Elemental Impurity Risk Assessment

INTRODUCTION:

The ICH Guideline for Elemental Impurities Q3D is come into force for new marketing authorization applications for medicinal products in June 2016 and for already authorized medicinal products in December 2017 (EMA/CHMP/QWP/109127/2015).

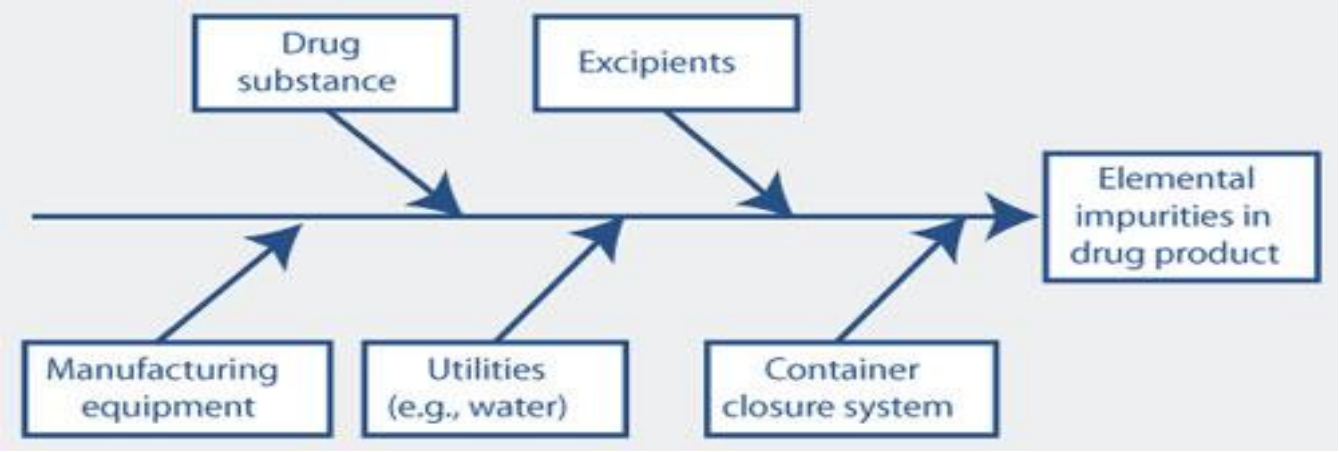
The guideline presents a process to assess and control elemental impurities in the medicinal product using a risk assessment approach as described in ICH Q9.

We are following the approach of the Guideline ICH Q3D based on a risk assessment with regard to the finished products by evaluating the impact of metal contamination of all potential sources. The approach followed and level of information provided has to be evaluated based on the identified level of risk in relation to the presence of Elemental Impurities.

..... is manufacturing a product PARACETAMOL TABLET 500 mg. The manufacturing and packing process is completely integrated till finished product. Thus .....controls the complete process, including intermediate and finished product release steps.

RISK ASSESSEMENT APPROACH:

Focus is on the final product – the evaluation of the potential risk posed by elemental impurities within a formulated drug product requires a holistic approach taking into account all potential sources of elemental impurities. **Figure 1** illustrates potential sources that should be considered in such an evaluation.



Drug substance and Excipients are the more likely source.
Manufacturing equipment, Utilities and container closure system are of low risk.

Figure 1

PRODUCT DETAILS

Product	Paracetamol Tablet 500 mg
Dose Form	Tablet
Strength	500 mg
Therapeutic Target (Why patients take this product)	Pain reliever and a fever reducer.
Dosing Regimen (Frequency & Duration of dosing)	8 Tablets (4.0 g)
Mass of Dosage Unit	580.00 mg
Route of Administration	Oral
Site of Manufacture	GMP
Packing Site	GMP

Section: Potential sources of contamination:

1. Drug substance and excipients.
2. Container Closure System.
3. Manufacturing process:
4. Manufacturing Equipments
5. Utilities.

1. DRUG SUBSTANCE AND EXCIPIENTS:

As presented in **Figure 1**, the drug substance is a key component that can contribute elemental impurities to the finished drug product. The risk of inclusion of elemental impurities from a drug substance is considered during conducting a drug product risk assessment. Control of the elemental impurity content of a drug substance can be assured through a thorough understanding of the manufacturing process including equipment selection, equipment qualification, GMP processes, packaging components, and the selection and application of appropriate control strategies.

