Purpose of Case Study 3: The following case study provides one example of a summary of an elemental impurities risk assessment for a hypothetical product, biologic parenteral drug product "Greatproduct" manufactured at a hypothetical facility "Greatplace". Greatproduct is one of the drug products within the portfolio of the Greatplace Biologicals Parenteral Filling Site, which consists of different product families, and dosage strengths. 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 3 provides one example of the execution and documentation of an elemental impurity risk assessment that will be maintained in the Greatplace Pharmaceutical Quality System.

This case study is an example intended to illustrate one approach to implementing the recommendations described in Q3D. It is **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.

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.

Case Study 3: Parenteral recombinant protein drug product

Internal Summary Document

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1 Introduction to the Risk Based Approach

ICH Q3D recommends a science- and risk-based approach to evaluate the potential for introduction of elemental impurities into the drug product and to determine if additional controls need to be included in the overall Control Strategy to ensure product quality and safety. The overall process follows the sequence "Identify", "Evaluate", "Summarize":

Initially, no previously obtained data were available for products manufactured at "Greatsite". Therefore an initial risk assessment was performed prior to actual data collection as shown in Fig. 1. The objective behind this iterative approach was to enable an evaluation of the potential for EI contamination to the Drug Product in order to enable informed decision making regarding options for control strategies and/or analytical testing.

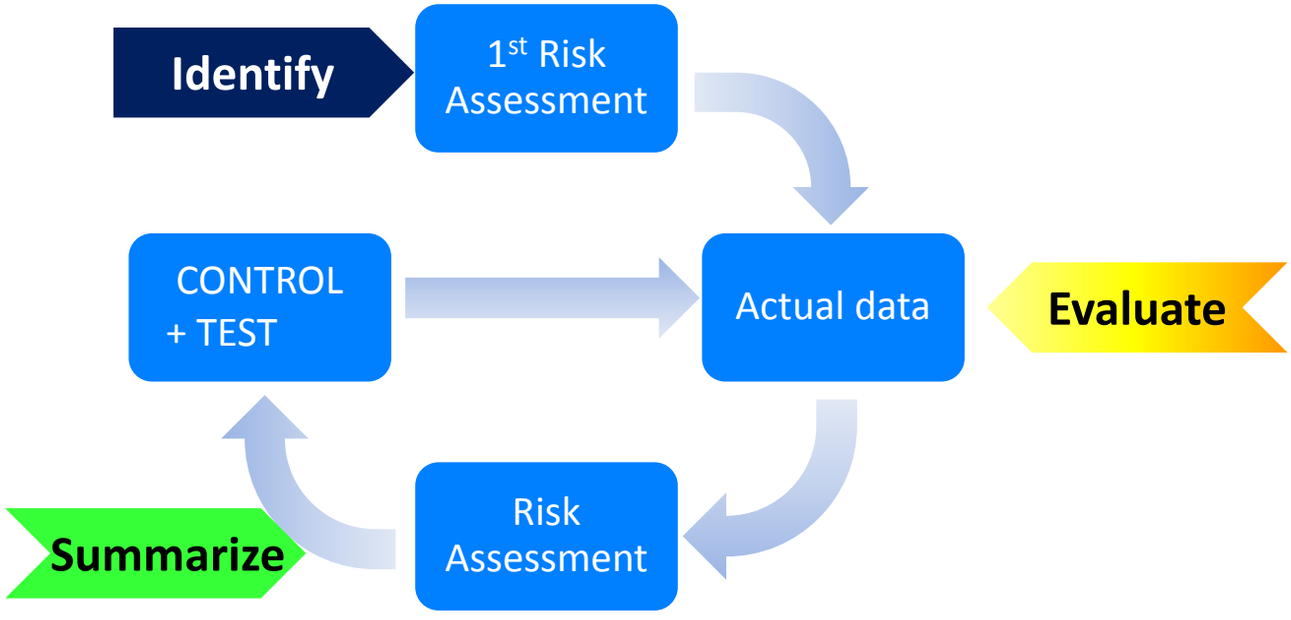


Figure 1 Iterative Risk Based Approach

1.1 Overall Process

Identify:

- "Greatproduct" was identified as the representative drug product within its platform/"technology stream" (see chapter 0).
- Identify known and potential sources of elemental impurities that may find their way into the drug product (DP) and identify which elemental impurities are likely to be present.

Evaluate:

- Initial Risk Assessment: Compare the predicted or known levels of elemental impurities (EIs) for each component with the established PDEs (adjusted for Maximum Daily Dose "MDD" of Product) and control thresholds.
- Predicted or known levels of EIs in “Greatproduct” feed into a second/subsequent Risk Assessment where actual observed levels are compared with the predicted levels and the

established PDE/ control threshold for each potential elemental impurity (See ***Figure 1*** below):

- < control threshold ⇒ no additional control measures needed
- > control threshold ⇒ e.g. establish short term and long term control and testing strategy to ensure that the elemental impurity levels do not exceed the PDE in the drug product.

