Case study 2: Parenteral Drug Product

Purpose of Case Study 2: The following case study provides one example of a summary of an elemental impurities risk assessment for a hypothetical new drug product, Greatdrug sterile solution, 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 2 provides one example of the execution and documentation of an elemental impurity risk assessment that will be maintained in the NewCo Pharmaceutical Quality System. This case study is examples intended to illustrate one approach to implementing the recommendations described in Q3D. They are **not** intended as a template 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. The specific examples chosen are for illustrative purposes only.

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.

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Introduction

This document provides a summary of the product risk assessment prepared in response to the requirements set forth in ICH Q3D: Elemental Impurities. This specific assessment has been prepared for the Greatdrug drug product.

Key Components of the Quality Target Product Profile (QTPP)

Greatdrug is a new therapy intended to treat Type I diabetes. It represents a novel class of insulin mimetic compounds and is formulated as a ready to use (RTU) liquid formulation provided as a 100 mg/mL sterile solution. Typical dosing is up to 3x per day (typically 0.2 – 0.4 mL per injection) with a recommended maximum daily dose of 100 mg (1 mL total volume per day). The formulation composition of the drug product is shown in Table 1. The drug product is packaged in individual septum cap Type 1 glass vials (10 and 20 mL fill volumes).

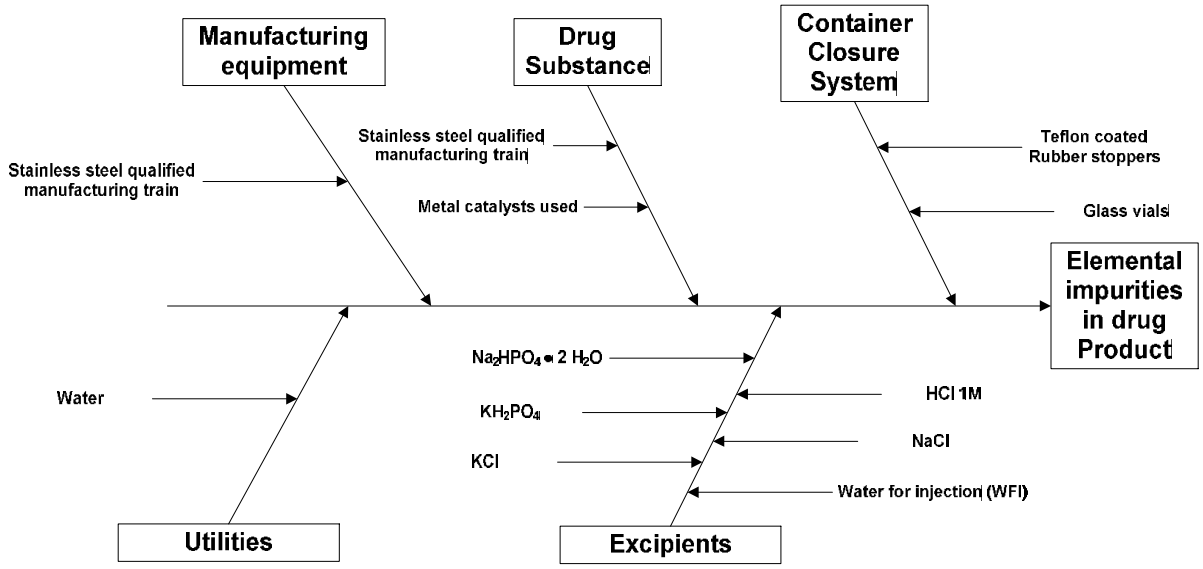
Table 1: Greatdrug RTU liquid – quantitative formulation composition

Component	Formulation composition (per 1000 L)	Formulation composition per unit dose (1 mL)
Greatdrug drug substance	100 kg	100 mg
Sodium chloride	8 kg	8 mg
Potassium chloride	0.2 kg	0. 2 mg
Sodium dihydrogen phosphate dihydrate	1.44 kg	1.44 mg
Dipotassium phosphate	0.24 kg	0.24 mg
Hydrochloric acid (1 M)	1 L	0.001 mL
Water for Injection	980 L	0.98 mL

Drug product elemental impurity risk assessment

The following elemental impurities risk assessment is an integral part of the overall drug product control strategy. Figure 1 shows a summary of the potential sources of elemental impurities that will be considered in the risk assessment.

