European Federation of Pharmaceutical Industries and Associations

Elemental Impurity Risk Assessment - Case Studies

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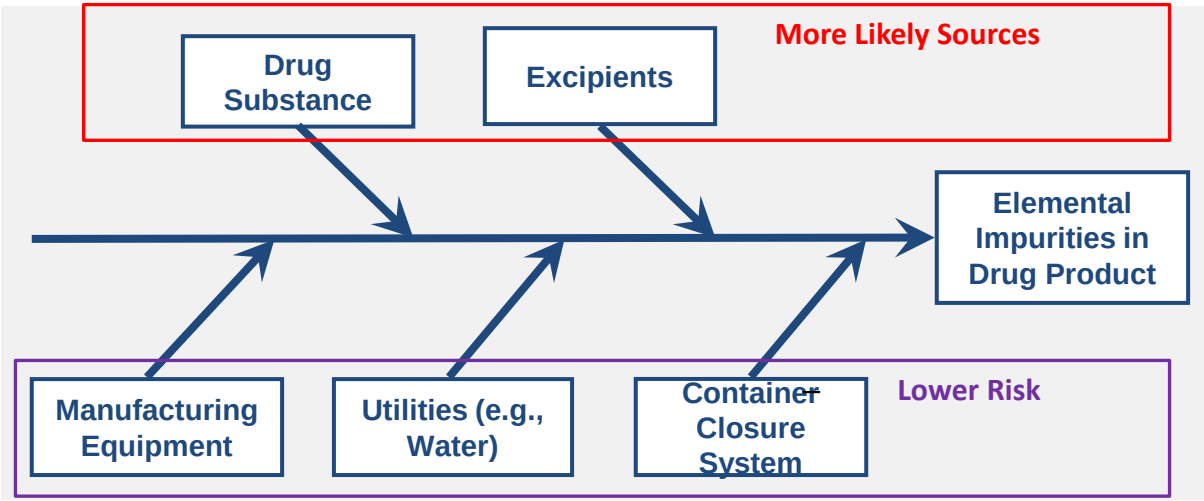
Overview

Using the principles outlined in ICH Q3D and training modules we will:

- Present a series of risk assessments based on actual products.
  - *Examining different routes of administration.*
- Through this seek to highlight there is more than one approach, illustrated through the examples shown.
- Marketing application – example summary and proposed location.
- Approach to products during clinical development.

ICH Q3D Guideline for Elemental Impurities – Practical Implementation of ICH Q3D

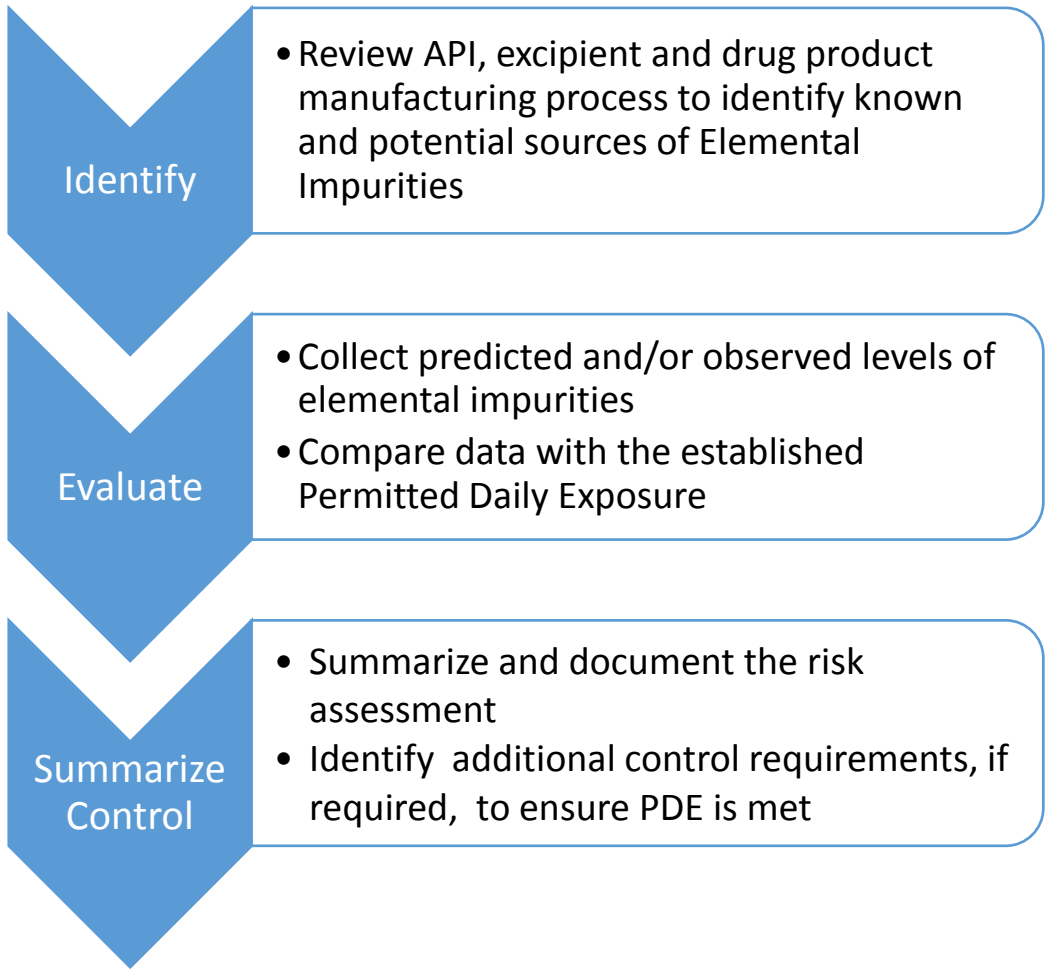
- ICH Q3D recommends taking a **risk based approach.**
- Focus is on the **final product** – the fishbone diagram assists by advising on the components for consideration: **all** potential sources of elemental impurities should be considered and evaluated for their contribution to the drug product.
- The product assessment will form the basis of a specific control strategy for EIs and should be available to be presented to Regulators during an inspection upon request.
- An industry position paper has been jointly authored and published in PharmTech.



Risk Process – General Principles

- **ICH Q3D advocates a 3 step process**:
  - Identify
  - Evaluate
  - Summarize Control

- Different approaches to each stage are now examined through a series of actual risk assessments.



Industry Risk Assessment Example 1

Synthetic API – tablet

Industry Risk Assessment
Example 1 – Oral Solid Dose

Product	Compound X
Dose Form	Tablet
Strength	200/ 400 mg compound X
Therapeutic Target (Why patients take this product)	Osteoarthritis
Dosing Regemine (Frequency & Duration of dosing)	Daily, one tablet
Maximum Daily Dose of Active	400mg Compound X
Mass of Dosage Unit	638.6 mg
Route of Administration	Oral
USP Monograph for Product	No
Site of Manufacture	GMP
Packing Site	GMP
Elements being Evaluated	
Class 1	Cd, Pb, AS, Hg
Class 2A	Co, V, Ni
Class 2B	Pd – Metal catalyst used in API synthesis
Class 3	Sn - Hypromellose