Summarize (Control):

- Document the Risk Assessment and its conclusions and implement a control strategy for "Greatproduct" to limit elemental impurities in the drug product

2 Identify Potential sources of elemental impurities

ICHQ3D considers categories of potential sources of elemental impurities. Each of these potential sources may contribute elemental impurities to the drug product, individually or through any combination (see Figure 2).

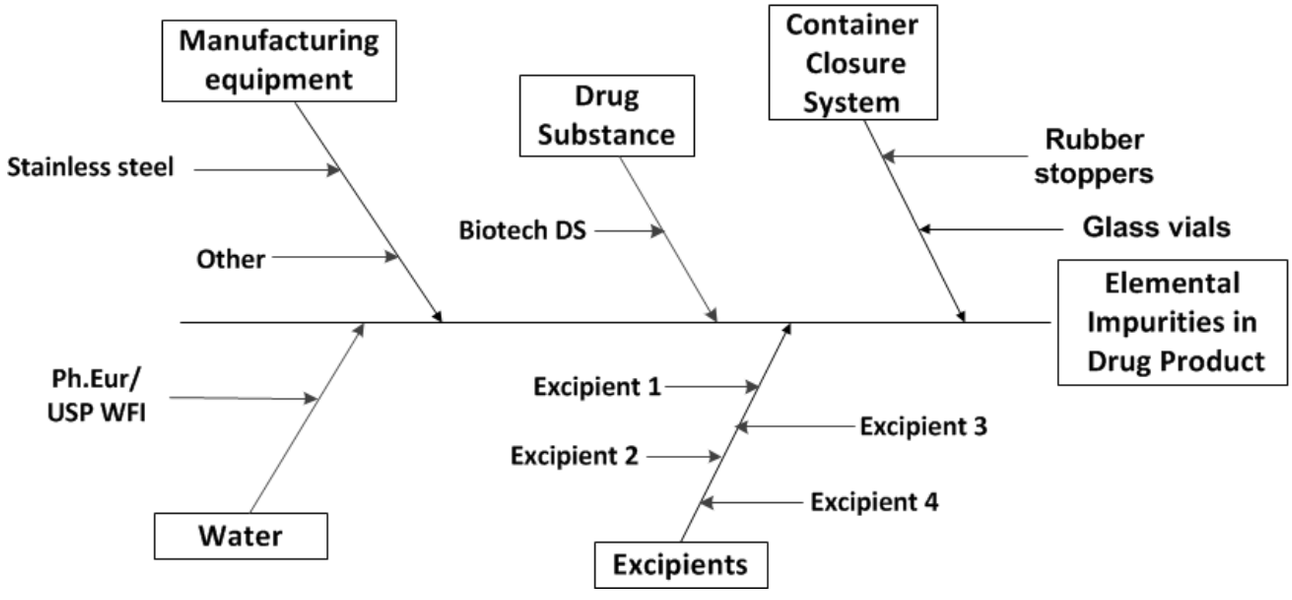


Figure 2 ICH Q3D Potential Sources of Elemental Impurities

2.1 Q3D Option 2b Component Approach

The total contribution by all potential sources of elemental impurities was calculated by the component approach (ICH Q3D Option 2b). The component approach allows for the evaluation of the potential EI contributions from individual sources (see Section 2.3), permitting increased degrees of freedom in controlling the total EIs contributed to the drug product. For example, it is possible for one component to have a higher level of individual EIs that is balanced by lower levels of another component; provided that the summation of the contributions of each individual EI from all components is below the PDE in the drug product.

2.1.1 Limits:

In order to facilitate evaluation of the analytical data which are obtained as concentrations, the PDE values of the elemental impurities in scope were converted to concentration limits while taking the MDD of "Greatproduct" into account, see Equation (1) below. The "control threshold" was defined as 30% of the respective "Concentration Limit". The concentration limits and thresholds for "Greatproduct" are listed in *Table 7*.

2.1.2 Expected Levels:

The total (expected) amount of EI in the finished Drug Product "Greatproduct" was calculated by summation over all components/materials (see equations (2) and (3)). E.g. for Excipients, summation is performed over all relevant excipients (and so on for each potential source of contamination). The expected values are listed in *Table 7*, expressed as contributions to the overall drug product concentration. E.g., a component comprising 50% of the drug product with an EI "X" present at a level of 10ppm, would contribute 5ppm to the overall EI level in the drug product. The levels per each component/material were taken from supplier certificates/questionnaires.

Note: Each "branch" / "fishbone" shown in Figure 2, i.e. "potential source of contamination" is abbreviated by "POS" in the formulas below.