Figure 1: Potential Sources of Elemental Impurities in Greatdrug RTU Liquid



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 several of the excipients used in the drug product. In considering whether to approach the risk assessment from a drug product perspective or through an assessment of the components, a decision was made to conduct the assessment based on an evaluation of the components of the drug product. This approach was selected for several reasons:

- The manufacturing processes and equipment used do not have a a high risk for inclusion of elemental impurity.
- All of the excipients selected are common excipients of compendial/pharmacopeial grade procured from qualified vendors and are well characterized in the literature and through the internal qualification program.
- The assessment of the components provides an improved ability to control any identified elemental impurities upstream of the drug product

Each category and the potential to contribute elemental impurities to the drug product will be discussed in the following sections.

Drug substance

The synthesis of Greatdrug drug substance involves five (5) steps combining 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. Purging 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 penultimate step of which employs a Pd/C catalyst. During development, the synthetic scheme underwent three separate process changes from the enabling 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. Purging studies and monitoring of the final four commercial scale batches confirmed that Pd levels were maintained reproducibly below 3 µg/g in the drug substance.

As part of the release testing 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, As, Cd, Hg, Pb, Cr, V, Ni and Co. The results of these analyses are provided in Table 2 (reference 4). It should be noted that the screening data collected provided monitoring for the catalysts used in the process but also for potential inclusion of the class 1 elements (As, Cd, Hg, and Pb) and for potential elemental impurities related to the manufacturing equipment (primarily comprised of stainless steel).

Table 2*: Greatdrug drug substance elemental impurity profile*

Lot number	Process	Scale, kg	Observed levels, ug/g									
			Rh	Pd	As	Cd	Hg	Pb	Cr	V	Ni	Co
ABC-10-01	I	5	nd[2]	15.4	nd	nd	nd	nd	nd	nd	nd	nd
ABC-10-02	I	5	nd	14.8	nd	nd	nd	nd	nd	nd	nd	nd
ABC-10-03	II	25	nd	8.9	nd	nd	nd	nd	nd	nd	nd	nd
ABC-10-04	II	25	nd	8.5	nd	nd	nd	nd	nd	nd	nd	nd
ABC-11-01	III	25	nd	3.6	nd	nd	nd	nd	nd	nd	nd	nd
ABC-11-02	III	50	nd	4.2	nd	nd	nd	nd	nd	nd	nd	nd
ABC-11-03	III	50	nd	4.7	nd	nd	nd	nd	nd	nd	nd	nd
ABC-12-01	IV[1]	200	nd	2.5	nd	nd	nd	nd	nd	nd	nd	nd
ABC-12-02	IV[1]	200	nd	2.4	nd	nd	nd	nd	nd	nd	nd	nd
ABC-12-03	IV[1]	200	nd	2.3	nd	nd	nd	nd	nd	nd	nd	nd
ABC-12-04	IV[1]	200	nd	2.2	nd	nd	nd	nd	nd	nd	nd	nd

[1] Proposed commercial route

[2] nd = not detected below the method limit of quantitation of 0.000001 μg/g for all elemental impurities.

Manufacturing equipment

While manufacturing equipment presents a potential source of elemental impurities during the production of the Greatdrug 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) suitable for parenteral products and a few specialty glass lined stainless steel vessels. The quality system procedures that ensure control of elemental impurities include:

- Equipment design and installation qualification
- Reaction compatibility studies for the Greatdrug 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 for several years. 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: As, Cd, Hg, Pb, Ni, Cr, Co, and V. The synthetic routes cover a broad range of reaction chemistries including acidic, alkaline, high temperature, and aggressive reaction conditions (e.g. high pressure/high temperature/high reactivity reagents). The results of these analyses confirmed the conclusion of the overall manufacturing equipment assessment that there were no substantial contributions of the targeted elements in the drug substances examined. The data for the Greatdrug drug substance lots analyzed in this monitoring program (Table 2) also confirm the assumption that there is no contribution of elemental impurities from the manufacturing equipment used in the drug substance process.

