Purpose of Case Study 1B: The following case study provides one example of a summary of an elemental impurities risk assessment for a hypothetical product, Greatstuff tablets, manufactured by a hypothetical applicant, NewCo. The case study describes one approach to summarizing a risk assessment for elemental impurities in a drug product, and is only intended as an example to help illustrate the risk assessment process describe in ICH Q3D: Guideline for Elemental Impurities. Case Study 1 includes two documents, Case Study 1A, which provides one example of the execution and documentation of an elemental impurity risk assessment that will be maintained in the NewCo Pharmaceutical Quality System, and Case Study 1B, which provides one example of a summary of the elemental impurity risk assessment that will be submitted in a new drug application. Taken together, these two case studies provide examples to illustrate how the complete product risk assessment can be performed, and how it can be summarized to effectively communicate the outcome to regulatory authorities in new drug applications. These case studies are examples intended to illustrate one approach to implementing the recommendations described in Q3D. They are **not** intended as templates for performing these tasks and other approaches to performing and documenting the risk assessment may also be acceptable. The data used in this example are fictitious, and are **not** intended to illustrate expectations for elemental impurity levels typically found in drug substances and excipients or contributions to elemental impurity levels in drug products from utilities, processing equipment or container/closure systems.

It should be noted that this specific risk assessment and recommended controls are a small part of the overall product risk assessment and drug product control strategy. Further, the risk associated with direct toxicity from elemental impurities is expected to be low in most drug products.

The specific examples chosen are for illustrative purposes only. For example, in the assessment that follows, the level of Pd determined is below the control threshold and would not trigger additional controls. Documentation submitted to regulatory authorities would be limited to a brief justification. However, it was included in this case study as it was part of the penultimate manufacturing step and used to illustrate the point of how potential elemental impurities may find their way into the drug product and provide a typical example of the type of justification that could be used.

Case Study 1B: Solid Oral drug product
Proposed Dossier Submission Summary Document v 1.3
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Elemental impurity product risk assessment - overall summary

This document provides a summary of the product risk assessment prepared in response to the expectations set forth in ICH Q3D: Elemental Impurities. The risk assessment for Greatstuff film-coated tablets (50 and 100 mg) was conducted following the components based approach. The risk assessment involved a review of all potential sources of elemental impurities in the components and associated processes used in the production of Greatstuff tablets. Measurable levels of elemental impurities that could be incorporated into the drug product were identified or predicted in three components. These components included: the drug substance (Pd), talc (Pb) and calcium hydrogen phosphate dihydrate (Pb). Based on the controls established for the drug substance, no additional action is proposed to control Pd in the drug product. In order to ensure that the level of Pb is maintained at or below the PDE for Pb in the drug product, incoming material specification limits for Pb were established for talc and calcium dihydrogen phosphate dihydrate. The controls in place for the drug substance and the added Pb limits for talc and calcium hydrogen phosphate dihydrate ensure that elemental impurities in the drug product will be maintained at or below the respective PDEs. The following sections describe the risk assessment process that was followed, the assumptions used during the assessment, the evaluation of the assessment results and the conclusions of the assessment.

Elemental impurity product risk assessment – component process followed

The elemental impurity risk assessment for Greatstuff tablets was executed using a component assessment approach. The maximum daily dose of Greatstuff is 100 mg (2 x 50mg tablets or 1 x 100 mg tablet) (see section 3.2.P.1 for the formulation description and composition). During the assessment, the component assessments were based on dosing two (2) 50 mg tablets per day. This approach took into account the maximum daily intake of each component (relative to using a single 100 mg tablet). The recommended considerations described in Table 5-1 in ICH Q3D: Elemental Impurities were used in the risk assessment for Greatstuff drug product and its components. In this case, the assessment included Class 1 and 2A elements and any elements that were intentionally added. Elements other than Class 1 and 2A that were not intentionally added do not require consideration in the risk assessment for oral drug products. Using these assumptions and recommendations, along with data generated internally and vendor supplied information, the starting point for the risk assessment was identified and is described in Table 1.