Additional metals identified by risk Assessment

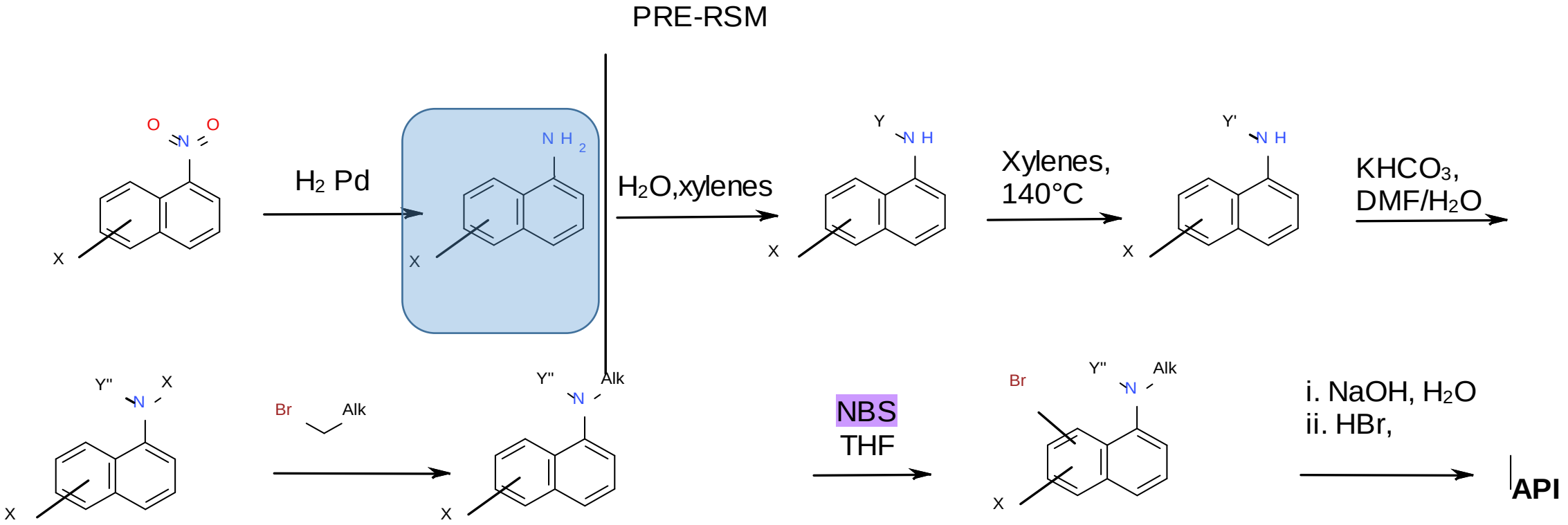
Example 1 – Oral Solid Dose

Component	Functionality	Amount per 400 mg tablet (mg)	% in coated tablet	Type (Excipient)
Core				
API	Drug substance	400.00	62.64	
Hypromellose 2910	Binder	21.70	3.40	Plant
Microcrystalline Cellulose	Diluent	37.20	5.83	Plant
Lactose Monohydrate	Diluent	111.50	17.46	Animal
Crospovidone	Disintegrant	43.40	6.79	Synthetic
Magnesium stearate	Lubricant	6.20	0.97	Mineral
Coating				
Hypromellose 2910	Film-former	11.16	1.75	Plant
Titanium dioxide	Pigment	5.55	0.87	Mineral
Triacetin	Plasticiser	1.49	0.23	Synthetic
Blue Aluminium Lake #2	Colorant	0.37	0.06	Mineral
Blue Aluminium Lake #1	Colorant	0.03	0.005	Mineral

The theoretical mathematics work

Components that make up a small part of the daily dose are unlikely to "tip-the-balance"

Product Information – API Synthesis



cf. 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.*")

Product Information – drug product manufacture

Pharmacopeial Grade

Formulation and components		Unit operations
API Lactose Microcrystalline Cellulose Crospovidone Hypromellose	→	**Stage 1: Dry Mix** High shear wet granulator
Hypromellose Purified water	→	**Stage 2: High Shear Wet Granulation** High shear wet granulator
		↓
		Stage 3: Wet Milling Screening Mills **Stage 4: Fluidised Bed Drying** Direct heating, fluidised solids bed
		↓
		Stage 5: Milling Screening mill

Formulation and components		Unit operations
Crospovidone Magnesium stearate	→	**Stage 6: Blending** Diffusion mixers (tumble) **Stage 7: Lubrication** Diffusion mixers (tumble)
		↓
		Stage 8: Compression Tablet press
		↓
Film Coat	→	**Stage 9: Film Coating** Pan coating **Stage 10: Packing**

Evaluation process not just data driven

- Can be based on first principles.
- With regards to the process described an evaluation was conducted prior to manufacture
  - Concluded that risk very low given lack of any extremes of pH and low residence times.
  - Visual inspection / cleaning also part of GMP.

Section 5.2 – Risk can be reduced through process understanding / equipment selection / qualification and GMP processes.

Product Information – packaging

Drug Substance packaging

- Drug substance stored in double low density polyethylene bags individually closed with plastic tie wraps. The closed bags are stored inside a rigid outer container/drum.

Drug Product packaging

- X tablets are presented as blister packs formed from unplasticized polyvinyl chloride (PVC) film laminated to a polychlorotrifluoroethene (PCTFE) and sealed to push-through blister foil

Risk factors:

- Contact Solid to Solid – **no mechanism***
- Data relating to PE / PVC show very low EI risk

Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review PDA J Pharm Sci Technol January/February 2015 69:1-48;

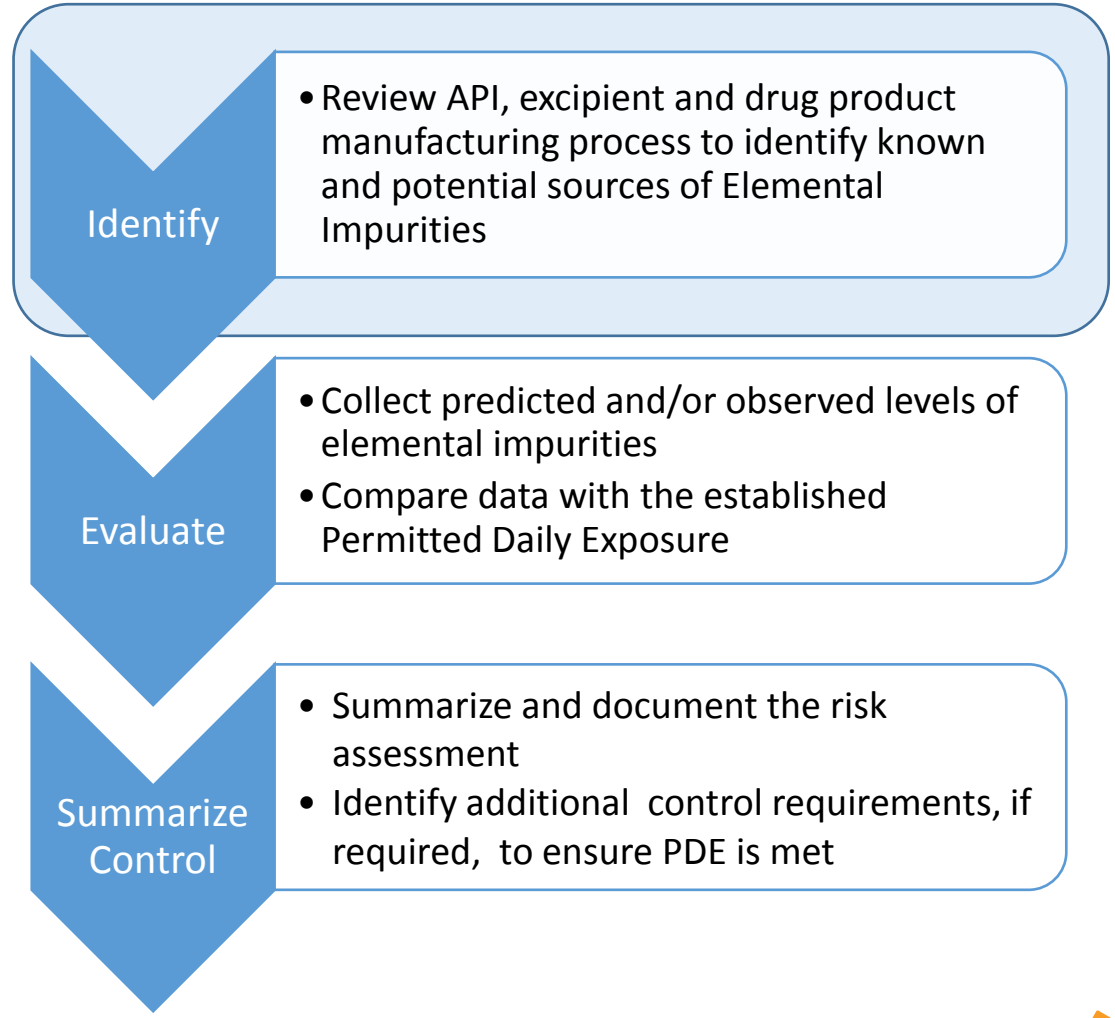
Section 5.3 – ***Probability of elemental leaching into solid dosage forms is minimal and does not require further consideration in the risk assessment***

Step 1 – Identify

- In this example all input materials were recorded and a specific risk assessment tool used to evaluate each potential EI source
  - Using a pre-defined scoring system.

- This is then represented graphically coding risk in terms of red/amber/green as well as the numerical risk factor.

