

Case study 1A: Solid Oral Drug Product

Purpose of Case Study 1A: The following case study provides one example of a summary of an elemental impurities risk assessment for a hypothetical new drug product, Greatstuff tablets, manufactured by a hypothetical applicant, NewCo. This example assumes that this is the first dossier to be assembled for the drug product. 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 necessarily trigger significant controls, so discussion in 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.

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Case Study 1A: Solid Oral drug product

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Table of Contents

Introduction	33
Key Components of the Quality Target Product Profile (QTPP).....	33
Drug product elemental impurity risk assessment	44
Drug substance.....	55
Manufacturing equipment.....	77
Container Closure Systems	77
Excipients	88
Water	1212
Conclusion of product risk assessment	1212
Components that contribute elemental impurities to the drug product	1212
Drug substance	1212
Excipients (calcium hydrogen phosphate dihydrate and talc)	1212
Components that do not contribute elemental impurities to the drug product	1313
Manufacturing equipment	1313
Container closure system.....	1313
Excipients (MCC, magnesium stearate, croscarmellose sodium, HPMC, water)	1313
Control strategy development.....	1313
Testing recommendations	1313
References	1414

List of Figures and Tables

Table 1: Greatstuff 50 mg Tablets – formulation composition	33
Table 2: Greatstuff 100 mg Tablets – formulation composition	44
Figure 1: Greatstuff tablets process overview	44
Figure 2: Greatstuff Tablets – potential sources of elemental impurities	55
Table 3: Greatstuff drug substance elemental impurity profile	66
Table 4: Elemental Impurity Monitoring Studies – Selected Excipients	1010
Table 7: Elemental impurity assessment and controls for Greatstuff tablets	1414

Introduction

This document represents the product risk assessment prepared in response to the recommendations set forth in ICH Q3D: Elemental Impurities. This specific assessment has been prepared for the Greatstuff drug product (50 and 100 mg tablets). The information used and samples tested were procured from the development site and planned commercial drug substance and drug product manufacturing sites listed below:

- Drug substance development: Anywhere, Kansas
- Drug product development: Anywhere, Kansas
- Drug substance and drug product manufacturing: Humacao, Puerto Rico

Key Components of the Quality Target Product Profile (QTPP)

Greatstuff tablets are a new product for the treatment of hypertension. The drug product is formulated as a film coated tablet, provided in two strengths, 50 and 100 mg, and is intended to be dosed once per day. The maximum daily dose of Greatstuff is 100 mg. The formulation composition of the drug products are shown in Tables 1 and 2. The drug product is packaged in individual blister packages (PVC-Aclar) and HDPE bottles.