2.1.3 Formulas; Component Approach:

(1) $$\boldsymbol{conc_{EI}[ppm]} = \frac{\boldsymbol{PDE}[\mu \boldsymbol{g/d}]}{\boldsymbol{MDD}[\boldsymbol{g/d}]}$$

$conc_{EI}[ppm]$ = PDE converted to concentration of EI in Drug Product, adjusted for actual MDD

(2) $$\boldsymbol{conc_{DPTotal}[ppm]} = \sum_{x} \boldsymbol{c_{POSx\ total}}$$

= (Total) Concentration of EI in DP = Sum over all potential sources (POS)

x = index number of potential source contributing to total EI in DP

(3) $$\boldsymbol{c_{POSx\ total}\ [ppm]} = \sum_{k}^{n} \boldsymbol{c_{k(POS)}} \times \boldsymbol{p_{POS}}$$

$c_{POSx\ total}$ = EI contribution from one potential source = Sum of all components of that potential source

n = number of components contributing to the POS

c_k = concentration in ppm of Elemental Impurity per component k

Note: Calculation of c_k requires adaptation of formulae as appropriate per POS (see below), i.e.

p = % of component k in DP (for Excipients), or

% of k in manufacturing equipment (equipment materials), or

% of k in container closure materials

2.2 Platform Approach: Selecting a Representative Drug Product

"Platforms"/"technology streams" were defined based on different combinations of products, dosage strengths, compounding approaches/processes, and filling line/equipment combinations. A representative Drug Product was identified and evaluated for each platform (see internal document TR-2015-01). "Greatproduct" was identified as the representative product within its specific platform/technology stream. Further the technology stream in this risk assessment was selected because it is representative of all streams at Greatsite.

*Figure 3*a and 3b illustrate the concept with regards to equipment. The equipment shown in Figure 3b for example may be grouped into 4 different "platforms"/"technology streams", as indicated by the respective arrows. While the decision whether to evaluate each platform/technology stream in separate vs grouped Risk Assessments needs to be assessed on a case-by-case basis, at "Greatsite" each platform/technology stream identified was addressed by a Risk Assessment specific to that particular platform/technology stream.

Figure 3a Compounding and Liquid filling process equipment train for the "Greatproduct" platform

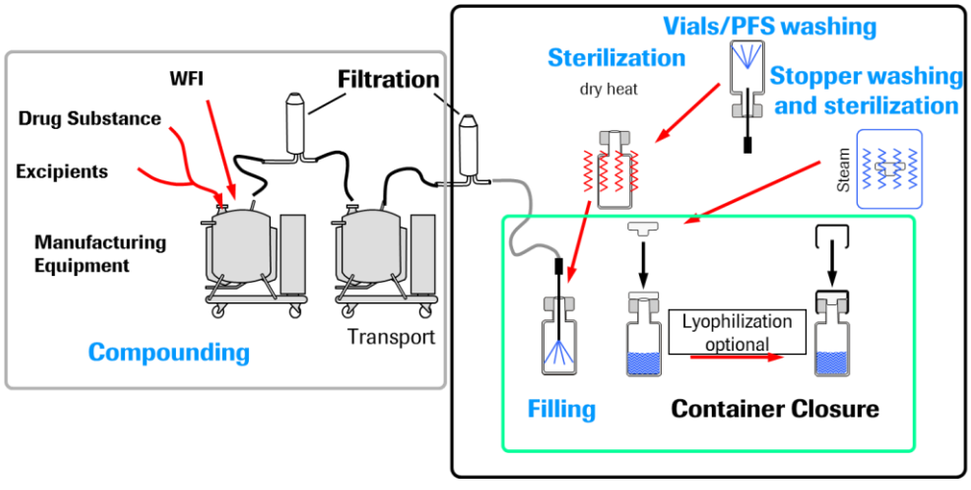
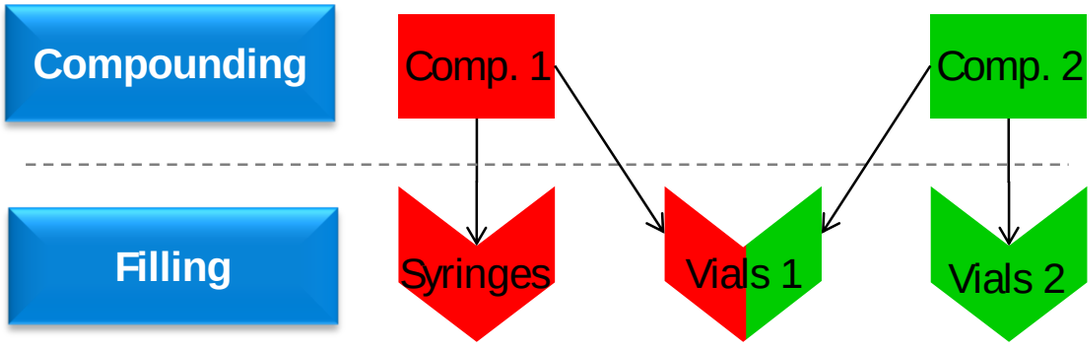


Figure 3b Schematic of equipment shared by different drug products



The product discussed in this Case Study - "Greatproduct" - was selected as representative among all products in its platform/technology stream based on the criteria described below (see following

sections) in conjunction with the component approach. Note that the compilation of factors below is not considered as being exhaustive for all/any products equipment trains. Other/additional factors may need to be considered for other production scenarios.