Table 1: Initial evaluation of the elements to be considered in the risk assessment

Element	Class	Intentionally added?	Consider in risk assessment	Justification
Cd	1	no	Yes	Included in risk assessment for all components
Pb	1	no	Yes	Included in risk assessment for all components; vendor provided information on observed levels in talc and calcium dihydrogen dihydrate
As	1	no	Yes	Included in risk assessment for all components
Hg	1	no	Yes	Included in risk assessment for all components
Co	2A	no	Yes	Included in risk assessment for all components
V	2A	no	Yes	Included in risk assessment for all components
Ni	2A	no	Yes	Included in risk assessment for all components
Tl	2B	no	No	Not intentionally added in any component.
Au	2B	no	No	Not intentionally added in any component.
Pd	2B	Yes	Yes	Pd is used in the penultimate step of the drug substance process
Ir	2B	no	No	Not intentionally added in any component.
Os	2B	no	No	Not intentionally added in any component.
Rh	2B	yes	Yes	Rh is used to prepare one of the starting materials.
Ru	2B	no	No	Not intentionally added in any component.
Se	2B	no	No	Not intentionally added in any component.
Ag	2B	no	No	Not intentionally added in any component.
Pt	2B	no	No	Not intentionally added in any component.
Li	3	no	No	Not intentionally added in any component.
Sb	3	no	No	Not intentionally added in any component.
Ba	3	No	No	Not intentionally added in any component.
Mo	3	No	No	Not intentionally added in any component.
Cu	3	No	No	Not intentionally added in any component.
Sn	3	No	No	Not intentionally added in any component.
Cr	3	No	No	Not intentionally added in any component.

Eight elementals identified in Table 1 (As, Cd, Hg, Pb, Co, V, Ni, Pd) were the only potential elemental impurities evaluated during the component assessments for the Greatstuff tablets. Seven of these (Class 1 and 2A) are recommended for inclusion by Q3D for oral dosage forms, and Pd is included because it is intentionally added during drug substance synthesis. No other elements (Class 2 B and Class 3) are intentionally added to the excipients or drug substance, and these are not considered further in the risk assessment. The results of the assessment of the potential elemental impurity contributions are summarized in Table 2.

Table 2: Evaluation of Potential Contributors of Elemental Impurities to the Drug Product

Potential source of elemental impurities	Information evaluated	Further consideration in the risk assessment?
Drug substance	Pd is used in the penultimate step of the synthesis. Batch data and commercial scale data review. Class 1 or 2A elements are not intentionally added and are not found as impurities in the drug substance.	Consider potential impact of Pd levels in the drug substance on the drug product.
Excipients	Information supplied from vendors confirms no elements (Class 1, 2 or3) are intentionally added. Vendor certificates of analysis indicate negligible levels of the following Class 1 and 2A elements: Cd, As, Hg, Co, Ni and V. Vendor certificates of analysis for talc and calcium hydrogen phosphate dihydrate indicate the presence of Pb.	Consider the potential impact of Pb levels in the 2 identified excipients on the Pb levels in the drug product. The currently observed levels can be found in Table 1. Elemental impurity data are generated using a validated method where the Limits of quantitation are below the control threshold, based on the ICH Q3D: Table A2-2 concentrations.
Water	Compendial grade water used throughout associated processes.	Use of compendial water ensures minimization of potential elemental impurities from water used during processing.
Container closure system	HDPE bottles are primary contact surface. Solid oral tablets have limited mechanism for transfer of elemental impurity (if present) from bottle surface to tablets. Jenke et.al. publication[1]	No further consideration in the risk assessment – negligible contribution of any potential elemental impurities to the drug product.
Manufacturing equipment (drug substance and drug product equipment)	Internal quality program for monitoring of equipment used in drug substance synthesis shows absence of Co, Ni, V in drug substance batches. The Greatstuff drug product process is less likely to degrade the equipment contact surfaces (compared with the drug substance) ensuring negligible contribution from the drug product processing equipment.	No further consideration in the risk assessment. Documentation and data generated confirm negligible contribution of elemental impurities from the manufacturing equipment. Elemental impurity data are generated using a validated method where the Limits of quantitation are below the control threshold based on the ICH Q3D: Table A2-2 concentrations.

[1] Jenke, D. et.al., "A Compilation of Metals and Trace Elements Extracted from Materials Relevant to Pharmaceutical Applications Such as Packaging Systems and Devices", PDA J. Pharm. Sci. Technol., 67(4):354-75, 2013

Components that contribute elemental impurities to the drug product

The data and information obtained in the product assessment identified only Pb and Pd as elemental impurities of concern. Analytical measurements were performed on 3 components to support the risk assessment during drug product development. The results are given in Table 3.

Table 3: Summary of elemental impurity (EI) data for potential components of concern – Greatstuff 50 and 100 mg tablets. Data from analysis using a validated ICP-MS method.