Table 1: Greatstuff 50 mg Tablets – formulation composition

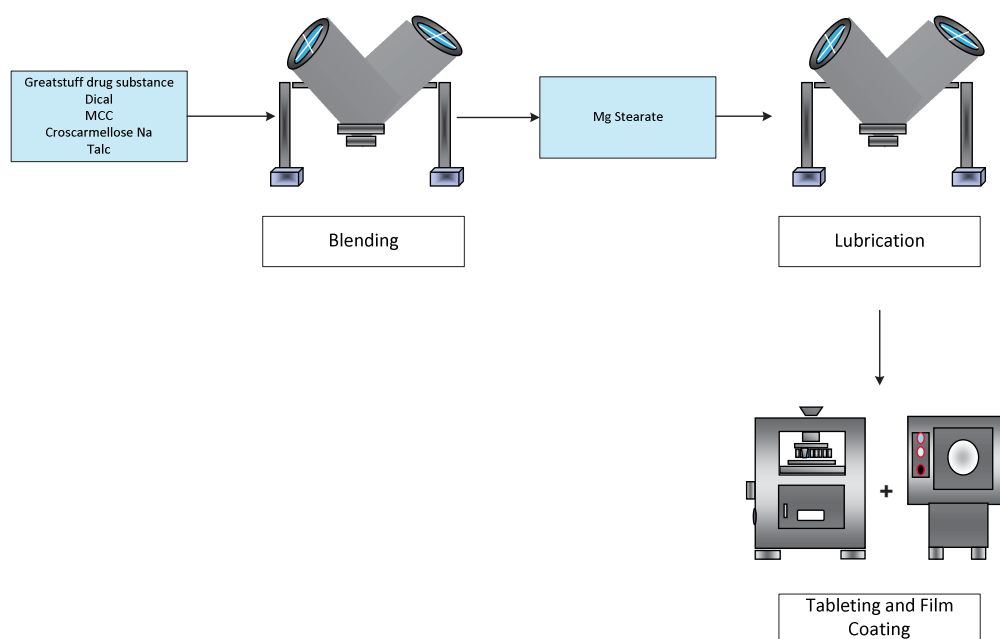
Component	Weight per tablet, mg
Greatstuff drug substance	50
Microcrystalline cellulose (PH102) (MCC)	90
Calcium hydrogen phosphate dihydrate	460
Magnesium stearate	3
Croscarmellose sodium	300
Talc	57
Tablet core weight, mg	960
Tablet coating	
Purified Water	q.s.
Hydroxypropylmethylcellulose	40
Total tablet weight, mg	1000

Table 2: Greatstuff 100 mg Tablets – formulation composition

Component	Weight per tablet, mg
Greatstuff drug substance	100
Microcrystalline cellulose (PH102) (MCC)	90
Calcium hydrogen phosphate dihydrate	410
Magnesium stearate	3
Croscarmellose sodium	300
Talc	57
Tablet core weight, mg	960
Tablet coating	
Purified water	q.s.
Hydroxypropylmethylcellulose (HPMC)	40
Total tablet weight, mg	1000

The Greatstuff tablets are produced using a dry blend, direct compression process. The primary product contact surfaces are stainless steel. The tablets are coated with an aqueous based immediate release film coating. The general process diagram is shown below.