There are multiple ways to conduct an assessment



Identify

Typical high risks:
metal catalysts/reagents,
mined excipients

Risks controlled by GMP:
purified water,
equipment compatibility

Unit Operation/Source of Metal	Failure Mode, (Material)	Failure Effect (Metal of interest)	PDE/ product daily dose (ug/g)	Typical range, (ug/g)	Probability (failure mode)	Severity	Criticality Number	General Comments/Control Strategy	Current control limit (ug/g)	Detectability	Risk Priority Number	Action
Drug substance												
		environmental metal impurities			5	5	25	Inorganic reagents used in later stages of synthesis.		1	25	Test for environmental metals
		Pd			10	1	10	Residues controlled to 10ppm in drug substance intermediate X (typical levels 0.3ppm).	10 ppm	0.1	1	
		Hg			5	5	25	Potentially introduced with sodium hydroxide		1	25	
Excipients	Hypromellose											
		environmental metal impurities	2.3	<20ppm heavy	5	5	25	USP, Ph Eur and JP 20 ppm heavy metals	20 ppm	1	25	Test for environmental metals.
		Sn	10021.9	<0.6 ppm	5	1	5	Identified as likely to be present in supplier survey (< 0.6 ppm in 12 samples by ICP-OES).		1	5	
	Microcrystalline Cellulose											
		environmental metal impurities	2.3	≤10ppm	5	5	25	USP, Ph Eur and JP 10 ppm heavy metals	10 ppm	1	25	Test for environmental metals.
	Lactose monohydrate											
		environmental metal impurities	2.3	≤5ppm	5	5	25	USP, Ph Eur and JP 5 ppm heavy metals	5 ppm	1	25	Test for environmental metals.
	Crospovidone											
		environmental metal impurities	23.5	≤10ppm	1	5	5	USP and Ph Eur 10 ppm heavy metals	10 ppm	1	5	
		Catalyst (?)			10		50	Pharmaceutical excipient handbook suggests that a catalyst is used. Contact supplier.		1	50	Contact supplier to confirm if a metal catalyst is used.
		Lead	7.8	≤5ppm	1	1	1	Test is on current supplier CofA		1	1	
		Arsenic	2.3	≤2ppm	1	1	1	Test is on current supplier CofA		1	1	
	Magnesium stearate											
		environmental metal impurities	2.3	≤20ppm	5	5	25	20 ppm only in JP		1	25	Test for environmental metals.
		Nickel	391.5	≤ 1ppm	5	1	5	USP and Ph Eur 5 ppm. Identified as present in a raw material by supplier survey.	5 ppm	0.2	1	
		Cadmium	7.8	≤ 1ppm	5	1	5	USP and Ph Eur 3 ppm	3 ppm	0.2	1	
		Lead	7.8	≤ 1ppm	5	1	5	USP and Ph Eur 10 ppm. Specification 5 ppm from supplier survey.	5 ppm	0.2	1	
		As	2.3	<0.05 ppm	5	1	5	Periodic testing by ICP-OES confirmed by supplier survey.	1 ppm	0.2	1	
		Hg	23.5	<0.05 ppm	5	1	5	Periodic testing by ICP-OES confirmed by supplier survey.	1 ppm	0.2	1	
Coating	Film coating Hypromellose											
		environmental metal impurities	2.3	<20ppm heavy	5	5	25	USP, Ph Eur and JP 20 ppm heavy metals	20 ppm	1	25	Test coating for environmental metals.
	Titanium Dioxide											
		environmental metal impurities	7.8	≤20 ppm	10	5	50	USP, Ph Eur and JP 20 ppm heavy metals	20 ppm	1	50	Test coating for environmental metals.
		Antimony	1878	≤ 100ppm	10	1	10	Ph Eur 100 ppm	100 ppm	0.2	2	
		Arsenic	2.3	≤ 1 ppm	10	1	10	USP 1 ppm, Ph Eur 5 ppm, JP 10 ppm	1 ppm	0.2	2	
		Barium	20357		10	1	10	limit is absence by the test used. Unlikely to exceed allowed 2%		1	10	
		Iron	20857	≤ 200ppm	10	1	10	Ph Eur 200 ppm	200 ppm	0.2	2	
		Lead	156.6	≤60 ppm	10	1	10	JP 60 ppm		1	10	
	Triacetin											
		environmental metal impurities			1	5	5			1	5	
	Blue #2											
		environmental metal impurities			10	5	50	No information available on this component. Testing of coating will inform risk-level.		1	50	Test coating for environmental metals.
		Al	N/A		10	0		Al colourant, low toxicological concern		1		
	Blue #1											
		environmental metal impurities			10	5	50	No information available on this component. Testing of coating will inform risk-level.		1	50	Test coating for environmental metals.
		Al	N/A		10	0		Al colourant, low toxicological concern		1		
Equipment	Equipment											
					10	1	10			1	10	
Packing	Primary Pack: PVC blisters											
		Potentially leached metals			1	1	1			1	1	
Process materials	Water											
		environmental metal impurities			1	5	5			1	5	

Identify

Other factors

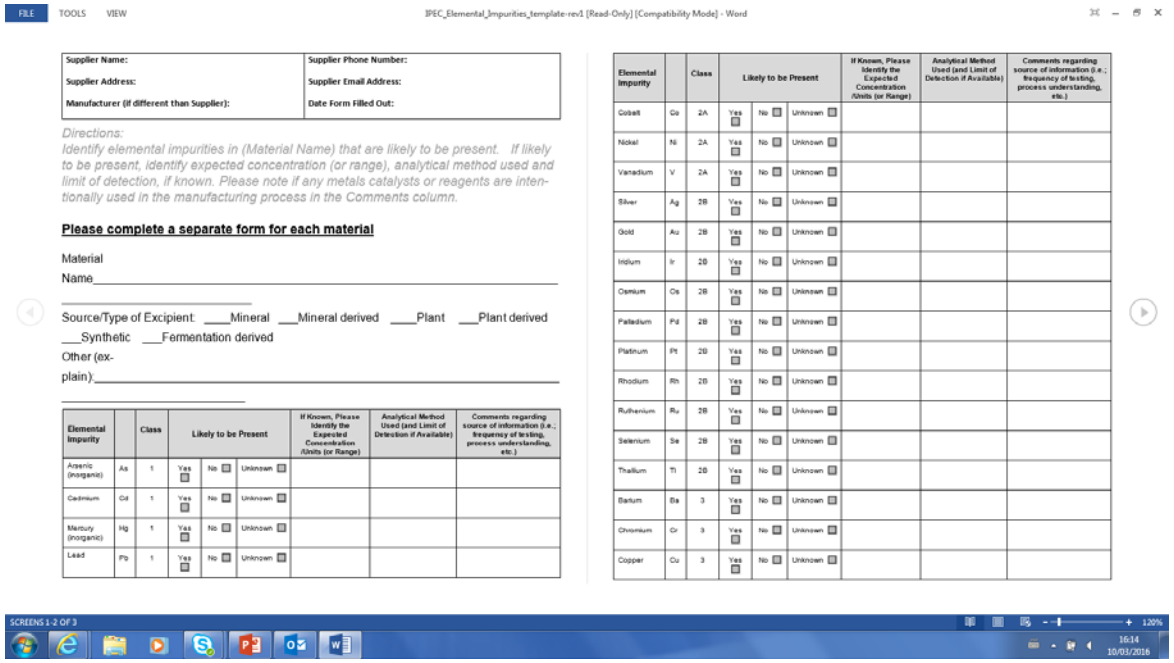
- Any risk assessment needs to be supported by an appropriate overall quality system. Key aspects of this would typically include:
  - Vendor Assurance
  - Change Control
  - Supplier Information
  - Certificate of Analysis
  - EI risk assessment

- **In this example for Crospovidone the following information available:**
- Pharmaceutical excipient handbook suggests that a catalyst can be used in the production of crospovidone.
- Supplier provided a statement to confirm that no metal catalysts are used in the manufacture of their xx grade crospovidone.

Evaluation process not just data driven

Can be based on first principles

IPEC Questionnaire



FILE TOOLS VIEW — IPEC_Elemental_Impurities_template-rev1 [Read-Only] [Compatibility Mode] - Word

Supplier Name:	Supplier Phone Number:
Supplier Address:	Supplier Email Address:
Manufacturer (if different than Supplier):	Date Form Filled Out:

Directions:
Identify elemental impurities in (Material Name) that are likely to be present. If likely to be present, identify expected concentration (or range), analytical method used and limit of detection, if known. Please note if any metals catalysts or reagents are intentionally used in the manufacturing process in the Comments column.

