 1.

The maximum potential daily intake of an elemental impurity is determined using the actual drug product daily intake and the concentration limit for the elemental impurity in Table A.4.3 (concentration multiplied by the actual daily intake of the drug product of 2.5 grams). The maximum daily intake given for each elemental impurity is not a summation of values found in the individual columns.

This calculation also demonstrates that no elemental impurities exceed their PDEs. Thus if these concentrations in each component are not exceeded, the drug product is assured to meet the PDEs for each identified elemental impurity.

The factor of 4 increase in Option 2a for permitted concentration seen when comparing Option 1 and Option 2a concentration limits is due to the use of 10 grams and 2.5 grams respectively as daily intake of the drug product.

Table A.4.3: Calculation of Maximum Permitted Concentrations Assuming Uniform Concentrations in a Product with a Specified Daily Intake:

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	2	6	2	16	40	48	240
MCC	2	6	2	16	40	48	240
Lactose	2	6	2	16	40	48	240
Ca Phosphate	2	6	2	16	40	48	240
Crospovidone	2	6	2	16	40	48	240
Mg Stearate	2	6	2	16	40	48	240
HPMC	2	6	2	16	40	48	240
Titanium Dioxide	2	6	2	16	40	48	240
Iron Oxide	2	6	2	16	40	48	240
Maximum Daily intake, µg	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

Option 2b: Permitted concentration limits of elemental impurities across drug product component materials for a product with a specified daily intake:

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients, see Table A.4.1) used in Option 1 and 2a. The drug substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of the risk assessment. To use Option 2b, the applicant must use the composition of the drug product and have additional knowledge regarding the content of each elemental impurity in the components. The applicant has generated the following data on elemental impurities in the components of the drug product:

Table A.4.4: Measured Concentrations of Elemental Impurities (µg/g) in the Components

Component	Measured Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	ND	0.5	ND	ND	20	ND	50
MCC	0.1	0.1	0.1	0.1	*	ND	ND
Lactose	0.1	0.1	0.1	0.1	*	ND	ND
Ca Phosphate	1	1	1	1	*	10	5
Crospovidone	0.1	0.1	0.1	0.1	*	ND	ND
Mg Stearate	0.5	0.5	0.5	0.5	*	ND	0.5
HPMC	0.1	0.1	0.1	0.1	*	ND	ND
Titanium Dioxide	20	1	1	1	*	1	ND
Iron Oxide	10	10	10	10	*	2000	50

ND = Below the detection limit

* = The risk assessment identified that Pd was not a potential elemental impurity; a quantitative result was not obtained.

The applicant also knows the maximum daily intake of the drug product is 2.5 grams and determines the maximum daily intake for each component as shown in Table A.4.5.

Based on the observed levels (see Table A.4.4), the applicant evaluated the potential maximum permitted concentrations of each elemental impurity in the components. The concentrations selected (see Table A.4.5) were set at levels that would ensure the PDE is met if the maximum permitted concentration was reached for each component. The maximum daily intake in Table A.4.5 is the summation of the values obtained by multiplying the actual weight of the component by the maximum permitted concentration for each elemental impurity across all components.

Table A.4.5: Maximum Permitted Concentrations of Elemental Impurities in the Components

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	**	5	**	**	500	**	2000
MCC	0.5	5	1	10	*	**	**
Lactose	0.5	5	1	10	*	**	**
Ca Phosphate	5	5	5	40	*	125	475
Crospovidone	0.5	5	1	10	*	**	**
Mg Stearate	5	10	5	100	*	**	50
HPMC	2.5	5	1	10	*	**	**
Titanium Dioxide	40	20	10	25	*	50	**
Iron Oxide	20	100	50	200	*	5000	2000
Maximum Daily intake, µg	**4.3**	**14.5**	**4.8**	**39.9**	**100**	**120**	**598**
PDE, µg/day	**5.0**	**15**	**5.0**	**40**	**100**	**120**	**600**

* The risk assessment identified that Pd was not a potential elemental impurity; a quantitative result was not obtained.

** Quantitative results demonstrated less than the limit of detection.

Option 3: Finished Product Analysis

For this example, consider the same solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients) used in Option 1, 2a and 2b. The drug substance synthesis uses Pd and Ni catalysts, and the applicant is also concerned about Pb, As, Cd, Hg, and V on the basis of the risk assessment. The maximum concentration of each elemental impurity in the drug product may be calculated using the daily intake of drug product and the PDE of the elemental impurity using equation 1. The total mass of each elemental impurity should be not more than the PDE.

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{2.5(g / day)}$$

Table A.4.6: Calculation of Concentrations for the Finished Product

		Maximum Permitted Concentration (µg/g)						
	Daily Intake (g)	Pb	As	Cd	Hg	Pd	V	Ni
Drug Product	2.5	2	6	2	16	40	40	800
Maximum Daily Intake (µg)		5	15	5	40	100	120	600

Illustrative Example – Elemental Impurities Assessment

The following example is intended as illustration of an elemental impurities risk assessment. This example is intended for illustrative purposes and not as the only way to document the assessment. There are many different ways to approach the risk assessment process and its documentation.

This example relies on the oral drug product described in Appendix 4. Consider a solid oral drug product with a maximum daily intake of 2.5 grams, containing 9 components (1 drug substance and 8 excipients). The drug substance synthesis uses Pd and Ni catalysts.