2.2.1 Equipment

The typical manufacturing equipment used in the drug product filling process consists mainly of stainless steel and a few other materials that are food grade certified. A range of Quality System elements are in place to ensure continued suitability of all equipment and in particular those equipment surfaces with product contact.

The platforms/technology streams at “Greatsite” were defined according to equipment used. Thus the parameter "Equipment" was –by definition- constant within each platform/technology stream (see Fig. 3).

2.2.2 pH

EI leaching from steel occurs mostly at pH < 5.0, while the extent of leaching above pH 5.0 is reduced. The process used to produce "Greatproduct" occurs at pH 4.5, lower than for any other product in the same platform/technology stream. The low pH was the major consideration in identifying "Greatproduct" as the "worst-case" product within its platform/technology stream (see *AAPS PharmSciTech, Vol. 12, No. 1, March 2011*).

2.2.3 DP fill volume to surface ratio of the container closure system

A low fill volume per cm^2 surface of the container implies a higher potential concentration level of elemental impurities in the DP solution. "Greatproduct" is formulated as a ready to use liquid in multiple use glass septum sealed vials (1.0 mL total fill). For "Greatproduct" the worst-case volume to surface ratio is with 1 mL fill volume in a 2 mL vial

2.2.4 Batch Size

All other factors being equal, a larger batch size would reduce the risk of contamination (dilution effect). For "Greatproduct", the smallest batch size is 300 kg.

2.2.5 Maximum Daily Dose (MDD)

- All other factors being equal, the product with the highest MDD would represent the "worst-case" for a given platform/technology stream. Using equation (1), converted PDEs for all products were calculated from ICH Q3D PDEs and the MDDs. The converted PDEs for "Greatproduct" are listed in *Table 7*.
- The MDD for "Greatproduct" is 2.4g/day (total product including excipients) corresponding to a maximum of 0.72mg/day drug substance. The limit concentrations for "Greatproduct" (See *Table 7*) are derived using Q3D Calculation Option 2A.

2.3 Potential contribution of EI to "Greatproduct" by Components

The formulation of "Greatproduct" is displayed in ***Table 1***. The composition/ formulation, i.e. presence/ absence of high/ low EI burden excipients of the drug product is a factor in determining the potential of EI contamination in both, product-specific assessments and worst case scenario evaluations.

"Greatproduct" is formulated as a ready to use liquid in multiple use glass septum sealed vials (1.0 mL total fill). The maximum amount of "Greatproduct" (DP) administered is 2.4g/day (1 mL injection), corresponding to a maximum daily dose (MDD) of 0.72mg/day drug substance (API).

Table 1 DP formulation of "Greatproduct"

	Excipient				API	WFI	Sum
	1	2	3	4			
Composition [w/w %]	0.060	0.013	0.797	4.921	0.030	94.18	100.0
Maximum Amount Administered [g/day]	0.0014	0.0003	0.0191	0.1181	0.0007	2.2603	2.4

2.3.1 Drug Substance

The contribution from the Drug Substance (the API is a recombinant protein) itself was considered as being of no added concern for two reasons:

- The low contribution to the overall formulation;

- The specific provision in ICH Q3D: "For biotechnology-derived products, the risks of elemental impurities being present at levels that raise safety concerns at the drug substance stage are considered low".

2.3.2 Excipients

EI contents for the excipients in scope (Excipients 3+4, see previous section/ Table 1) were taken from the suppliers' Certificates of Analysis. For these excipients, information on the EI profiles were assessed using a questionnaire submitted to the respective suppliers and - where available - the certificates of analysis of the excipients provided by the suppliers. The relevant EI for each excipient were listed on the suppliers' certificates of analysis. Only those EI identified as being relevant for any given component were included in the risk assessment. Therefore, e.g. Lithium is not included in this case study, because there was no source of Li identified.

The EI contribution for each EI and Excipient were calculated from the CoA values by equation (3), e.g. 4.921% x 1.3ppm (As) ≈ 0.064ppm etc. (See Table 2 and Table 7).

Excipients 1 and 2 were excluded from further consideration, because of their low contribution to the overall formulation:

- For example an EI present at a level of 100ppm in Excipient 1 with its MDD of 1.4mg/day (Table 2) would contribute only 0.14µg/day to the total daily intake for that EI;
- For Excipient 2 the same EI present at the same level of 100ppm EI would contribute only approximately 0.03 µg/day to the drug product;
- None of the EIs present in Excipients 1+2 were observed at levels exceeding 2ppm.

Assurance of continued suitability of the excipients is performed either via questionnaire, acceptance of suppliers' CoAs, or in-house QC-testing of incoming material, as appropriate.