Given that the drug substance manufacturing equipment does not significantly contribute to the overall elemental impurities profile, it can be concluded that the contribution from the drug product manufacturing equipment would also not have a significant contribution. The drug product manufacturing process is conducted at ambient temperatures using buffered aqueous solutions. These conditions are significantly less aggressive unit operations than experienced in the drug substance process. As a result, the probability of inclusion of elemental impurities from the drug product manufacturing equipment is less than that observed from the drug substance. Therefore, no additional consideration is required with respect to potential contributions of elemental impurities from the drug product manufacturing equipment.

Container Closure Systems

The drug substance is a solid that is packaged in polyethylene bags prior to final formulation. There are no significant mechanisms that would permit transfer of elemental impurities from the polyethylene bag

to the drug substance. Therefore, contribution of elemental impurities to the drug product from the drug substance container closure system will not be considered further.

The Greatdrug RTU Liquid is provided in two different sizes of Type 1 glass vials designed to contain 10 and 20 mL of the drug product. The vials sourced are borosilicate glass and have been shown to provide suitable protection and stability for the drug product. The vials are sealed with a fluoropolymer bromobutyl rubber stopper which is then crimp sealed in place with an aluminum seal.

In considering the potential for the container closure system to contribute elemental impurities to the drug product, a literature review was completed as well as consultation of vendor supplied information. Recently, Jenke, *et al.*, (*PDA J Pharm Sci and Tech* **2015**, *69* 1-48), published a paper that represented a survey of the literature regarding elemental impurities in common packaging components. Summaries of the available elemental impurity data in the review article, related to the vials and stoppers used in the drug product, are provided in Tables 3 and 4.

Table 3: Measured amount of elemental impurities from Type 1 Glass (Total extraction)

Container closure component	Amount of elemental impurity in the material ppm (µg/g)					
	As	Cd	Hg	Pb		
Type 1 glass vial	0.3	0.5	<0.5	1.0		
	Cr	Ba	Cu	Sb	Co	Ni
	0.2	21	0.1	0.5	<0.1	0.1

Table 4: Measured amount of elemental impurities from Stoppers (Total extraction)

Container closure component	Amount of elemental impurity in the material ppm (µg/g)					
	As	Cd	Hg	Pb		
Bromobutyl rubber	3.0	<0.1	<0.1	1.1		
	Cr	Ba	Cu	Sb	Co	Ni
	2.6	3.6	2.3	<0.1	0.2	1.0

It should be noted that the data are obtained through the use of total extraction methods using exhaustive conditions to remove all possible elemental impurities in the components.

Tables 5 and 6 were constructed to determine if either of these components would have a substantial impact on the introduction of elemental impurities into the drug product. The calculation summarized below assumes 100% transfer of the observed level of each elemental impurity into the drug product.

The amount of additional elemental impurity that could be included in the drug product from vials and stoppers is calculated using the following equations:

$$Predicted\ elemental\ impurity\ level = (observed\ level\ of\ elemental\ impurity) \times weight\ of\ the\ component$$

$$Potential\ additional\ elemental\ impurity\ in\ the\ drug\ product = \frac{(predicted\ elemental\ impurity\ in\ the\ vial)}{total\ amount\ of\ liquid\ in\ the\ vial} \times daily\ dose$$

Table 5: Potential contribution of elemental impurities to the drug product – Type 1 glass vials