Please complete a separate form for each material

Material Name_____

Source/Type of Excipient: ___Mineral ___Mineral derived ___Plant ___Plant derived ___Synthetic ___Fermentation derived

Other (explain):_____

Elemental Impurity		Class	Likely to be Present			If Known, Please Identify the Expected Concentration /Units (or Range)	Analytical Method Used (and Limit of Detection if Available)	Comments regarding source of information (i.e.; frequency of testing, process understanding, etc.)
Arsenic (inorganic)	As	1	Yes	No	Unknown			
Cadmium	Cd	1	Yes	No	Unknown			
Mercury (inorganic)	Hg	1	Yes	No	Unknown			
Lead	Pb	1	Yes	No	Unknown			

Elemental Impurity		Class	Likely to be Present			If Known, Please Identify the Expected Concentration /Units (or Range)	Analytical Method Used (and Limit of Detection if Available)	Comments regarding source of information (i.e.; frequency of testing, process understanding, etc.)
Cobalt	Co	2A	Yes	No	Unknown			
Nickel	Ni	2A	Yes	No	Unknown			
Vanadium	V	2A	Yes	No	Unknown			
Silver	Ag	2B	Yes	No	Unknown			
Gold	Au	2B	Yes	No	Unknown			
Iridium	Ir	2B	Yes	No	Unknown			
Osmium	Os	2B	Yes	No	Unknown			
Palladium	Pd	2B	Yes	No	Unknown			
Platinum	Pt	2B	Yes	No	Unknown			
Rhodium	Rh	2B	Yes	No	Unknown			
Ruthenium	Ru	2B	Yes	No	Unknown			
Selenium	Se	2B	Yes	No	Unknown			
Thallium	Tl	2B	Yes	No	Unknown			
Barium	Ba	3	Yes	No	Unknown			
Chromium	Cr	3	Yes	No	Unknown			
Copper	Cu	3	Yes	No	Unknown			

SCREENS 1-2 OF 3 — 120% — 16:14 10/03/2016

Step 2 - Evaluate

- Based on the risk analysis – screening requirements were defined.
- Screening focused on Class 1 and Class 2A metals + Identified metals.
  - Section 5.6 - 3 production or 6 pilot scale lots
- Analysis performed using 'fit for purpose' methodology

Section 9 – *The determination of EIs should be conducted using appropriate procedures suitable for their intended purpose*

Potential source of metal impurities	No. of batches to be analysed	Elemental l impurities to include in analytical screening		Comments
		Environmental and naturally abundant elements	Intentionally added' metals e.g. metal catalysts/reagents	
Hypromellose	3 batches representative of the quality/supplier/grade to be used during commercial manufacture	Class 1: As, Cd, Hg, Pb Class 2A: V, Co, Ni	Sn	
Microcrystalline cellulose	3 batches		None	
Lactose monohydrate	3 batches		None	
Magnesium stearate	3 batches		None	
Crospovidone	None		None	Addressed through detailed supplier response
Coating	3 batches	Class 1: As, Cd, Hg, Pb Class 2A: V, Co, Ni		Aluminium lakes are used to colour the coating blue.
API	3 batches		Pd - catalyst	

Step 2 – Evaluate

- Negligible levels of Class 1 / Class 2A metals across API and excipients tested

Potential source of elemental impurities	Batch Number	Elemental impurity concentration in µg/g							
		As	Pb	Cd	Hg	V	Co	Ni	Pd
API	Batch 1	<0.1	<0.1	<0.1	1.8	<0.1	<0.1	1.0	<5
	Batch 2	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	1.0	<5
	Batch 3	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.3	<5
Limit of detection (µg/g)		**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	**5**
Option 2a target limit µg/g (0.64 g/day drug product)		**23**	**7.8**	**7.8**	**47**	**160**	**78**	**310**	**160**
30% Option 2a target limit µg/g		**7.0**	**2.3**	**2.3**	**14**	**47**	**23**	**94**	**47**

Step 3 – Summarize Control - Actions

The overall risk to Patients is very low.

Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high environmental abundance	Manufacturing equipment	Leached from container closure systems	Acceptable variability of elemental impurity contribution	Control threshold µg/day (30% PDE)	Action
As	No	Negligible levels	No	No	Yes	4.5	no further controls required. See control section for summary of existing controls
Pb	No	Negligible levels	No	No	Yes	1.5	no further controls required. See control section for summary of existing controls
Cd	No	Negligible levels	No	No	Yes	1.5	no further controls required. See control section for summary of existing controls
Hg	Potentially introduced into drug substance with sodium hydroxide	Negligible levels	No	No	Yes	9.0	no further controls required. See control section for summary of existing controls

Summarize Control - Actions

Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high environmental abundance	Manufacturing equipment	Leached from container closure systems	Acceptable variability of elemental impurity contribution	Control threshold µg/day (30% PDE)	Action
V	No	Negligible levels	No	No	Yes	30	no further controls required. See control section for summary of existing controls
Co	No	Negligible levels	No	No	Yes	15	no further controls required. See control section for summary of existing controls
Ni	No	Negligible levels	No	No	Yes	60	no further controls required. See control section for summary of existing controls
Pd	Catalyst used pre-RSM	Negligible levels in drug substance	No	No	Yes	30	no further controls required. See control section for summary of existing controls
Sn	Potentially introduced with Hypromellose	Negligible levels in Hypromellose	No	No	Yes	1800	no further controls required. See control section for summary of existing controls.

Summarize Control

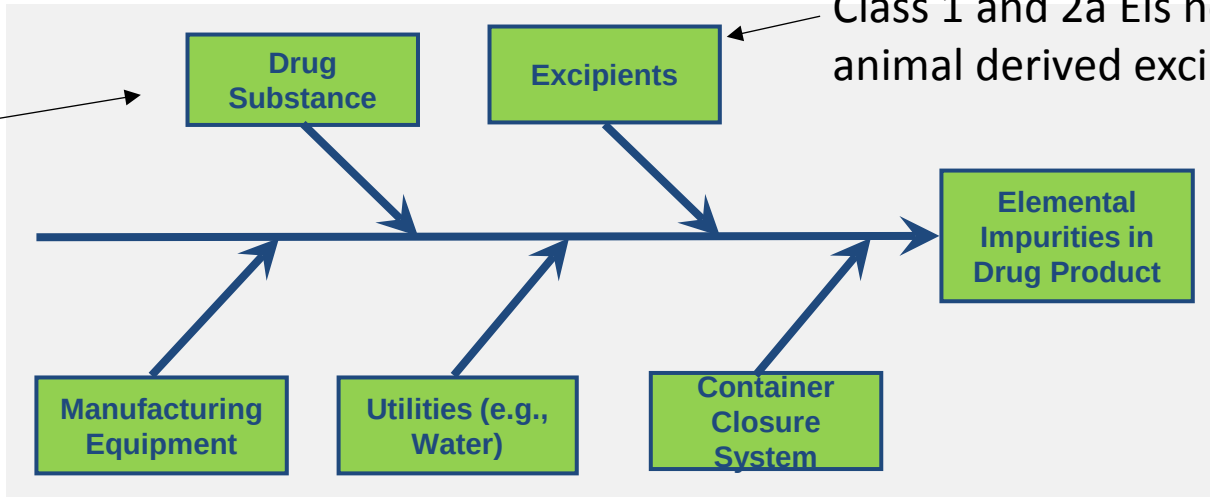
The overall risk to Patients is very low.

- No requirement for additional control measures has been identified in the evaluate stage.

- The existing measures adequately control the levels of metal impurities in the drug product

Mined excipients constitute small % of formulation
Class 1 and 2a Els not detected in synthetic / plant / animal derived excipients

Pd catalyst – Pre- Registered Starting Material



GMP control

Solid dosage form

Industry Risk Assessment Example 2

Inhaled formulation – dry powder

Step 1 - Identify

Product	Drug Product Y (DPY)
Dose Form	Dry Powder Inhalation
Strength	500 µg
Therapeutic Target (Why patients take this product)	Asthma
Dosing Regemine (Frequency & Duration of dosing)	One inhalation once a day; daily
Maximum Daily Dose of Active	500µg of DPY drug substance
Mass of Dosage Unit	25 mg
Route of Administration	Inhalation
USP Monograph for Product	No
Site of Manufacture	Manufacturing Site 1
Packing Site	Manufacturing Site 1
Elements being Evaluated	
Class 1	Cd, Pb, As, Hg
Class 2A	Co, V, Ni
Class 2B	Pd, Pt
Class 3	Li, Sb, Ba, Mo, Cu, Sn, Cr
Other Elements	N/A

API and Excipients
Product Components & Sources

Component	Amount /Unit (mg)	Max Daily Intake (mg)	Percent of Daily Intake	Supplier	Information Available from Supplier		Natural/ Synthetic	Natural Material Source
					General Declarations	Risk Assessment		
DPY Drug Substance (micronized)	0.500	0.500	2.0	Manufacturing Site 1	Yes	No	Synthetic	N/A
Lactose monohydrate,	24.5	24.5	98	Vendor A	Yes	No	Natural	Animal
				Vendor B	Yes	No		
Unit Weight (mg)	**25**							
Units per day	**1**							
Daily Intake (mg)	**25**							