Table 2 Elemental Impurities in excipients: from supplier certificates

Excipient		EI Content [ppm]		EI contribution to DP [ppm]
Name	**Formula %**			
Excipient 3	0.797	As	≤0.2	0.002
		Hg	<5	0.040
		Pb	≤0.5	0.004
Excipient 4	4.921	As	≤ 1.3	0.064
		Pb	≤ 0.5	0.025
		Ni	≤ 1	0.049

2.4 Manufacturing Equipment

Table 3 lists the materials composing the contact surfaces in the manufacturing equipment, and the calculated surface areas to which the components of the drug product may be exposed during manufacturing.

The product contacting surfaces were known from Cleaning Validation. The single use equipment parts of the equipment chain and the product-contact surface area of the microbial retention filters (PVDF) were included in the evaluation. Filling equipment is designed to resist corrosion from products/media (see also items "pH", "adjuvants" above).

Table 3 Manufacturing Equipment: Direct Product-Contact Materials

Material	**Stainless Steel[1)]**	**Silicone**	**Teflon**	**PVDF[2)]**	**Glass**	**EPDM[3)]**	**Sum**	**Total Equipment Surface Area [cm^2]**
Surface in % of total	59.32	5.57	3.63	10.91	20.25	0.31	100.0	126 537
Density of material in g/cm^3	8.00	1.16	2.16	1.78	2.33	1.23		

[1)] EN 1.4435 -- ASTM type 316L

[2)] PVDF = Polyvinylidenefluoride

[3)] EPDM = Ethylene-Propylene-Diene rubber; the contribution from EPDM is ≈ 0 due to the low surface area.

2.4.1 Hypothetical (maximum) EI Contribution from Equipment

The potential maximum contributions to the EI levels from the equipment were calculated based on an extreme case of erosion and the composition data of the equipment materials (e.g. percentage of Ni, Cr, Co in stainless steel) by the formulas below. Predicted amounts of EIs, based on this calculation, are listed in Table 7 in the column "Manufacturing Equipment". Estimates of potential leaching of Elemental Impurities from manufacturing equipment into the Drug Product were calculated from the product contacting surfaces of primary materials of construction of the equipment chain (see ***Table 3***).

To estimate an upper limit for potential EI contamination by corrosion, a hypothetical scenario, stipulating homogenous erosion over the entire surface of the equipment material(s), was considered:

- It was assumed that the most rigorous cleaning conditions used at “Greatsite”, i.e. a strongly acidic medium (HNO_3) to passivate the manufacturing equipment, would incur an erosion of approx. 10 nm of the equipment surface:
  - Reference is made to: European Patent EP 2352860 A1: O. Boehme, S. Piesslinger-Schweiger, Poligrath GmbH, "Method for the surface treatment of stainless steel”,
    Quote: "*[…] stainless steel containing more than 12% chromium (such as 1.4435 stainless steel […]) forms a protective passive layer on its surface, when it is exposed to air. Such a passive layer is generally about 10 molecular layers (~10nm/ ~0.01µm) thick*"
- It is evident that actual filling conditions are much less severe. In reality passivation has never been observed to cause erosion over the entire equipment surface. However, the intention was to thereby enable calculation of an extreme upper bound for potential EI contamination.

2.4.2 Risk Potential from Equipment

Stainless steel:

All steel equipment – as verified from available documentation - was EN 1.4435/ASTM 316L.

All other materials:

The compositions were taken from the equipment suppliers' material specification documentation. Where a concentration range was given in the documentation, all calculations were carried out with the upper range limits. Contributions of EI from equipment are summarized in ***Table 4***.

Table 4 ***Certified EI contents of relevant manufacturing equipment materials***

		Concentrations all in [ppm] = [µg/g], except Steel [%]						
Metal	**Class**	**Steel EN 1.4435 [%]**	**Silicone**	**Teflon**	**PVDF**	**Glass**	**EPDM**	**Sum**
As (Inorg.)	1		1	0.1	0.1	0.1		< 0.001
Cd	1		1	0.1	0.1	0.01		<0.001
Hg (Inorg.)	1		1	0.1	0.1	0.004		<0.001
Pb	1	0.05	1	0.1	0.1	0.3		0.001
Co	2A	0.5	1	0.1	0.1			0.010
Ni	2A	15	0.001	0.1	0.1	0.1		0.300
V	2A	0.2	1	0.1	0.1		13	0.004
Pt	2B		30	0.1	0.1			< 0.001
Ba	3		1	0.1	0.1	1.0		
Li	3							
Cu	3	0.7	1	0.1	0.1	0.3		0.014
Sb	3	0.1	1	0.1	0.1	0.005		0.002

Note: grey fields = NA

2.4.3 Example calculation for c_k [mg/kg]; k=Ni in stainless steel

The hypothetical predicted contribution (to the concentration) of the EIs to the Drug Product was calculated from the product of *Erosion x Surface Area (see Table 3) x Composition % (Table 4)* divided by the batch size.