Figure 1: Greatstuff tablets process overview

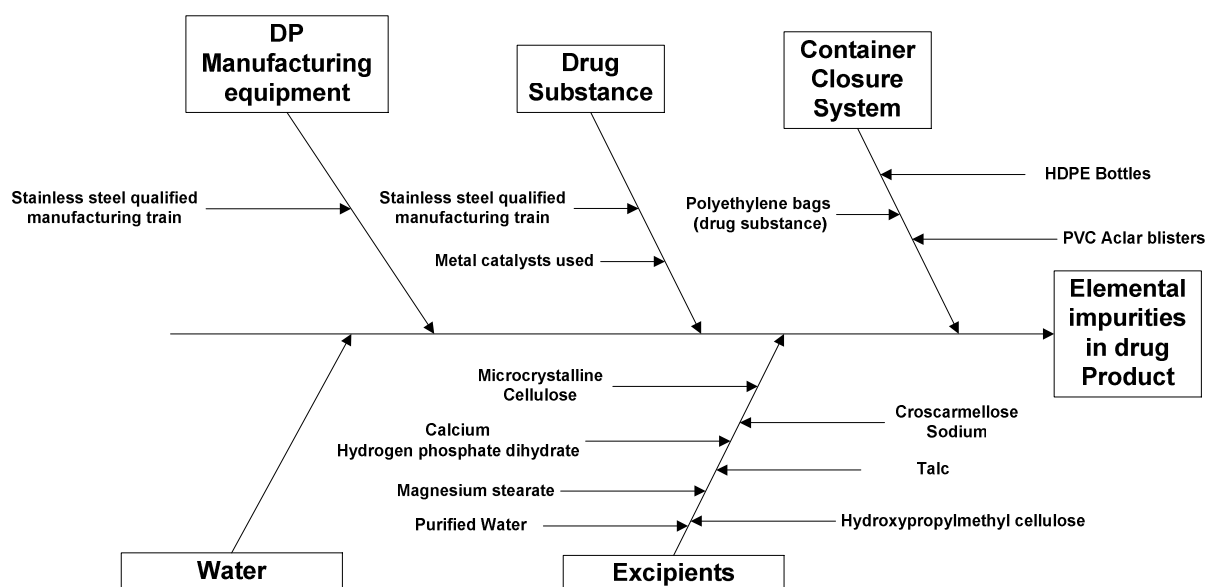


Drug product elemental impurity risk assessment

The following elemental impurities risk assessment is an integral part of the overall drug product control strategy. The elemental impurity risk assessment of Greatstuff drug product was initiated following the

component approach as described in ICH Q3D: Elemental Impurities section 5.1. The following diagram shows the primary areas for consideration during the risk assessment.

Figure 2: Greatstuff Tablets – potential sources of elemental impurities



Of the five main categories of potential sources of elemental impurities (drug substance, excipients, manufacturing equipment, water and the container closure system), the components with the greatest potential for transfer of elemental impurities to the drug product are the drug substance and the excipients used in the drug product.

Drug substance

The synthesis of Greatstuff drug substance involves five (5) steps combining the three starting materials (SMs). Each of the SMs has an associated specification controlling the quality of the material. The preparation of SM1 uses a Rh catalyst in the penultimate step. Based on the 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. 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. Since this is below the control threshold no additional monitoring of Rh will be performed in the drug substance (or drug product). The remaining 2 SMs utilize no catalysts in their synthesis.

The final drug substance is assembled in five chemical reactions; the next to the last step (penultimate step) employs a palladium on carbon (Pd/C) catalyst. During development, the synthetic scheme

Case study 1A: Solid Oral Drug Product

underwent three separate process changes from the route used to prepare the preliminary clinical drug substance used in Phase 1 clinical trials. The final changes in the process (included in process IV, the proposed commercial process) included optimization of the isolation and washing sequences for the isolated intermediate that resulted from the catalytic conversion using Pd catalyst in the penultimate step. Clearance studies and monitoring of the final three commercial scale batches confirmed that Pd levels were maintained reproducibly below 40 µg/g in the drug substance. If Pd was present at this level in the drug substance, the level would translate to a maximum of 4 µg/day (40 µg/g x 0.1 g maximum daily dose of Greatstuff). This level is below the control threshold for Pd (PDE = 100 µg/day; Control Threshold = 30 µg/day).

As part of the screening program of the drug substance throughout development, elemental impurity monitoring data were collected for each drug substance lot manufactured. The validated method monitored for the presence of levels of the following potential elemental impurities: Rh, Pd (intentionally added catalysts), As, Cd, Hg, Pb, (Class 1) V, Ni, and Co (Class 2A). The results of these analyses are provided in Table 3 (reference 4).

Table 3: Greatstuff drug substance elemental impurity profile

Lot #	Process	Scale, kg	Observed levels, µg/g ¹								
			Rh	Pd	As	Cd	Hg	Pb	V	Ni	Co
ABC-10-01	I	5	1.5	154	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-10-02	I	5	2.1	148	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-10-03	II	25	1.9	89	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-11-01	II	25	1.5	85	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-11-02	III	25	1.1	36	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-11-03	III	50	1.2	42	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-11-04	III	50	1.0	47	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-12-01	IV ²	200	<1.0	35	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-12-02	IV ²	200	<1.0	39	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0
ABC-12-03	IV ²	200	<1.0	33	<0.50	<0.50	<0.50	<0.30	<1.0	<1.0	<1.0

¹ Maximum values observed. Values reported as < x.xx were less than the limit of quantitation

² Proposed commercial route

Manufacturing equipment

While manufacturing equipment presents a potential source of elemental impurities during the production of the Greatstuff drug substance and drug product, the current quality system of NewCo has been designed to minimize and control any potential contribution from the manufacturing equipment. The typical manufacturing equipment used to produce the drug substance consists exclusively of stainless steel (various grades) and a few specialty glass lined stainless steel vessels. The quality procedures that ensure control of elemental impurities include:

- Equipment design and installation qualification
- Reaction compatibility studies for the Greatstuff process
- Equipment cleaning verification and validation
- Visual inspection/line clearance procedures
- Routine maintenance inspections and schedules

As part of the development process, an elemental impurities monitoring procedure has been a part of the drug substance release testing program. This monitoring program was established to collect data to support the conclusion that the manufacturing equipment does not contribute to the overall impurity profile of the drug substance. A general validated method, employing ICP-OES and ICP-MS was established to monitor the following potential elemental impurities: class 1 elements (As, Cd, Hg, and Pb) and potential elemental impurities arising from stainless steel (Ni, , Co, and V). During development of Greatstuff tablets, the elemental impurity profile of the Greatstuff drug substance lots manufactured were analyzed using the referenced method and monitoring program. Table 3 shows that there are no contributions of elemental impurities from the manufacturing equipment used in the Greatstuff drug substance process.

The manufacturing process used to produce the Greatstuff drug product uses significantly less aggressive unit operations than experienced in the Greatstuff drug substance process. Given the absence of elemental impurity contributions from the drug substance manufacturing equipment, considering that the processes and reagents used in the drug product process are milder and less corrosive or reactive, it can also be concluded that the contribution of elemental impurities from the drug product manufacturing equipment is consistently lower than the contribution from the drug substance manufacturing equipment. Based on the results of the drug substance screening studies, no further consideration of contributions of elemental impurities from the manufacturing equipment is required.

Container Closure Systems

The Greatstuff tablets are provided in two packages, a PVC-Aclar blister and an HDPE bottle. The drug substance is packaged in polyethylene bags. Due to the nature of the drug product and drug substance (solids), there are no significant mechanisms that would permit transfer of elemental impurities from the container closure system to the drug product. Therefore, contribution of elemental impurities to the drug product from the container closure system will not be considered further.

Excipients

In order to assess the potential for the inclusion of elemental impurities from the excipients used in the Greatstuff tablets, three approaches were explored:

- A literature survey was conducted to identify the potential elemental impurities that could be found in any of the excipients used.
- The vendors and manufacturers of the excipients were contacted to obtain information and data on their knowledge of potential elemental impurities in the excipients provided. This information was collected in the form of a standard questionnaire.
- Generation of potential elemental impurity data for excipients for which the literature or vendor information was limited.

The survey results, including available data and vendor certification statements are documented in technical report TR-2014-017 (reference 5). This report was developed in order to provide a single source of common information and results, where available, that can be shared across NewCo products which use the same excipients supplied by the same vendors and manufacturers.

This assessment indicated for Greatstuff DP that Pb and Cd were potential impurities in talc and calcium hydrogen phosphate dihydrate. A review of the information provided by the vendors for the other excipients confirmed that no other elemental impurities were identified as potential concerns. Evaluation of the information provided and data obtained for the remaining excipients, microcrystalline cellulose, magnesium stearate, hydroxypropylmethyl cellulose and croscarmellose sodium, confirmed that no catalysts or intentionally added elements were used in each of their manufacturing processes. As a result, the remainder of the excipient assessment focused on talc and calcium hydrogen phosphate dihydrate.

Compendial grades of talc and calcium hydrogen phosphate dihydrate are used in the Greatstuff drug product. The compendial monograph specifies limits for both Pb and As (but not Cd). The compendia do not list a mercury limit and during the component assessment, it was confirmed that Hg and related mercury compounds were not used in any of the materials. The compendial limits were used to estimate an elemental impurity level in the drug product (based on the limit multiplied by the daily dose of the excipient). When this value was calculated for As and Pb in calcium hydrogen phosphate dihydrate, the calculation projects that the compendial limits would permit approximately <4.6 µg/day arsenic (PDE = 15 µg/day) and 18.4 µg/day lead (PDE = 5 µg/day). By using compendial grade calcium hydrogen phosphate dihydrate, the level of As is projected to be below the control threshold (4.5 µg/day). However, the calculated amount of Pb that would be permitted by using compendial grade material is projected to exceed the PDE. As a result, additional evaluation of calcium hydrogen phosphate dihydrate was conducted.