Section 5 – *The level of effort and formality of the risk assessment should be proportional to the level of risk*

Known Information Regarding Elemental Impurity Content

Component	Supplier	Metals Intentionally Added (used in process)	Metals as Naturally Occurring/ Contaminants	Testing For Metals Performed	Current Limits	Data Available	Comments
DPY Drug Substance (micronized)	Manufacturing Site 1	Yes Pd/Pt heterogeneous catalyst used	Negligible risk • Class 1 • Class 2A • Class 3	Pd Pt USP<231>	NGT 5ppm NGT 5ppm NGT 20ppm	Yes Yes Yes	Pd & Pt determined by ICP-OES on a routine basis
Lactose monohydrate,	Vendor A	No	Negligible risk • Class 1 • Class 2A • Class 3	USP <231>	NMT 5µg/g	On CoA	Heavy Metals testing reported on COA as limit test
	Vendor B	No	Negligible risk • Class 1 • Class 2A • Class 3	USP<231>	NMT 5µg/g	On CoA	Heavy Metals testing performed weekly and reported on COA, limit test

Manufacturing Equipment

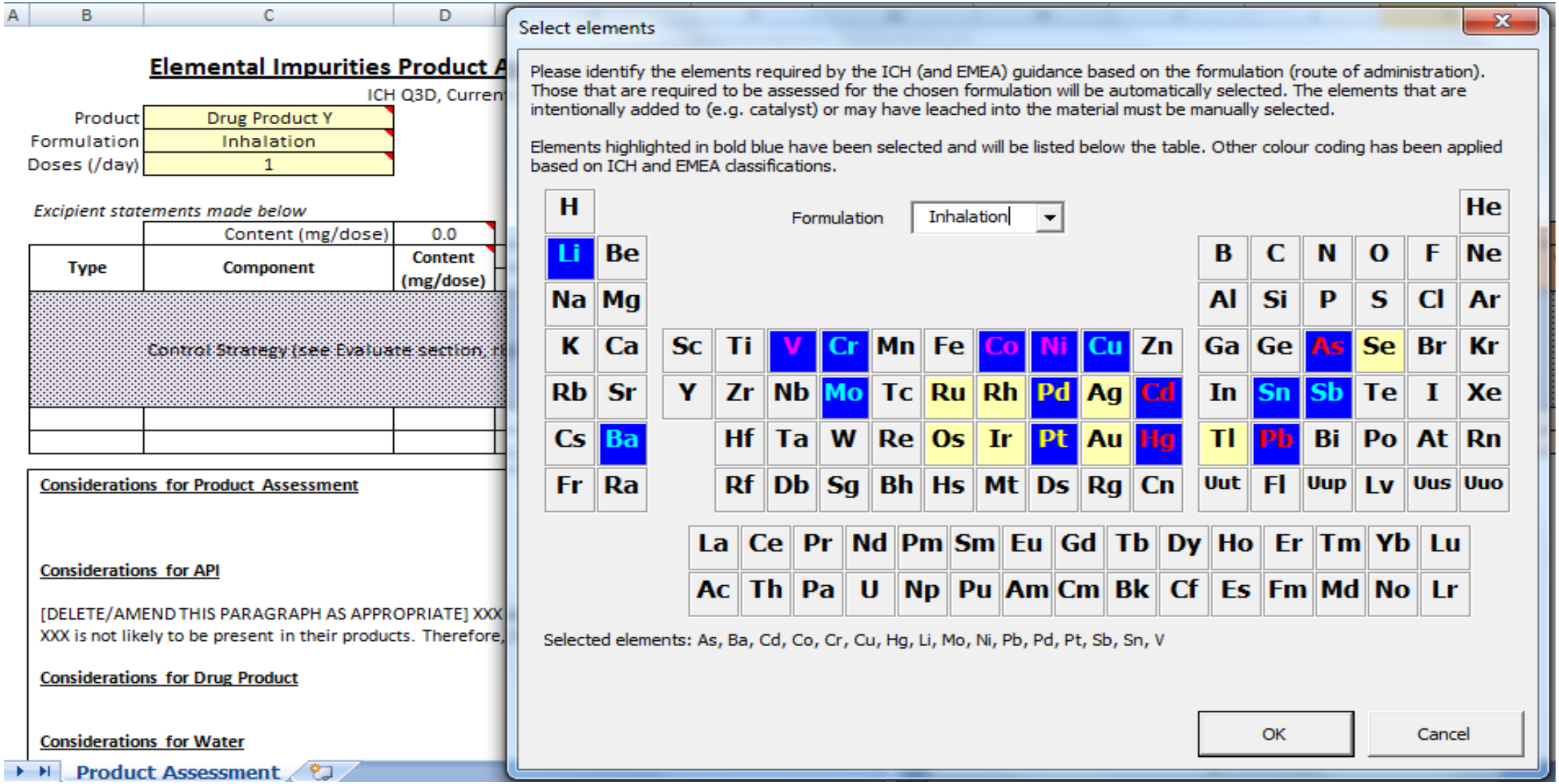
Step	Notes (e.g. Machine type)	Contact Material	Risk from Abrasion/ Attrition	Risk from Corrosion, Leaching or Chelating	Overall Risk Relative to PDE	Actions
Blending	Bowl 1	Stainless Steel	Moderate	Very Low	Low	Low Risk – no action needed
Filling	EQUIP 1	Stainless Steel	Very Low	Very Low	None	Low Risk – no action needed

Utilities/Water

- Water is not used in the manufacture of Drug Product Y Dry Powder Inhaler 500 µg. Utilities (such as air) used in the manufacture of the product will comply to USP/Ph.Eur. and appropriate Manufacturing Site 1 standards.
- As such, the probability of elemental impurities being introduced into the product by the utilities is very low.

Container Closure

Pack Type	Supplier	Contact Material	Does Component Contain Elemental Impurities?	Overall Risk Relative to PDE	Actions
Polyethylene Bag	N/A	Polyethylene	No	None	None – used to store blend before filling strips.
Lid Foil Laminate	N/A	Heat Seal Lacquer	Yes Aluminium	None	Low Risk – no action needed
Base Foil Laminate	N/A	PVC (Polyvinyl Chloride)	Yes Aluminium	None	Low Risk – no action needed


Elemental Impurities Product A
ICH Q3D, Curren
Product
Drug Product Y
Formulation
Inhalation
Doses (/day)
1
Excipient statements made below
Content (mg/dose)
0.0
Type
Component
Content (mg/dose)
Control Strategy (see Evaluate section, r
Considerations for Product Assessment
Considerations for API
[DELETE/AMEND THIS PARAGRAPH AS APPROPRIATE] XXX
XXX is not likely to be present in their products. Therefore,
Considerations for Drug Product
Considerations for Water
Product Assessment
Select elements
Please identify the elements required by the ICH (and EMEA) guidance based on the formulation (route of administration). Those that are required to be assessed for the chosen formulation will be automatically selected. The elements that are intentionally added to (e.g. catalyst) or may have leached into the material must be manually selected.
Elements highlighted in bold blue have been selected and will be listed below the table. Other colour coding has been applied based on ICH and EMEA classifications.
Formulation
Inhalation
H
He
Li Be
B C N O F Ne
Na Mg
Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr
Rb Sr Y Zr Nb Mo Tc Ru Rh Pd Ag Cd In Sn Sb Te I Xe
Cs Ba Hf Ta W Re Os Ir Pt Au Hg Tl Pb Bi Po At Rn
Fr Ra Rf Db Sg Bh Hs Mt Ds Rg Cn Uut Fl Uup Lv Uus Uuo
La Ce Pr Nd Pm Sm Eu Gd Tb Dy Ho Er Tm Yb Lu
Ac Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr
Selected elements: As, Ba, Cd, Co, Cr, Cu, Hg, Li, Mo, Ni, Pb, Pd, Pt, Sb, Sn, V
OK
Cancel

Step 2 - Evaluate – Option 2b

Elemental Impurities Product Assessment

Template version 1.0

ICH Q3D, Current Step 4 version, dated 16 December 2014 (Option 2b)

Product	Drug Product Y	Document ID	Risk Assessment 2
Formulation	Inhalation		
Doses (/day)	1	Components	2

Excipient statements made below

						Assess (µg/g)															
	Content (mg/dose)	25.0																			
Type	**Component**	**Content (mg/dose)**	**Manufacturer**		**Batch / Lot Number**	Cadmium Cd	Lead Pb	Arsenic As	Mercury Hg	Cobalt Co	Vanadium V	Nickel Ni	Palladium Pd	Platinum Pt	Lithium Li	Antimony Sb	Barium Ba	Molybdenum Mo	Copper Cu	Tin Sn	Chromium Cr
			Company	**Site**																	
Control Strategy (see Evaluate section, right)																					
API	DPY Drug Substance	0.5	DP Company	Manufacturing Site 1	DPY-API 123		20						5	5							
Excip	Lactose Monohydrate	24.5	Vendor A	LAC site	LAC 456		5														

Levels for Pb based on Pharmacopeial Monograph limit

Evaluate – Option 2b

Option 2b – permitted concentration limits of elements in individual components of a product with a specified intake.