The product contacting surfaces (Surface Areas) are known from Cleaning Validation, as are the material compositions.

Calculations were based on the data in Table 3+4 using Equation 3a - adapted from Equation 3 for convenience:

(3a) $$c_{Ni(Steel)}\left[\frac{mg}{kg}\right] \times p_{Steel} = \frac{\text{Erosion [µm]} \times \text{A}[cm^2] \times \rho\ \text{Steel}\left[\frac{\text{g}}{\text{cm3}}\right] \times\ \text{Ni\%}_{(Steel)} \times 1000[\frac{\text{mg}}{\text{g}}]}{10\ 000[\text{µm/cm}] \times \text{Batch Size [kg]} \times 100\%} \times p_{Steel}$$

Using the following numbers (see also ***Table 4***):

Erosion = Material erosion (assumed worst-case, see above) = 0.01 µm

A = Overall equipment product contact surface = 126 537 cm^2

Ni%(steel) = Max. specified Ni content in steel = 15%

p_{steel} = Fraction of steel relative to entire equipment train = 0.5932

ρ_{steel} = density of steel = 8.0 g/cm^3

Entering the numbers into the equation yields:

$$c_{Ni(Steel)} \times p_{Steel} = \frac{0.01\ \mu m \times 126\ 537 cm^2 \times 8.0 \frac{g}{cm3} \times 15\ \times 10}{10\ 000\ \times\ 300\ kg} \times 0.5932$$

$$= 0.5061\ ppm\ \times 0.5932 = 0.3002\ ppm$$ Nickel from Stainless Steel.

For e.g. Nickel: The contribution from Manufacturing Equipment according to equation 3 is:

$$\sum c_{Ni(Equipment)} = (c_{Ni(Steel)} \times p_{Steel}) + (c_{Ni(Si)} \times p_{Si}) + (c_{Ni(Tf)} \times p_{Tf}) + c_{Ni(PVDF)} \times p_{PVDF}) + c_{Ni(Glass)} \times p_{Glass}$$

Since the projected contributions of EI from any of the materials other than Stainless Steel,

c_i x p_i are negligible, finally: $\sum c_{Ni(Equipment)} = 0.3002\ ppm$

The same calculation approach was applied for each relevant EI, with the values from Tables 3 + 4. The expected contribution of EI from equipment as calculated is thus very low (< Control Threshold) despite the excessive erosion scenario assumed. Thus, equipment at Greatsite is not deemed to present significant potential of EI contamination to Greatproduct.

In practice the continued suitability of the relevant equipment is assured via existing quality systems, throughout the equipment lifecycle, e.g.:

- Qualification, inspection, and maintenance
- Visual inspection/line clearance procedures
- Equipment cleaning verification and validation
- Change Control / Lifecycle Management

2.5 Container Closure System (CCS)

In considering the potential for the container closure system to contribute elemental impurities to "Greatproduct", the following materials were in scope:

Glass vials (Hydrolytic Resistance Type I):
At normal or moderately elevated temperatures encountered during the filling processes at "Greatsite", this glass type is chemically fully resistant towards all common mineral acids, diluted alkaline solutions, most aqueous saline solutions as well as organic solutions and solvents; see. e.g. *Jenke, et al., PDA J Pharm Sci and Tech* **2015**, *69(1) p*1-48). Therefore, the glass is considered as not contributing Elemental Impurities to the Drug Product.

Neither Cobalt nor Vanadium (or their compounds) are added to Pharma Type I glass. Extractable studies conducted by the glass supplier failed to detect any Cobalt or Vanadium (<0.1ppm).

Rubber Stoppers:
Studies of rubber stopper materials published in the literature (e.g. *Jenke, et al., PDA J Pharm Sci and Tech* **2015**, *69(1) p*1-48, and *PDA J Pharma Sci and Tech* **2013** 67(4) p354-75) have shown that

rubber (stopper) closures can be considered as not contributing significant amounts of elemental impurities to the DP.

Table 5 Container Closure Systems: Direct Product Contacting Materials for "Greatproduct"

Material:	Mass [g]
GFLI glass Type I vial	3.1
Rubber stopper	0.67

Nonetheless, in order to identify any EI that might be of potential concern a hypothetical scenario of complete leaching of EI from the CCS into the DP was assumed. The individual EI contents per CCS and the expected contributions assuming complete leaching are shown in Table 6. Individual values were taken from certificates of analysis or other information provided by qualified vendors.

- No information was available for Li, and V regarding the stoppers, therefore these EI were tested in the DP.
- The expected contributions from As and Pb are close to their respective control thresholds. When these EI contributions from the CCS are added to the contributions from other sources As and Pb are above their control thresholds. (See Table 7).