Element	Observed level, ug/g	Predicted elemental impurity level per vial in the drug product[1]	Potential additional elemental impurity contributed in each daily dose (µg)[2]	Parenteral PDE, µg/day
Co	< 0.1	<2 µg	<0.1	5
Pb	1.0	20 µg	1.0	5
Sb	0.5	10 µg	0.5	90
Cd	0.5	10 µg	0.5	2
Cu	0.1	2 µg	0.1	300
As	0.3	6 µg	0.3	15
Hg	<0.5	<10 µg	<0.5	3
Cr	0.2	4 µg	0.2	1100
Ba	21	420 µg	21	700
Ni	0.1	2 µg	0.1	20

[1] Assumes the vial weight is 20 g (representing the 20 mL vial)

[2] The total daily dose is administered in 1 mL

Table 6: Potential contribution of elemental impurities to the drug product – stoppers

Element	Observed level, ug/g	Level per vial in the drug product[1]	Potential additional elemental impurity in each daily dose (µg)[2]	Parenteral PDE, µg/day
Co	0.2	0.4 µg	<0.1	5
Pb	1.1	2.2 µg	0.1	5
Sb	<0.1	<0.2 µg	<0.1	90
Cd	<0.1	<0.2 µg	<0.1	2
Cu	2.3	4.6 µg	0.2	300
As	3.0	6 µg	0.3	15
Hg	<0.1	<0.2 µg	<0.1	3
Ba	3.6	7.2 µg	0.4	700
Cr	2.6	5.2 µg	0.3	1100
Ni	1.0	2 µg	0.1	20

[1] Assumes the stopper weight is 2 g
[2] The total daily dose is administered in 1 mL

The results of the calculations in Tables 5 and 6 show that in all cases the estimated elemental impurity levels is significantly below the control threshold. This is the case even considering that the estimate assumed total extraction of the elemental impurities from each component. Since the conditions, cited in the referenced publication, used to remove the elemental impurities from the vials and stoppers are significantly more exhaustive than the conditions to which the drug product will be exposed during manufacture, shipment and storage, the potential for elemental impurity contribution to the drug product from the container closure system is negligible and requires no additional consideration or control.

Excipients

In order to assess the potential for the inclusion of elemental impurities from the excipients used in the Greatdrug RTU Liquid(see Table 1), 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 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 key or critical excipients for which the literature or vendor information was limited.

The excipients used in the drug product have pharmacopeial requirements (USP, Ph.Eur. and/or JP monographs) with associated elemental impurity limits. During the assessment, it was confirmed that Hg. Cd. Li., Sb, and Cu (and/or related compounds) were not used in the manufacture of any of the excipients. For sodium chloride, the use of compendial grade material (< 1 µg/g As and < 5 µg/g Pb) ensures that the respective contributions are < 0.008 µg/day As and < 0.04 µg/day Pb. For potassium chloride, the use of compendial grade material (< 10 µg/g Pb) ensures that the respective contribution is < 0.002 µg/day Pb. All these contributions are less than the corresponding PDEs. The only excipient that had an elemental impurity that necessitated further analysis was sodium dihydrogen phosphate dihydrate. The current USP monograph permits arsenic (As) levels of up to 16 µg/g and in the current Ph. Eur. monograph As is limited to 2 µg/g. To determine if the compendial limits provide suitable control for Greatdrug RTU liquid, calculations were performed using the following equation.

Potential µg/day Arsenic = (USP limit, µg/g) x (wt of excipient in solution, g/mL) x (volume of solution/day)

Potential µg/day Arsenic = (Ph. Eur. limit., µg/g) x (wt of excipient in solution, g/mL) X (volume of solution/day)

Assessment for As in sodium dihydrogen phosphate dihydrate:

USP grade (16 µg/g As) x (1.44 mg Na_2HPO_4/mL) x (1 g/1000 mg) x 1 mL/day = 0.023 µg/day As

Ph. Eur grade (2 µg/g As) x (1.44 mg Na_2HPO_4/mL) x (1 g/1000 mg) x 1 mL/day = 0.003 µg/day As

The calculation of the potential level of As in sodium dihydrogen phosphate dihydrate used in the Greatdrug RTU liquid formulation indicates that the control provided by using a compendial grade excipient limits will limit the contribution of As to below the control threshold. There were no other excipients with elemental impurities of concern in the formulation based on the risk assessment and information provided by the vendors. As a result, no additional controls are necessary to ensure compliance with elemental impurity limits in the drug product.