A scientific, risk-based approach combined with knowledge and control of the key sources of elemental impurities in the drug-substance manufacturing process such as catalysts, provides an efficient and comprehensive elemental impurity control strategy for finished drug substances.

PARACETAMOL TABLET 500 mg

S.No.	INGREDIENTS	SPEC.	VENDOR	RATIONALE	UNIT FORMULA mg/TAB	SOURCE OF MATERIAL
1.	Paracetamol	Ph. Eur				
2.	Pre-gelatinised Starch	Ph. Eur				
3	Maize Starch	Ph. Eur				
4	Povidone (K-30)	Ph. Eur				
5	#Purified Water	BP				
6	Sodium Starch Glycolate (Type A)	Ph. Eur				
7	Magnesium Stearate (Ligamed MF 2V)	Ph. Eur				
	TOTAL					

Based on the available information through vendor declaration and COA of individual material following evaluation was done and risk is identified.

S.No	Name of component	Manufacturer	Potential Impurities	Limits as per manufacturer Declaration	Intentionally added Elemental Impurity	Summary of expected impurities
1.	Paracetamol		Heavy Metals	NMT 20 ppm	No intentionally element added as per manufacturer declaration.	Information not available **Risk is High**
2.	Pre-gelatinized Starch		Fe	NMT 20 ppm	Information not available	Information not available **Risk is High**
	Magnesium Stearate		Pb	NMT 10 ppm	Information not available	Information not available **Risk is High**
			Cd	NMT 3 ppm		
			Ni	NMT 5 ppm		
3.	Povidone-K30		Heavy Metals	NMT 10 ppm	Information not available	Information not available **Risk is High**
			Pb	NMT 10 ppm		
	Sodium Starch Glycollate		Heavy metals	≤ 20 ppm	None of the metal listed in ICHQ3D is used in the production.	Class 2A metal Ni. Is used as a catalyst **Risk is Low**
			Fe	≤ 20 ppm	Information not available	Information not available **Risk is High**
4.	Maize Starch		Fe	≤ 10 ppm	Information not available	Information not available **Risk is High**

2. CONTAINER CLOSURE SYSTEM:

Name of Component	Manufacturer	Potential Impurities	Limits as per manufacturer Declaration	Intentionally added Elemental Impurity	Summary of expected impurities
White Opaque PVC and CR Aluminium foil.		Not Applicable	Not Applicable	Not Applicable	Being oral solid dosage **Risk is low.**

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:

Tablets are presented as blister packs formed from PVC film 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**

3. MANUFACTURING PROCESS:

The manufacturing process involves following stages.

- Dispensing.
- Sieving of Raw material using Vibratory sifter
- Preparation of granulating solution, spatula
- Granulation using RMG.
- Sampling of in-process using sampling Rod
- Drying of wet granules using FBD
- Grading of dried granules using Multimill .
- Blending and lubrication.
- Storage of bulk in IPC bins & square bin.
- Compression.
- Packing using 198mm/20mic Alu/15 Mic Pvc Para Tab. 500mg &

  Blister PVC Op. White 250mic./ 202mm

The entire manufacturing and packing process is carried out in GMP facility, in controlled environment, using validated methods. All processing area is provided with individual AHUs and are classified as class 100,000 (Grade D).

Manufacturing and packing process is clearly defined in the Batch Manufacturing and packing Record and each batch is manufactured against approved batch Manufacturing record.

Each stage of manufacturing and packing has been optimised and process is monitored through critical process parameter and in-process test against agreed acceptance criteria.
Qualified equipments, utilities and trained personnel are used in the process.
None of the metal listed in ICHQ3D are used in the manufacturing and packing of product Paracetamol 500mg Tablet.

Also manufacturing of this product does not require the use of high temperature, extremes of pH or involve corrosive raw material or processing aids. No metals are intentionally added in manufacturing process.