Table 6 Elemental Impurities in container closure materials

Container Material	**Max. EI content as per Supplier Information**									
GFLI Glass	**As**	**Cd**	**Hg**	**Pb**	**Co**	**Ni**	**V**	**Cu**	**Li**	**Sb**
(Pharma Type I) [µg/g]	0.1	0.01	0.004	0.3	<0.001	0.1	<0.001	0.3	<0.001	<0.001
Rubber stopper [µg/g]	3.0	<0.1	<0.1	1.1	0.2	1.0	NT	2.3	NT	<0.1
Total EI in CCS [µg]	2.32	0.10	0.08	1.65	0.13	0.98	*0.03*	2.46	*0.03*	0.08
EI Contribution to DP [µg/g = ppm]	1.93	0.08	0.07	1.38	0.11	0.81	*0.03*	2.05	*0.03*	0.07
PDE Limits (µg/day)	15	2	3	5	5	20	*10*	300	250	90

Note: The elemental impurity contents were expressed as µg/g (concentration) in the suppliers/vendor information. Total EI content was calculated both in µg (absolute) for the CCS and in µg/g (concentration) for the resulting expected contribution to the DP.

2.6 Water

The water used in the manufacture of the "Greatproduct" drug product is Water for Injection (WFI).

ICH Q3D states that: "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 manufacturing process(es)".

However, for theoretical reasons, meeting the compendial WFI conductivity limits does not in itself guarantee a sufficiently low risk of inclusion of elemental impurities. To ensure that the final drug product complies with the appropriate PDEs, the following additional points have to be taken into consideration:

- The water selected as the starting material for the WFI process meets local and global requirements for drinking water. These starting water requirements limit the amounts of the most toxic of the relevant elemental impurities (Ref: *Pharmacopoeial Forum 39(1) "Elemental Impurities in Pharmaceutical Waters", 2013*).
- The system is constructed of materials that are non-additive, non-absorptive, and non-reactive so as not to impact the quality of the WFI.
- Further, existing Quality Systems elements such as routine surveillance of water quality (periodically, and after changes/ maintenance) ensure that water will not contribute elemental impurities to the drug product.
- The source water is subject to a series of steps involving pre-treatment and deionization that progressively remove impurities to achieve the required Compendial specification of WFI. The primary deionization step achieves in general at least 3 log reduction in any potential elemental impurities from the source water.
- For example the most toxic (Group 1) elements As, Cd, Hg, Pb with limits of 0.01/ 0.003/ 0.006/ 0.01 ppm (Ref: *WHO-Guidelines for Drinking-Water Quality, 3d Ed. Vol 1 Annex 4, 2008*), would not exceed 0.01ppb (µg/kg) levels after 3log reduction. In absolute terms: 1L of WFI in the formulation would not contribute more than 0.01 µg of EI to the patient, well below any level of concern.

2.7 Comparing Predicted EI Contamination with EI PDE Limits

To assess the overall contribution of potential Elemental Impurities in the "Greatproduct" Drug Product, all relevant potential sources of elemental impurities described in the section above (excipients, manufacturing equipment, container closure systems) were summed up using equation (2), i.e. for the purposes of the risk assessment, the contribution from manufacturing equipment and container closure systems were treated as additional components of the drug product. The resultant total EI concentration represents the maximum estimated concentration of all EIs in the drug product.

Note: Where contributions from container closure systems and manufacturing equipment exist, the Q3D guideline recommends adjusting the PDE by subtracting these contributions from the PDE, which is mathematically equivalent to this approach.

The calculated levels were then compared with the permitted concentrations based on the MDD for the drug product, see equation (4). The Drug Product is calculated to meet the limits contained in ICH Q3D whenever the condition in equation (4) is true:

(4) $conc[ppm] \geq conc_{DPtotal}[ppm]$

$conc[ppm]$ = PDE converted to concentration of EI in Drug Product as per equation (1), adjusted for actual MDD (i.e when MDD $\neq$ 10g/day)

$conc_{DPtotal}[ppm]$ = Predicted concentration of EI in DP calculated by Equation (2)

The detailed predicted contributions of the individual EIs are provided in *Table 7*. All concentration values are in [ppm, µg/g].

The MDD for "Greatproduct" is 2.4g/day. The limits in *Table 7* have been adjusted accordingly to reflect this. The following terms are used in *Table 7* and *Table 8* for limits:

- Limit: (Converted) PDEs taking into account the MDD of DP as displayed in equation (1)

- Control Threshold: 30% of converted PDEs as displayed in equation (1)

Table 7 Predicted vs. found amounts of EI for "Greatproduct"