Takes into account the amount of each component in the formulation

Elemental Impurities Product Assessment

Template version 1.0

ICH Q3D, Current Step 4 version, dated 16 December 2014 (Option 2b)

Product	Drug Product Y	Document ID	Risk Assessment 2
Formulation	Inhalation		
Doses (/day)	1	Components	2

Excipient statements made below

						Evaluate (µg/day)														
	Content (mg/dose)	25.0																		
Type	**Component**	**Content (mg/dose)**	**Manufacturer**		**Batch / Lot Number**	Cadmium Cd	Lead Pb	Arsenic As	Mercury Hg	Cobalt Co	Vanadium V	Nickel Ni	Palladium Pd	Platinum Pt	Lithium Li	Antimony Sb	Barium Ba	Molybdenum Mo	Copper Cu	Tin Sn	Chromium Cr
			Company	**Site**																
Evaluate			**ICH Q3D Permitted Daily Exposure (µg/day)**			**2**	**5**	**2**	**1**	**3**	**1**	**5**	**1**	**1**	**25**	**20**	**300**	**10**	**30**	**60**	**3**
			30 % Control Threshold (µg/day)			0.6	1.5	0.6	0.3	0.9	0.3	1.5	0.3	0.3	7.5	6	90	3	9	18	0.9
			Final Evaluated Value (adjusted for dose)(µg/day)			*0.00*	*0.13*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
			Actual Values (µg/g)(overrides sum evaluation)			*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*	*Override*
			Action or No action			**Action**	No action	**Action**	**Action**	**Action**	**Action**	**Action**	No action	No action	**Action**	**Action**	**Action**	**Action**	**Action**	**Action**	**Action**
API	DPY Drug Substance	0.5	DP Company	Manufacturing Site 1	DPY-API 123	NO DATA	0.01	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	0.00	0.00	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA
Excip	Lactose Monohydrate	24.5	Vendor A	LAC site	LAC 456	NO DATA	0.12	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA	NO DATA

Evaluate - Option 2b

Template version 1.0

Elemental Impurities Product Assessment

ICH Q3D, Current Step 4 version, dated 16 December 2014
(Option 2b)

Product	Drug Product Y	Document ID	Risk Assessment 2
Formulation	Inhalation		
Doses (/day)	1	Components	2

Elemental Impurity Levels for components– based on

- Screening data on API
- Data from the excipient Vendor

Where observed levels <LOD, use LOD as observed level to represent worst case.

Excipient statements made below

						Assess (µg/g)														
	Content (mg/dose)	25.0																		
Type	**Component**	**Content (mg/dose)**	**Manufacturer**		**Batch / Lot Number**	Cadmium Cd	Lead Pb	Arsenic As	Mercury Hg	Cobalt Co	Vanadium V	Nickel Ni	Palladium Pd	Platinum Pt	Lithium Li	Antimony Sb	Barium Ba	Molybdenum Mo	Copper Cu	Tin Sn	Chromium Cr
			Company	**Site**																
Control Strategy (see Evaluate section, right)																				
API	DPY Drug Substance	0.5	DP Company	Manufacturing Site 1	DPY-API 123	0.1	0.1	0.1	0.1	42	0.1	26	0.1	0.1	0.1	0.1	0.1	0.3	6.3	0.1	0.2
Excip	Lactose Monohydrate	24.5	Vendor A	LAC site	LAC 456	0.005	0.02	0.01	0.003	0.005	0.001	0.03	N/A	N/A	0.001	0.005	0.01	0.03	0.001	0.01	0.03

Evaluate - Option 2b

Elemental Impurities Product Assessment

Template version 1.0

ICH Q3D, Current Step 4 version, dated 16 December 2014 (Option 2b)

Product	Drug Product Y	Document ID	Risk Assessment 2
Formulation	Inhalation		
Doses (/day)	1	Components	2

Comparison of Elemental Impurity Levels against PDE – based on

- Screening data on Drug Substance
- Data from the excipient Vendor

Excipient statements made below

						Evaluate (µg/day)														
	Content (mg/dose)	25.0																		
Type	**Component**	**Content (mg/dose)**	**Manufacturer**		**Batch / Lot Number**	Cadmium Cd	Lead Pb	Arsenic As	Mercury Hg	Cobalt Co	Vanadium V	Nickel Ni	Palladium Pd	Platinum Pt	Lithium Li	Antimony Sb	Barium Ba	Molybdenum Mo	Copper Cu	Tin Sn	Chromium Cr
			Company	**Site**																
			ICH Q3D Permitted Daily Exposure (µg/day)			**2**	**5**	**2**	**1**	**3**	**1**	**5**	**1**	**1**	**25**	**20**	**300**	**10**	**30**	**60**	**3**
			30 % Control Threshold (µg/day)			0.6	1.5	0.6	0.3	0.9	0.3	1.5	0.3	0.3	7.5	6	90	3	9	18	0.9
	Evaluate		*Final Evaluated Value (adjusted for dose)*(µg/day)			*0.00*	*0.00*	*0.00*	*0.00*	*0.02*	*0.00*	*0.01*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
			Actual Values (µg/g)(overrides sum evaluation)			*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*	*override*
			Action or No action			No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action	No action
API	DPY Drug Substance	0.5	DP Company	Manufacturing Site 1	DPY-API123	0.00	0.00	0.00	0.00	0.02	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Excip	Lactose Monohydrate	24.5	Vendor A	LAC Site	LAC456	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Evaluate – Option 3

Comparison of Elemental Impurity Levels against PDE – based on screening data on Product

Product Daily Intake = 25 mg	Metal	Cadmium	Lead	Arsenic	Mercury	Cobalt	Vanadium	Nickel	Palladium	Platinum	Lithium	Antimony	Barium	Molybdenum	Copper	Tin	Chromium
	Symbol	**Cd**	**Pb**	**As**	**Hg**	**Co**	**V**	**Ni**	**Pd**	**Pt**	**Li**	**Sb**	**Ba**	**Mo**	**Cu**	**Sn**	**Cr**
Maximum Result (µg/g)	**Batch 1**	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.4	<0.1	<0.1	0.3	<0.1
	Batch 2	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.4	<0.1	<0.1	0.3	<0.1
	Batch 3	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.4	<0.1	<0.1	0.2	<0.1
Element Daily Intake (µg)	Batch 1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Batch 2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Batch 3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Element Max Daily Intake (µg)		**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
PDE (µg/day)		2	5	2	1	3	1	5	1	1	25	20	300	10	30	60	0.3
MDI as % of PDE		0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Step 3 – Summarize Control

The overall risk to Patients is very low.

Summary Table for Submission, based on Existing Controls – Class 1 & 2

Element	Class	Added during Process?	Present in API	Present in Excipients	Manuf. Equipment	Packaging Components	Utilities/Water	Observed Level (µg/day)	Control Threshold (30% of PDE)	Actions/Control Strategy
Cd	1	No	Negligible risk	Negligible risk	No	No	No	0	0.6	No further controls required
Pb	1	No	Negligible risk	Negligible risk	No	No	No	0.12	1.5	No further controls required
As	1	No	Negligible risk	Negligible risk	No	No	No	0	0.6	No further controls required
Hg	1	No	Negligible risk	Negligible risk	No	No	No	0	0.3	No further controls required
Co	2A	No	Negligible risk	Negligible risk	No	No	No	0	0.9	No further controls required
V	2A	No	Negligible risk	Negligible risk	No	No	No	0	0.3	No further controls required
Ni	2A	No	Negligible risk	Negligible risk	No	No	No	0	1.5	No further controls required
Pd	2B	API Cat	Potentially, but Controlled	No	No	No	No	0	0.3	No further controls required
Pt	2B	API Cat	Potentially, but Controlled	No	No	No	No	0	0.3	No further controls required

Summarize Control

The overall risk to Patients is very low.