The applicant conducts the risk assessment starting with the identification of potential elemental impurities following the process described in Section 5. Since the applicant had limited historical data for the excipients used in the drug product, the applicant determined that the Class 1 elementals (As, Cd, Hg, Pb) would be taken through the evaluation phase. The table below shows a summary of the findings of the identification stage of the assessment.

Table A.4.7: Identification of Potential Elemental Impurities

	Potential Elemental Impurities			
Component	Intentionally added	Potential elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents	Potential elemental impurities from manufacturing equipment	Potential elemental impurities from container closure systems
Drug Substance	Pd, Ni	As	Ni	None
MCC	None	As, Cd, Hg, Pb		None
Lactose	None	As, Cd, Hg, Pb		None
Ca Phosphate	None	As, Cd, Hg, Pb	V, Ni	None
Crospovidone	None	As, Cd, Hg, Pb		None
Mg stearate	None	As, Cd, Hg, Pb	Ni	None
HPMC	None	As, Cd, Hg, Pb		None
Titanium Dioxide	None	As, Cd, Hg, Pb	V	None
Iron Oxide	None	As, Cd, Hg, Pb	V, Ni	None

The identification phase of the assessment identified seven potential elemental impurities requiring additional evaluation. Three of the identified elemental impurities were found in multiple components. The applicant continued the risk assessment collecting information from the vendor and available development data. The summary of the results can be found in Table A.4.3. The application of the individual component data to the evaluation in the assessment process is shown below in Table A.4.8.

Table A.4.8: Elemental Impurity Assessment – Evaluation of Daily Contribution to the Total Mass of Elemental Impurities in the Drug Product

Component	Daily intake, g	Measured Concentration (µg/g)							Total Daily Mass of Elemental Impurity, µg						
		Pb	As	Cd	Hg	Pd	V	Ni	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.2	ND	0.5	ND	ND	20	ND	50	0	0.1	0	0	4	0	10
MCC	1.1	0.1	0.1	0.1	0.1	*	ND	ND	0.11	0.11	0.11	0.11	0	0	0
Lactose	0.45	0.1	0.1	0.1	0.1	*	ND	ND	0.045	0.045	0.045	0.045	0	0	0
Ca Phosphate	0.35	1	1	1	1	*	10	5	0.35	0.35	0.35	0.35	0	3.5	1.75
Crospovidone	0.265	0.1	0.1	0.1	0.1	*	ND	ND	0.0265	0.0265	0.0265	0.0265	0	0	0
Mg stearate	0.035	0.5	0.5	0.5	0.5	*	ND	0.5	0.0175	0.0175	0.0175	0.0175	0	0	0.0175
HPMC	0.06	0.1	0.1	0.1	0.1	*	ND	ND	0.006	0.006	0.006	0.006	0	0	0
Titanium Dioxide	0.025	20	1	1	1	*	1	ND	0.5	0.025	0.025	0.025	0	0.025	0
Iron Oxide	0.015	10	10	10	10	*	400	50	0.15	0.15	0.15	0.15	0	6	0.75
							total daily mass, µg/day		1.2	0.8	0.7	0.7	4.0	9.5	12.5

Table A.4.9: Assessment Example – Data Entry Descriptions

Column 1: Review the components of drug product for any elements intentionally added in the production (the primary source is the drug substance). For those used, record the elements for further consideration in the assessment.

Column 2: Identify any potential elements or impurities that are associated with excipients or reagents used in the preparation of the drug product. Record the source(s) for further consideration in the assessment.

Column 3: Identify any elemental impurities known or expected to be leached from the manufacturing equipment. Record the specific elemental impurities for further consideration in the assessment.

Column 4: Identify any elemental impurities known or expected to be leached from the container closure system. Record the specific elemental impurities for further consideration in the assessment.

Column 5: Calculate the total contribution of the potential elemental impurity by summing the contributions across the components of the drug product.

Column 6: Assess the variability of the elemental impurity level(s) in the components
Column 7: Enter the control threshold of each potential elemental impurity identified. If the variability is known and it is within acceptable limits, the control threshold (30% of the PDE) for each elemental impurity can be applied.
Column 8: Describe action taken – none if the value in column 6 is less than or equal to the control threshold (column 7). Define control element if material variability is high or control threshold is exceeded.

	1	2	3	4	5	6	7	8
Element	**Intentionally added (if used in the process)**	**Elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents**	**Manufacturing equipment**	**Leached from container closure systems**	**Total elemental impurity contribution µg/day**	**Acceptable variability of elemental impurity contribution**	**Control threshold**	**Action**
As	No	Observed contaminant in all excipients and drug substance	No	No	0.8	yes	4.5	no further controls required
Cd	No	Observed contaminant in all excipients	No	No	0.7	yes	1.5	no further controls required
Hg	No	Observed contaminant in all excipients	No	No	0.7	yes	12	no further controls required
Pb	No	Observed contaminant in all excipients	No	No	1.2	yes	1.5	no further controls required
Pd	API catalyst	No	No	No	4.0	yes	30	no further controls required
Ni	API catalyst	Observed in 3 excipients	No	No	12.5	yes	180	no further controls required
V	No	Observed in 3 excipients	No	No	9.5	yes	36	no further controls required