Applying the same analysis to talc using the compendial limits, the calculations predicted that the level of As in the drug product from the talc contribution would be <0.57 µg/g which is about 11% of the PDE and is below the control threshold. The calculation indicates that no further action is needed to evaluate

Case study 1A: Solid Oral Drug Product

228 As in talc; however, there is no compendial limit for Pb and Cd in talc. Therefore additional evaluation of
229 talc was required as well.

230 The preliminary assessment identified potential elemental impurity risks for calcium hydrogen
231 phosphate dihydrate and talc. To address these risks, additional testing was performed to establish the
232 range of observed levels of Cd and Pb (as well as other elements included in the method employed) in
233 these two excipients. Samples from three different lots of each excipient were provided by the supplier
234 and were tested using validated methods. The results of the analyses of each excipient are summarized
235 in Tables 4.

Table 4: Elemental Impurity Monitoring Studies – Selected Excipients

Components	No. of Lots	Method	Observed level, ppm (µg/g)												
			As	Cd				Hg	Pb				V	Ni	Co
				Min	Max	Mean	SD		Min	Max	Mean	SD			
Talc	3	ICP-MS	<0.05	0.24	0.50	0.33	0.15	<0.50	0.30	9.7	3.5	5.4	<1.0	<1.0	<1.0
Calcium hydrogen phosphate dihydrate	3	ICP-MS	<0.05	0.06	0.20	0.12	0.07	<0.50	1.1	8.1	3.8	3.8	<1.0	<1.0	<1.0

Reference-5 TR-2014-017: Elemental impurities in Selected Excipients

The variability in the analytical results of Pb 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 6. Calculation of total Pb in Greatstuff at the proposed upper specification limits for talc and calcium hydrogen phosphate dihydrate 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 acceptance criteria.

Table 5: Summary of Pb (lead) data for potential components of concern – Greatstuff 50 and 100 mg tablets

Component	No. of lots ¹	Element	Mean µg/g	St. Dev. ² µg/g	Min µg/g	Max µg/g	Upper 95% Confidence Limit µg/g
Talc	3	Pb	4	5	0.3	10	12
Calcium hydrogen phosphate dihydrate	3	Pb	4	4	1	8	10

Table 6: 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).

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 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. Typically the purified water used in Greatstuff manufacturing has a measured conductivity of 2.1 $\mu\text{S}/\text{cm}$ or purer; 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 13.6 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 projected 13.6 mg of Cd would translate to 0.136 $\mu\text{g}/\text{tablet}$, 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.

Conclusion of product risk assessment

Components that contribute elemental impurities to the drug product

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 at the proposed commercial scale, it is clear that the drug substance has some residual Pd associated with the process. In the evolution of the drug substance process, it is clear that improvements were made to ensure that the level of Pd was reduced to an appropriate limit in the drug product (i.e. ensures that the Pd level is maintained at or less than the PDE). The observed Pd level in the Greatstuff drug substance using the proposed commercial process (also used in pivotal Phase 3 clinical trials) does not exceed 40 $\mu\text{g}/\text{g}$. However, since the planned 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 μg . This level of Pd in the drug product will result in an exposure that is significantly below the PDE (100 $\mu\text{g}/\text{day}$) as well as the control threshold for Pd (30 $\mu\text{g}/\text{day}$). As a result, it is not necessary to include a Pd limit in the specification for the Greatstuff drug substance.

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 and potentially Cd present that will be carried into the drug product. At the current observed levels, Cd levels were shown to be below the control threshold for Cd; therefore, no additional controls were required. However, controls will need to be established to ensure that the Pb level in the drug product is maintained at or below the PDE. The control strategy section defines the additional controls recommended for implementation (incoming material specification of Pb in both talc and calcium hydrogen phosphate dihydrate).