Summary Table for Submission, based on Existing Controls – Class 3

Element	Class	Added during Process?	Present in API	Present in Excipients	Manuf. Equipment	Packaging Components	Utilities/Water	Observed Level (µg/day)	Control Threshold (30% of PDE)	Actions/Control Strategy
Li	3	No	Negligible risk	Negligible risk	No	No	No	0	7.5	No further controls required
Sb	3	No	Negligible risk	Negligible risk	No	No	No	0	6	No further controls required
Ba	3	No	Negligible risk	Negligible risk	No	No	No	0	100	No further controls required
Mo	3	No	Negligible risk	Negligible risk	No	No	No	0	3	No further controls required
Cu	3	No	Negligible risk	Negligible risk	No	No	No	0	9	No further controls required
Sn	3	No	Negligible risk	Negligible risk	No	No	No	0	18	No further controls required
Cr	3	No	Negligible risk	Negligible risk	No	No	No	0	0.9	No further controls required

Conclusion

- As demonstrated by the summary above, the cumulative effect of the material specifications, in combination with adherence to the overall control strategy for Drug Product Y Dry Powder Inhaler, 500µg, is sufficient to control elemental impurities in the product to within safe levels, below 30% of the proposed ICH Q3D PDE, therefore elemental impurities are not included in the drug product specification.

Industry Risk Assessment Example 3

Parenteral

Step 1 - Identify

Product	Powder for reconstitution for IV infusion
Dose Form	Powder in a Type 1 glass vial
Strength	0.54 g API 1 and 2.4 g API 2
Therapeutic Target (Why patients take this product)	Infection
Dosing Regimen (Frequency & Duration of dosing)	Maximum of 3 vials per day
Maximum Daily Dose of Active(s)	1.6 g API 1 and 7.2 g API 2
Mass of Dosage Unit	9.4 g per day
Route of Administration	Parenteral
USP Monograph for Product	No
Site of Manufacture	GMP
Packing Site	GMP
Elements being Evaluated	
Class 1	Cd, Pb, AS, Hg
Class 2A	Co, V, Ni
Class 2B	To be confirmed via risk assessment
Class 3	Li, Sb, Cu
Other Elements	To be confirmed via risk assessment

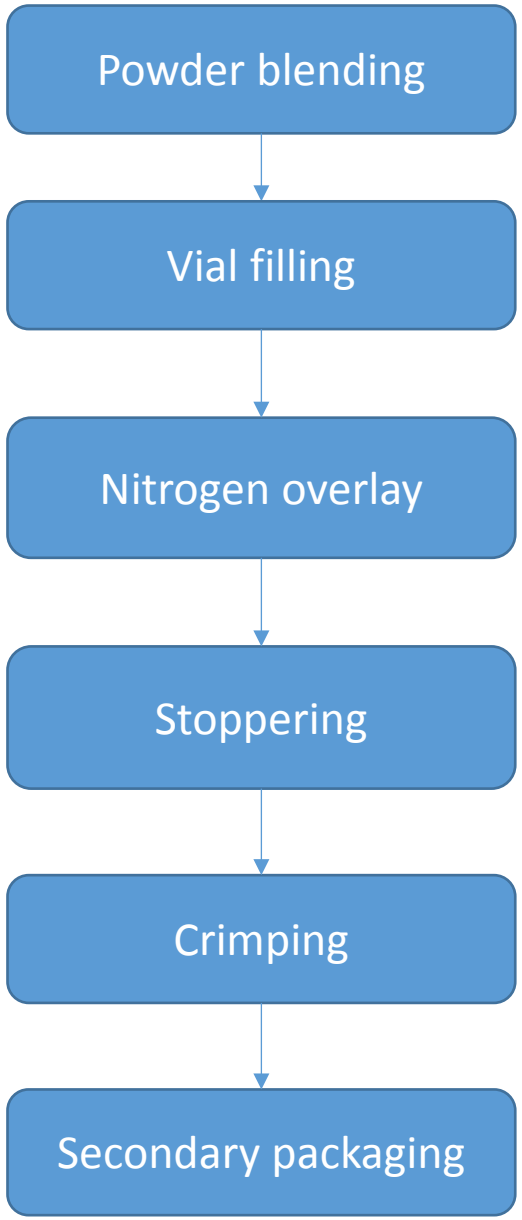
Example 3 – Parenteral, powder for reconstitution for infusion

- The vial is reconstituted with commercially available infusion fluid. The reconstituted vial is then further diluted with infusion fluid prior to administration by intravenous infusion.

  The infusion fluid is outside the scope of this risk assessment.

Component	Functionality	Amount per vial (g)	Type
API 1	Drug substance	0.54	Synthetic
API 2	Drug substance	2.4	Synthetic
Sodium carbonate	Buffer	0.7	Mined/mineral

Product Information – drug product manufacture



Evaluation process not just data driven

Can be based on first principles

Section 5.2 – Risk can be reduced through process understanding / equipment selection / qualification and GMP processes.

Product Information – packaging

- **Drug Substance packaging**

Low Density Polyethylene (LDPE)/Laminate bag.

- **Drug Product Intermediate Powder Blend packaging**

Low Density Polyethylene (LDPE)/Laminate bag.

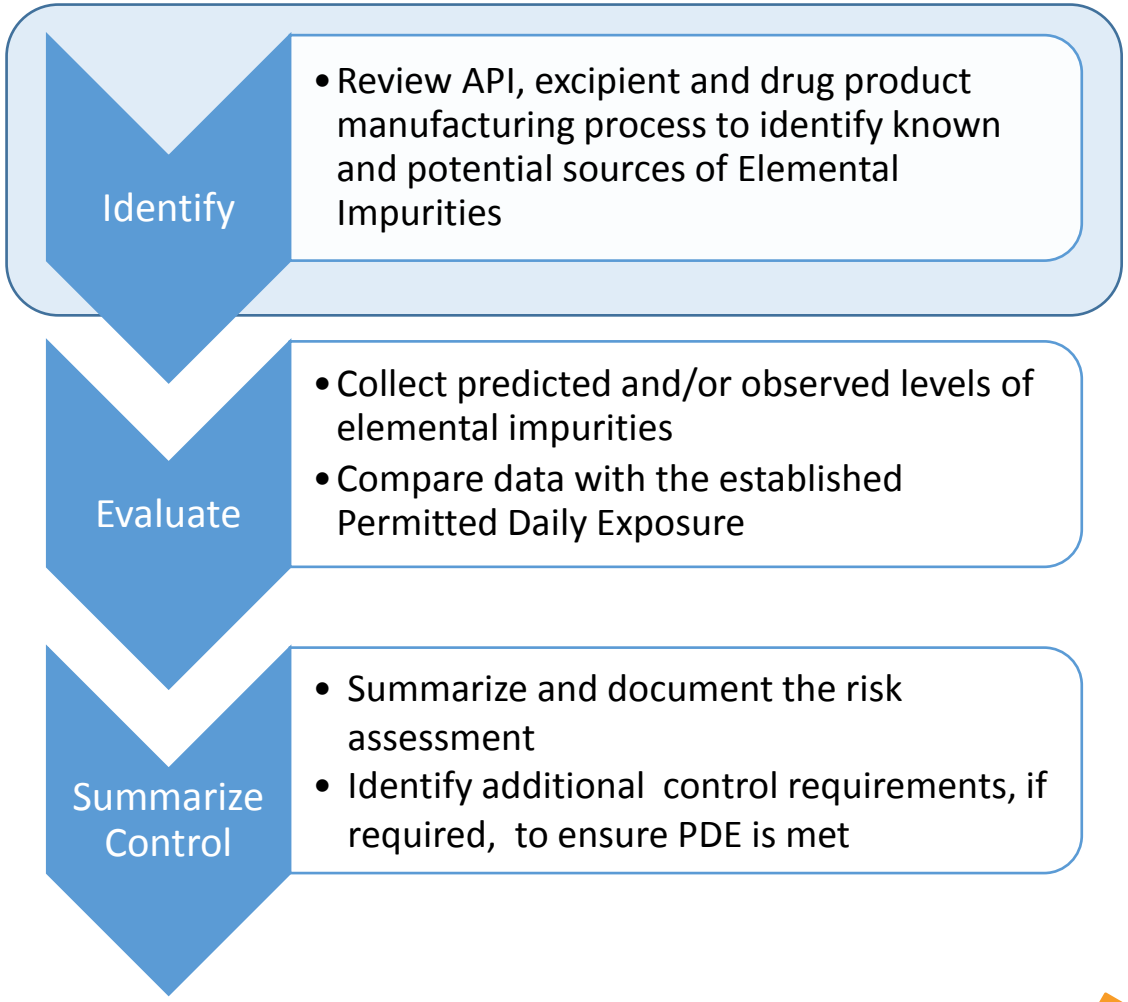
- **Drug Product packaging**

Clear, Type I glass vial with a bromobutyl rubber stopper with a fluorinated polymer coating and aluminium flip-off over seal.