Component	No. of lots[1]	Element	Mean µg/g	Std. Dev.[2] µg/g	Min µg/g	Max µg/g	Upper 95% Confidence Limit µg/g
Drug substance	3	Pd	36	3	33	39	41
Talc	3	Pb	4	5	0.3	10	12
Calcium hydrogen phosphate dihydrate	3	Pb	4	4	1	8	10

[1] Three commercial lots
[2] Std. Dev. = standard deviation

Drug substance

Based on the review of the development data as well as the data obtained from three primary stability/Phase 3 clinical lots manufactured at the proposed commercial manufacturing site (data can be found in section 3.2.S.4.4), the drug substance contains low level residual Pd. In the evolution of the drug substance process, improvements were made to ensure that the level of Pd was reduced to a level that would not be of concern in the drug product. Using ICH Q3D Option 2b, the maximum permitted concentration of Pd in the Greatstuff drug substance is 1000 µg/g. The observed Pd level in the Greatstuff drug substance, using the proposed commercial process (also used in pivotal Phase 3 clinical trials) at the proposed commercial scale, is shown in Table 3. The upper 95% confidence limit of the measured concentration is 41 µg/g. The maximum daily dose of Greatstuff is 100 mg/day; the resultant Pd contribution in the drug product would be expected to be no greater than 4.1 µg. This level of Pd in the drug product is significantly below the PDE (100 µg/day) as well as the control threshold for Pd (30 µg/day). As a result, a specific limit was not defined for Pd in the drug substance and no additional controls were added to the process since the existing process controls demonstrated adequate control of the Pd levels.

A catalyst based on Rh is used to synthesize one of the starting materials (SMs) and is used in the penultimate step of the SM synthesis. Based on development data for this SM, its specification includes a 100 µg/g (ppm) limit for Rh. Clearance studies that evaluated the removal of residual Rh during the execution of the drug substance synthetic route showed that there was a 100 fold reduction of Rh levels after the second of five reaction steps in the final drug substance synthesis. If this level (1 µg/g) was carried over into the drug product, it would represent 0.1 µg/day Rh in the drug product at that maximum daily dose of Greatstuff tablets. Since this level is below the control threshold, no

additional controls or monitoring of Rh will be included in the drug substance (or drug product). The other two starting materials used to prepare Greatstuff drug substance do not utilize catalysts in their synthesis and have no associated elemental impurities. No other reagents or materials used in the drug substance synthesis will intentionally add elemental impurities.

Excipients (calcium hydrogen phosphate dihydrate and talc)

The product risk assessment identified talc and calcium hydrogen phosphate dihydrate as excipients that have measurable levels of Pb present that will be carried into the drug product. Observed levels are displayed in Table 3. The variability in the analytical results for talc and calcium hydrogen phosphate dihydrate result in upper 95% confidence levels of 12 and 10 μg/g, respectively. These results indicate that, without additional controls it cannot be ensured that the Pb level in Greatstuff will not exceed the PDE with 95% confidence. To address this concern, an incoming material specification limit for Pb for each of the excipients has been established. The limit for Talc is proposed to be NMT 5 μg/g and that for calcium hydrogen phosphate dihydrate is proposed to be NMT 4 μg/g. The suitability of the proposed limits to control for Pb at or below the ICH Q3D PDE limits is shown in Table 4. Calculation of total Pb in Greatstuff at the proposed upper specification limits for talc and calcium hydrogen phosphate dehydrate demonstrates that adequate controls have been established to ensure that the level of Pb in the drug product will not exceed the PDE. NewCo has SOPs in place to qualify excipient vendors to ensure that these specifications can be met or to require lot selection with appropriate GMP controls if purification of mined excipients is insufficient to reduce levels of Pb to the specification limit.

Table 4: Calculated Concentrations of Pb in Greatstuff using Established Specification Limits and Q3D Option 2B.

Component	Mass of Component in a 50 mg tablet g	Mass of Component in a daily dose (2 tablets) [1] g	Pb specification limit µg/g	Total lead contribution to the drug product µg
Greatstuff drug substance	0.05	0.1	-	-
Microcrystalline cellulose (PH102) (MCC)	0.09	0.18	-	-
Calcium hydrogen phosphate dihydrate	0.46	0.92	4	3.68
Magnesium stearate	0.003	0.006	-	-
Croscarmellose sodium	0.3	0.6	-	-
Talc	0.057	0.114	5	0.57
Hydroxypropylmethylcellulose	0.04	0.08	-	-
Total tablet weight, g	1	2		
Maximum lead per daily dose when excipient levels are at the specification limits, µg/daily dose				4.25
Lead (Pb) PDE, µg/day				5

[1]Two 50 mg tablets were selected for use in the assessment as they represent the maximum amount of excipient dosed per day (relative to one 100 mg tablet).