Water

Water for injection is used in the preparation of Greatdrug RTU Liquid. The use of WFI ensures that the potential for introduction of EIs into the drug product is limited. However, this assurance of limited impact has not resulted in global acceptance of exclusion of water from risk assessments even in small volume products. In order to confirm the observed levels of elemental impurities in the WFI produced in the Greatdrug manufacturing facility, periodic testing of the water was performed using a validated elemental impurity screening method (ICP-MS, internal method 2014-143-001M) (reference-3). This method included the elements listed in Table 7 as the target analytes. The potential elemental impurities were selected as they represent the Class 1 elemental impurities and the potential elemental impurities most often found in various stainless steel alloys. The method performance and target analytes are included in Table 7.

Table 7: Method limit of quantitation (Method 2014-143-001M)

Elemental impurity	Limit of Quantitation, pg/mL
Arsenic	1.0
Cadmium	0.1
Mercury	3.0
Lead	0.3
Chromium	0.2
Molybdenum	7.0
Nickel	1.5
Vanadium	0.1

The observed elemental impurity levels in the WFI water produced in the manufacturing facility is summarized in Table 8 below. Based on the observed results, the WFI produced has sufficient controls to ensure that the level of elemental impurities will be maintained at or below the PDE for the respective elemental impurity. In order to generate additional data, the water quality will be monitored at a frequency defined by internal procedures.

Table 8: Representative Elemental Impurity screening results for WFI

	Elemental impurity level, µg/mL							
WFI sample description	As	Cd	Hg	Pb	Cr	Mo	Ni	V
Jan 2014	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
April 2014	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
July 2014	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
Oct 2014	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
Dec 2014 (Pre-plant maintenance shutdown)	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
Dec 2014 (post-plant shut down)	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
January 2015	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
April 2015	<0.001	<0.0001	<0.003	<0.0003	<0.0002	<0.007	<0.0015	<0.0001
Daily Exposure vs PDE								
Maximum observed level[1], µg/day	0.001 µg	0.0001 µg	0.003 µg	0.0003 µg	0.0002 µg	0.007 µg	0.0015 µg	0.0001 µg
PDE, µg/day	15	2	3	5	1100	1500	20	10
Control threshold, µg/day	4.5	0.6	0.9	1.5	330	450	6	3
Additional controls needed?	no	no	no	no	no	no	no	no

[1] The LOQ for each element was used to calculate a maximum level of each elemental impurity in water using the maximum daily dose (1 mL) of Greatdrug RTU.

Based on the screening results, it is clear that the WFI used to produce Greatdrug RTU liquid does not contribute to the elemental impurities in the drug product. Periodic WFI testing will be performed in alignment with internal procedures.

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 four primary stability/Phase 3 clinical lots manufactured at the proposed commercial manufacturing site it is clear that the drug substance has some residual Pd associated with the process. In the evolution of the drug substance process, improvements were made to ensure that the level of Pd was reduced to a limit that would ensure that the level of Pd in the drug product was at or below the PDE.

The observed Pd level in the Greatdrug drug substance, manufactured using the proposed commercial process (also used in pivotal Phase 3 clinical trials) approaches 3 µg/g but does not exceed 3 µg/g . Since the planned maximum daily dose of Greatdrug is 100 mg/day, the resultant Pd contribution in the drug product would be expected to less than 0.3 µg. This level of Pd in the drug product is below the parenteral PDE (10 µg/day) and below the control threshold for Pd (3 µg/day). The process has been validated and has been shown to be robust. As a result, the controls that are currently associated with the drug substance process ensure the quality of the drug product (from an elemental impurity perspective). At this time, the recommendation is not to include a Pd limit in the specification for the Greatdrug drug substance.