Components that do not contribute elemental impurities to the drug product

Manufacturing equipment

Based on the results of the elemental impurity monitoring program implemented for the drug substances produced during development and the results of the specific testing of representative lots of Greatstuff drug substance, it can be concluded that the manufacturing equipment does not contribute any elemental impurities to the drug substance. Because the manufacturing process used to produce Greatstuff tablets are significantly less aggressive than the drug substance process, the drug product process would also not contribute elemental impurities to the drug product.

Container closure system

The Greatstuff drug product is a solid oral dosage form packaged in plastic packaging. There is no potential for a solid-solid transfer of any elemental impurities (if any are present in the packaging components) to the drug product. Therefore, it is clear that there is no contribution of elemental impurities from the container closure system to the drug product.

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

The remaining excipients used in the Greatstuff formulation, MCC, magnesium stearate, croscarmellose sodium, HPMC, and water) present no risk of inclusion of elemental impurities into the drug product.

Control strategy development

During the risk assessment three potential sources of elemental impurities were identified, Greatstuff drug substance, talc and calcium hydrogen phosphate dihydrate. Of these three, only talc and calcium hydrogen phosphate dihydrate require additional controls to ensure that the Pb level is maintained at or below the PDE. Pb in the drug substance was found to be adequately controlled in the proposed commercial process. In order to ensure that the Pb level is controlled, an incoming material limit for Pb has been added to the Talc and calcium hydrogen phosphate dihydrate specification. The Pb limit added to the talc specification is 5 µg/g. The Pb limit added to the calcium hydrogen phosphate dihydrate specification is 4 µg/g. These limits ensure that the lead level in the drug product will not exceed the PDE. The calculation of the Pb levels in the drug product is summarized in Table 6.

Testing recommendations

The conclusion of the risk assessment identified only two areas for routine testing; testing for Pb in both talc and calcium hydrogen phosphate dihydrate. All other potential sources of elemental impurities are maintained in a state of control through quality system procedures and processes or process controls included in the drug substance and drug product processes.

No elemental impurity testing of the drug product is proposed at this time since all of the elemental impurity controls have been established up stream of the final drug product.

Conclusion

Based on ICH Q3D, a risk assessment was performed to determine the probability of inclusion of elemental impurities in the Greatstuff tablets and to establish the appropriate controls to ensure the quality of the drug product. The assessment examined the sources of elemental impurities and identified several components that had the potential to transfer elemental impurities into the drug product. The risks and the actions taken are summarized in Table 7 below.

Table 7: Elemental impurity assessment and controls for Greatstuff tablets

Potential risks	Action/mitigation
Elemental impurities from drug substance	No action required; process controls sufficient
Elemental impurities from equipment	No action required, Quality system controls sufficient
Elemental impurities from water	No action required, negligible risk
Elemental impurities from container closure systems	No action required, negligible risk
Excipients	Pb limit applied to talc (5 µg/g) and Calcium hydrogen phosphate dihydrate (4 µg/g) incoming material specification

The risk assessment for elemental impurities in Greatstuff tablets was completed and with the addition of 2 component specifications to the drug product control strategy. The design and implementation of the inherent controls in the manufacturing quality system processes ensure that the levels of identified elemental impurities are maintained at or below their respective PDEs. If the process is modified or suppliers of the drug product components are changed, the impact of the changes will be evaluated and this risk assessment will be updated as necessary.

References

- 1) ICH Q3D: Elemental Impurities
- 2) Elemental impurity monitoring method, ATM-2012-130v2.1
- 3) Elemental impurities in development compounds, NewCo technical report TR-2014-015
- 4) Assessment of the potential of elemental impurities from commonly used pharmaceutical excipients, NewCo technical report TR-2014-017.
- 5) Boyes, W. (2002). [Instrumentation Reference Book](#) (3rd. ed.).