Components that do not contribute elemental impurities to the drug product

Manufacturing equipment

The manufacturing equipment used in both the drug substance and drug product manufacturing processes is composed of stainless steel. Based on the results of the elemental impurity monitoring program implemented for the drug substances produced during development and the results of the testing of representative lots of Greatstuff drug substance at the commercial scale, where no elemental impurities were detected it can be concluded that the manufacturing equipment does not contribute any elemental impurities to the drug product. The results of the assessment of the elemental impurity profile for the elemental impurity contribution from manufacturing equipment can be used as a surrogate for the drug product equipment train. The drug product equipment train is also composed of stainless steel and the drug product process is executed under much less aggressive conditions than the drug substance process. Therefore, the Greatstuff drug product process is less likely to degrade the equipment contact surfaces compared with the drug substance process.

Container closure system

The Greatstuff drug substance is a solid material that is packaged in polyethylene bags. The Greatstuff drug product is a solid oral dosage form packaged in HDPE bottles. There is no potential for a solid-solid

transfer of any elemental impurities (if any elemental impurities are present in the packaging components) to the drug substance and product. Based on the limited opportunity for interaction between the component and the drug substance and product, there is no potential for contribution of elemental impurities from the container closure system to the drug product.

Excipients (MCC, magnesium stearate, croscarmellose sodium, HPMC)

Based on qualified vendor-supplied information, the remaining excipients used in the Greatstuff formulation (MCC, magnesium stearate, croscarmellose sodium, and HPMC) present no risk of inclusion of elemental impurities into the drug product.

Water

Water is used to prepare the film coating solution. In order to ensure compliance with ICH Q3D requirements and to minimize the potential for inclusion of elemental impurities in the drug product, compendial grade (USP, Ph. Eur., JP) purified water is used in the preparation of the film coating solution. The use of purified water ensures that the water reduces the potential to introduce elemental impurities to the drug product. For example, the USP standard for Purified Water is water that has a measured conductivity of 2.1 µS/cm; which translates to approximately 1.36 mg/L dissolved solids. Assuming 10 L of coating solution per batch and also assuming that all of the dissolved solids present were related to Cd (selected since it has the lowest PDE of all EIs of potential concern), a total of approximately 14 mg of Cd would be introduced into the entire batch of tablets. The batch size for Greatstuff tablets ranges from 100,000-300,000 tablets, so the calculated 14 mg of Cd would translate to approximately 0.1 µg/tablet, below the control threshold for Cd. As a result, the potential for inclusion of elemental impurities from purified water will not be considered further in the product assessment.

Controls proposed based on elemental impurity assessment

The elemental impurity risk assessment of Greatstuff tablets identified three components with the potential to introduce elemental impurities into the drug product. The three components are the drug substance, talc and calcium hydrogen phosphate dihydrate. The actions taken for each to ensure that the respective PDEs are not exceeded in the drug product are summarized below.

The drug substance process was designed and validated to ensure that the level of Pd incorporated into the Greatstuff drug product was not greater than 4.1 µg/day. This level is significantly less than the control threshold for Pd (30 µg/day). As a result, because the validated process ensures that the Pd level is consistently maintained at or below the control threshold, no additional controls for Pd are included in the drug substance process and a Pd specification limit is not proposed.

The presence of Pb in both talc and calcium hydrogen phosphate dihydrate will result in the inclusion of Pb in the final product. Based on the levels observed during monitoring of these two excipients, it was determined that limits should be included in the incoming material specifications for each excipient to ensure control. The limits proposed for the talc and calcium hydrogen phosphate dihydrate will be proposed as part of the overall drug product control strategy. With the additional incoming material controls implemented (4 µg/g for calcium hydrogen phosphate dihydrate and 5 µg/g for talc), the total lead level in the drug product would be limited to NMT 4.25 µg/day, below the PDE of Pb (5 µg/day).

Conclusions

The risk assessment identified two elemental impurities that could be observed in three of the components of Greatstuff tablets. The three components and the potential elemental impurity in each are: Greatstuff drug substance (Pd), Talc (Pb), and calcium hydrogen phosphate dehydrate (Pb). The

controls intrinsic to the validated drug substance process ensure that the limit of Pd in the drug product will be maintained below the control threshold. An elemental impurity specification and associated limit are not proposed for Greatstuff tablets; however, to ensure that Pb levels are maintained at or below the PDE for Pb, a specification and limit for lead in both talc and calcium hydrogen phosphate dehydrate were established. These incoming material controls ensure that the Pb level will be maintained at or below the Pb PDE in Greatstuff tablets.

In addition, the product assessment identified that control of Rh in one of the starting materials, SM1, ensured that the Rh levels would be below the control threshold in the drug product.

The risk assessment will be updated (as necessary), if the process is modified or suppliers of the drug product components are changed and that any subsequent changes to the control strategy will be reported to the Health Authorities within the current regulatory framework.