EI	Class	Values in [ppm=µg/g]								
		Excipients			Manuf. Equip-ment	Container closure system[2)]	Predicted EI in DP	Control threshold	Conc. Limit[1)]	EI found in DP
		#3	#4	#3+4 Total						
As (Inorg.)	1	0.002	0.064	0.066	< 0.001	1.93	2.00	1.88	6.25	< 0.05
Cd	1				< 0.001	0.08	0.08	0.25	0.83	< 0.01
Hg (Inorg.)	1	0.04		0.04	< 0.001	0.07	0.11	0.375	1.25	< 0.05
Pb	1	0.004	0.025	0.029	0.001	1.38	1.41	0.625	2.08	< 0.01
Co	2A				0.01	0.11	0.12	0.625	2.08	< 0.01
Ni	2A		0.049	0.049	0.300	0.81	1.16	2.5	8.33	< 0.05
V	2A				0.004	0.01	0.02	1.25	4.17	< 0.01
Pt	2B				0.004		< 0.01	1.25	4.17	< 0.05
Cu	3				0.014	2.05	2.06	37.5	125	< 0.1
Li	3					0.03	0.03	31.3	104	< 0.01
Sb	3				0.002	0.07	0.07	11.3	37.5	< 0.01

1) MDD of "Greatproduct" = 2.4g/day

2) When assuming complete leaching of all EI in CCS into DP (See Table 6)

3 Evaluate

It is noteworthy that even though the worst case assumptions made for the Risk Assessment were intentionally extreme, none of the potential sources of contamination were seen as adding any significant risk of EI contamination to "Greatproduct" (See *Table 8*), with the sole exception of As, and Pb due to the extreme worst case scenario chosen for CCS (See Sec. 0).

In keeping with the conservative approach taken and in order to verify the assumptions of the PHA, 3 commercial scale batches of the worst-case drug product "Greatproduct" were baseline - tested for the following EIs:

- Group 1 Elements: As, Cd, Hg, Pb,
- Group 2A Ni, Co, V *(Steel)*
- Group 2B Pt *(High content in Silicone - See Table 4)*,
- Group 3 Ba *(CSS)*

Table 8 describes the components (Potential sources for EI), the associated EIs of concern, the level of the EI predicted by the PHA, and the results of the initial testing. The column "Conclusions" also includes proposed actions (i.e. elements of a control + test strategy) as appropriate.

Table 8 Summary of elemental impurities (EIs) risk assessment and conclusions

Potential sources of EIs in DP	**Potential EIs**	**Contribution of EI to the DP, [µg/g]**		**Control threshold [µg/g]**	**Conclusions**
		Expected	**Found#**		
Drug Substance	N/A	N/A	N/A	N/A	Quote ICH Q3D: *"For biotechnology-derived products, the risks of elemental impurities being present at levels that raise safety concerns at the drug substance stage are considered low."*
Water for injection (WFI)	N/A	< LOQ	N/A	N/A	No additional Controls required. See Sec. 0
Excipient 3	As	0.002	< 0.05	1.88	No additional Controls required. See Sec. 2.3.2
	Hg	0.04	< 0.05	0.375	
	Pb	0.004	< 0.01	0.625	
Excipient 4	As	0.04	< 0.05	1.88	No additional Controls required. See Sec. 2.3.2
	Pb	0.025	< 0.01	0.625	
	Ni	0.049	< 0.05	2.5	
Equipment: Stainless steel	Ni	0.30	< 0.05	2.5	No additional risk to DP. Note that the expected values were derived as shown in Sec 3.5.
	Other	See *Table 7*			

Potential sources of EIs in DP	Potential EIs	Contribution of EI to the DP, [µg/g]		Control threshold [µg/g]	Conclusions
		Expected	Found[#]		
Equipment: Other	Pt	0.004	< 0.05	4.17	No additional Controls required. See Sec. 0
CCS	As	1.93	< 0.05	1.88	No additional Controls required. See Sec. 0
	Pb	1.38	< 0.01	0.625	No additional Controls required
	Other	<10% of PDE*	< LOD	See Table 7	*Expected levels of elemental impurities are < 10% of PDE. No additional Controls required
Other	Li	N/A	N/A	N/A	No potential source identified

N/A: Not Applicable; LOD: Limit of Detection

[#]Average test results of 3 DP batches of "Greatproduct"

4 Summary and Conclusion

The risk assessment for "Greatproduct" produced at "Greatsite", indicates that the established product and process controls inherent in the final commercial process ensure that the levels of potential elemental impurities are maintained below their respective PDEs. Verification of the Risk Assessment was performed by testing samples from 3 batches of "Greatproduct". The analytical results confirmed the assumptions of the Risk Assessment.

Further, the existing quality systems and manufacturing controls ensure the continued suitability of filling operations at Greatsite including not only the components of all drug products, but also the associated personnel, equipment, facilities, utilities as well as analytical methods/equipment. In this regard testing of EI content of the representative drug product "Greatproduct" at periodic intervals and/or after changes is foreseen.

In the event of changes in manufacturing equipment, materials (e.g., introduction of new products or new manufacturing trains to the facility), process details, excipient suppliers etc., the risk assessment, its conclusions, and the current control strategy will be reviewed. If changes are required based on this assessment, they will be documented following the corporate change control requirements. In addition, the risk assessment will be reviewed as part of the Annual Product Quality Review to capture any changes with potential impact.