Excipients

The product risk assessment evaluated the current excipients, suppliers and compendial monographs to determine if the predicted and monitored levels of elemental impurities would result in inclusion in the drug product. The only excipient that demonstrated levels of any elemental impurities of concern was sodium dihydrogen phosphate dihydrate. The compendial limits for arsenic for sodium dihydrogen phosphate dihydrate are currently set at 8 µg/g (USP) and 2 µg/g (Ph Eur). If this level was observed in lots of the excipient used to produce Greatdrug RTU liquid, the contribution of arsenic to the drug product is less than 0.1% of the parenteral PDE for arsenic. With the current controls and use of compendial excipients, the elemental impurity levels in the drug product will be maintained below the PDE.

The water for injection used to in the Greatdrug RTU Liquid process has been shown to not contribute elemental impurities to the drug product. The controls in place are appropriate to ensure that any contribution of elemental impurities is controlled.

Container closure system

The Greatdrug drug product is a ready to use injectable product. The assessment of the container closure system showed that there were no contributions of elemental impurities to the drug product.

Manufacturing equipment

Based on the results of the elemental impurity monitoring program implemented for the drug substance batches produced during development and the results of the specific testing of representative lots of Greatdrug drug substance produced using the proposed commercial process, it can be concluded that the manufacturing equipment does not contribute any elemental impurities to the drug product. In addition, the periodic monitoring of the WFI used to produce the drug product demonstrates no contribution from the manufacturing equipment used to produce the WFI.

Control strategy development

During the risk assessment, three potential sources of elemental impurities were identified, Greatdrug drug substance, the container closure system and one excipient, sodium dihydrogen phosphate dihydrate. Upon further review and evaluation of the available literature, vendor information, and data,

it was determined that no additional controls are required to ensure that the Greatdrug RTU liquid complies with the limits described in ICH Q3D.

For the drug substance, Pd was identified as an elemental impurity. However, the process controls currently in place demonstrate that the Pd will be controlled to at or below the control threshold for Pd, therefore, no additional controls are proposed..

The assessment and evaluation of the container closure system (specifically the vial and stopper) identified potential low level elemental impurities arising from these two components. However, if the total amount of each elemental impurity were introduced into the drug product, all levels would remain below the control threshold for each element.

The evaluation of the excipients (sodium dihydrogen phosphate dihydrate and WFI) concluded that the use of compendial grades of the excipients used to produce Greatdrug RTU liquid provided appropriate controls to ensure product quality. No additional controls beyond the compendial monograph testing and limits are required.

Testing recommendations

The conclusion of the risk assessment identified that routine elemental impurity testing was not required. All 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, in-coming material controls and material specifications 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 drug product.

Conclusion

Based on ICH Q3D, a risk assessment was performed to determine the probability of inclusion of elemental impurities in the Greatdrug RTU liquid 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 9 below.

Table 9: Elemental impurity assessment and controls for Greatdrug RTU Liquid

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 container closure systems	No action required, negligible risk
Excipients	No action required, negligible risk
Water for injection	Negligible risk, periodic confirmatory elemental impurity screening

The risk assessment for elemental impurities in Greatdrug RTU Liquid was completed. The design and implementation of the inherent controls in the manufacturing and 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 and control strategy will be updated as necessary.

References

1) ICH Q3D: Elemental Impurities
2) Elemental impurity monitoring method, ATM-2012-130v2.1
3) Elemental impurity screening method for WFI, 2014-143-001M
4) Elemental impurities in development compounds, NewCo technical report TR-2014-015
5) Jenke DR, Stults CLM, Paskiet DM, et al., PDA J Pharm Sci Tech 2015;69:1-48
6) Potential elemental impurities from NewCo manufacturing equipment, NewCo technical report TR-2015-002
7) Current JP, Ph. Eur. and USP monographs for <glass containers for pharmaceutical use>,<rubber closures for containers for aqueous parental preparations>, <purified water>, <water for injections>, <sodium chloride>, <sodium dihydrogen phosphate dihydrate>, <dipotassium phosphate>.