Step 1 – Identify

- In this example the review of the drug substance and drug product manufacturing process was facilitated by a **questionnaire** designed to aid identification of any high-risk sources of elemental impurities for further attention.

- Potential sources of EIs are captured alongside the elemental impurities of concern.



Identify

Simple templated process for identification of high-risks

Microsoft Word Document

Product: Parenteral Product X Date: April 2016

Please answer questions 1-6 below. For any 'yes' responses please document the potential source of elemental impurities and any particular elements of concern. If the response to a question is 'no' then move on to the next question.

1. METAL CATALYSTS		
Are any metal catalysts/reagents used in the manufacture of the drug substance or excipients?		Yes/No
Component:	Catalyst/reagent elements:	
Final intermediate stage	Pd	

2. ENVIRONMENTAL IMPURITIES		
Are there any mined or plant based excipients present in the drug product?		Yes/No
Excipient:	Environmental elements*:	
	*Oral dosage (As, Cd, Pb, Hg, Ni, V, Co)	
Sodium carbonate	*Intravenous dosage (As, Cd, Pb, Hg, Ni, V, Co, Li, Sb, Cu)	As, Cd, Pb, Hg, Ni, V, Co, Li, Sb, Cu
	*Inhalation dosage (As, Cd, Pb, Hg, Ni, V, Co, Li, Sb, Cu, Ba, Mo, Sn, Cr)	
	*Other	Not applicable

3. MANUFACTURING EQUIPMENT		
Are there any extreme or corrosive manufacturing conditions used in manufacture of the drug substance, excipients or drug product? E.g. high temperature and low/high pH		Yes/No
Are there any high-energy processes used in the manufacture of the drug substance, excipients or drug product? e.g. milling or micronisation		Yes/No
Manufacturing stage:	Equipment related elements*:	
Not applicable	*Stainless steel (Fe, Ni, Cr, Mo)	
	*Hastelloy (Ni, Mo, Cr, Fe (Co, W Cu, V)	
	Other	

4. WATER		
Has any non-GMP (see ICH Q7) water source been used in the manufacture of the drug substance, excipients or drug product? Eg. cooling water (see WHO guidance) or non-purified water (see pharmacopoeial standards) in final drug substance and drug product manufacturing stages.		Yes/No
Manufacturing stage:	Environmental elements*:	
Not applicable	*Oral dosage (As, Cd, Pb, Hg, Ni, V, Co)	

Step 2 - Evaluate

- Based on the templated assessment – screening requirements were defined.
- NB – The risk associated with the mined/mineral excipient, was based on absence of data to effectively quantify risk.

Potential source of metal impurities	No. of batches to be analysed	Metal impurities included in analytical screening	
		Environmental metals	'Intentionally added' metals e.g.. catalysts/reagents
API 1	A minimum of **3 commercially representative batches.**	None	Class 2B: Pd
API 2	None	None	None
Sodium Carbonate	A minimum of **3 commercially representative batches.**	Class 1: As, Cd, Hg, Pb Class 2A: V, Co, Ni Class 3: Li, Sb, Cu	None

Section 9 – *The determination of EIs should be conducted using appropriate procedures suitable for their intended purpose*

Section 5.6 - 3 production or 6 pilot scale lots

Step 2 – Evaluate

The Big 4, Class 1 metals are not as ubiquitous as feared in materials used in the Pharma Industry

- No EIs > 30% PDE across API 1 and excipient batches tested

Sample	Batch number	As	Pb	Cd	Hg	V	Co	Ni	Li	Sb	Cu	Pd
API 1	1											0.2
	2											0.2
	3											0.2
Sodium carbonate	1	<0.05	<0.1	<0.05	<0.05	<0.1	<0.1	0.4	<0.1	<0.1	0.5	
	2	<0.05	<0.1	<0.05	<0.05	<0.1	<0.1	0.2	<0.1	<0.1	<0.1	
	3	<0.05	<0.1	<0.05	<0.05	<0.1	<0.1	0.5	<0.1	<0.1	0.4	
Option 2A limit (µg/g)		**0.16**	**0.53**	**0.21**	**0.16**	**1.1**	**0.53**	**2.1**	**27**	**9.5**	**10.6**	**1.1**
30% Option 2A (µg/g)		**0.05**	**0.16**	**0.06**	**0.05**	**0.32**	**0.16**	**0.64**	**8.0**	**2.9**	**3.2**	**0.32**

Step 3 – Summarize Control - Actions

The overall risk to Patients is very low.

Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high environmental abundance	Manufacturing equipment	Leached from container closure systems	Maximum elemental impurity daily intake µg/day	Acceptable variability of elemental impurity contribution	Control threshold µg/day (30% PDE)	Action
As	No	Negligible levels	No	No		Yes		no further controls required
Cd	No	Negligible levels	No	No		Yes		no further controls required
Hg	No	Negligible levels	No	No		Yes		no further controls required
Pb	No	Negligible levels	No	No		Yes		no further controls required

Step 3 – Summarize Control - Actions

The overall risk to Patients is very low.

Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high environmental abundance	Manufacturing equipment	Leached from container closure systems	Maximum elemental impurity daily intake µg/day	Acceptable variability of elemental impurity contribution	Control threshold µg/day (30% PDE)	Action
Ni	No	Negligible levels	No	No		Yes		no further controls required
Co	No	Negligible levels	No	No		Yes		no further controls required
V	No	Negligible levels	No	No		Yes		no further controls required
Pd	Yes	Negligible levels	No	No		Yes		no further controls required
Li	No	Negligible levels	No	No		Yes		no further controls required
Sb	No	Negligible levels	No	No		Yes		no further controls required
Cu	No	Negligible levels	No	No		Yes		no further controls required

Option 3 Also an option

- Examples presented all involve component assessment.
- Can also utilize Option 3 – Test Final Drug Product:
- Advantages : less time and resource consuming + no need to get information from excipient suppliers/process etc. (or an alternative when they are not available…)
  - If the outcome of the DP risk assessment is elemental impurities > 30% PDE, a component risk analysis approach may then be set up to identify route cause.

Marketing Application – Key Principles

Performed in accordance with principles outlined in ICH Q3D – Section 6

- Will typically be presented in DP specification justification P5.6
  - Cross referenced to API section where relevant S4.5.

Summary of risk assessment

- Key aspects of process
- Key risks identified

Summary of control strategy

- Defined controls (limits and method) for specific EI as necessary
- Risk assessment and / or data supports that (other) EIs will not arise at levels >30% of target threshold

Clinical Applications

ICH Q3D SCOPE – Section 2

- *"This guideline does not apply to DP used during clinical research stages of development"*

- Patient Safety is assured during the clinical research stages as EIs are controlled by
  - Control of API specifically control of metal catalysts
  - Use of pharmaceutical grade Excipients

- Formal risk assessment initiated when commercial formulation and process is defined.

Key Learnings

- **The overall risk to Patients is very low.**
  - Drug product / API / excipient data generated to date has found very few issues.
  - The Big 4, Class 1 metals are not as ubiquitous as feared in materials used in the Pharma Industry.
- **There are multiple ways to conduct a risk assessment - Section 6**
  - The basic process and considerations are well aligned across product manufacturers.
  - Everyone does it slightly differently.
- **Evaluation process not just data driven**
  - Can be based on first principles.
- **Prior Knowledge can form an important part of the risk assessment**
  - Literature, test data from related materials, databases etc.
- **The theoretical mathematics work**
  - Components that make up a small part of the daily dose are unlikely to “tip-the-balance”.
- **Control Strategy should be based on the outcome of the risk assessment**
  - If the risk assessment demonstrates that EIs are not present then routine QC testing of drug substance, excipients or drug product for environmental elements should not be performed.

Key Learnings (cont.)

- **Appreciate the Analytical Challenges**
  - Validation should be fit for purpose.
  - ICP-MS is not a “magic answer”
    - Specific challenges in the use of ICP-MS e.g. interference / sample preparation challenges – digestion.
- **A New Way of Thinking is needed**
  - APIs and Excipients will not have the sort of EI specifications we are used to seeing.
  - ICH allows for multiple options for limit setting – one size does not fit all.
  - 30% control threshold routinely applied.
- **Marketing applications**
  - Presentation of risk assessment summaries in the submission should be high-level.
  - The full risk assessment would be available during inspection, if requested
- **Lifecycle management**
  - Product manufacturers do have a lifecycle approach: review, revise, update.

References

- ICH Q3D
- ICH Q3D IWG – Q3D Training Pack, Modules 0-7
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