Therefore, contamination with elemental impurities derives from equipments by either abrasion or leaching presents a very low risk.
Data relating to manufacturing and packing process **show very low EI risk**

4. MANUFACTURING EQUIPMENTS:

Following are the list of equipments used in the manufacturing of Paracetamol tablet 500mg .

Batch size: ..... Tablets
Area: Tablet Area

S.No.	Equipment		SOP No.
	Name	Identification No.	For Cleaning & Operation
1	Vibratory Sifter		
2	Multimill		
3	Steam Kettle		
4	RMG		
5	FBD		
6	Tippler		
7	L&P Devices		
8	Octagonal Blender (4500 Ltr.)		
9	IPC		
10	Square Bin		
11	Compression machine 45 Stn D Tooling		
12	L&P Devices		
13	De dusting Machine		
14	Metal Detector		

Sieve Details:

S.No.	Sieve size	Cleaning SOP number
1	18# sieve	
2	40# sieve	
3	16# sieve	

Screen Details:

S.No.	Screen size	Cleaning SOP number
1	2.5 mm (Multi mill)	

Tooling Details for Paracetamol Tablet 500 mg:

Dimension in mm	Upper Punch	Lower Punch	Dies
	16.5 x 8.2	16.5 x 8.2	16.5 x 8.2

MANUFACTURING EQUIPMENTS EVALUATION:

The risk of inclusion of elemental impurities through manufacturing equipments/accessories can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

Description	Control	Risk
Process Understanding	The manufacturing and packing process is thoroughly evaluated by doing extensive validation actively. Process is understood through review of critical material attributes of all raw material going in to product (CMA), critical process parameters (CPP) which controls the process and impact of CMA and CPP on critical quality attributed of final product is understood and process found validated and in control.	**Risk is low**
Equipment/Accessories selection and qualification Equipment, designed, location and maintenance	All Manufacturing, packing , processing and storage equipment are designed, located and maintained to suit its intended purpose. All individual equipments are qualified before putting it for usage, Equipment are installed as per design in designated place to prevent any risk of error or of contamination	Contribution of elemental impurities from the equipments is minimal as equipments are qualified and GMP controls are in place. **Risk is low**
MOC of machine contact parts.	Stainless Steel SS316 grade. MOC of each product contact components are reviewed and certified. Review confirmed production equipment do not present any hazard to products. For all equipments available at site, the parts of production equipment that come into contact with the product are of SS 316 which do not have impact on quality of the product and thus present any hazard.	Risk from Abrasion/ Attrition is Very low, Risk from Corrosion, Leaching or Chelating is Very Low Overall Risk Relative to PDE is Low Overall Low Risk – no action needed

Description	Control	Risk
Good Manufacturing Practice (GMP) processes.	SOP for operation and cleaning of each equipment is defined as per vendor recommendation and all individuals are trained on the procedure. Calibration and planned preventive maintenance scheduled is prepared and followed for each equipment to main in good state of repair. Repair and maintenance operations are handled in segregated area, in case in place repair and maintenance is to be done then it is handled as per defined procedure to avoid any hazard to the quality of the products. All Manufacturing, packing, processing, storage and sampling equipment and accessories are designed so that it can be easily and thoroughly cleaned. SOP is in place for cleaning of each individual piece of the equipment and accessories. Cleaned equipments and accessories are stored in clean and dry condition with proper status label. SOP is in place for cleaning of each individual piece of the equipment and accessories. Cleaning validation system is in place and cleaning method for each piece of equipments is validated. Line clearance procedure is in place to verify cleanliness and intactness of each piece of equipments and accessories to avoid source of contamination. Defective equipment are removed from production and quality control areas, and are clearly labelled as defective. Log books are maintained for each equipment and usage and cleaning records are maintained for each piece of equipments.	Good Manufacturing Practice (GMP) are in place and are followed at each stage of process and equipments are kept in good state of repair. **Data show very low EI risk**
Tooling used for compression	Punch and dies are procured from approved vendor with MOC of OHNS (Oil harden non shrinkage steel), and HCHC (high carbon and High Chromium). Each Punch is qualified before used and usage and cleaning log is maintained and are requalified on early basis or after defined usage period.	**Data show very low EI risk**

Description	Control	Risk
	SOP is in place for cleaning of punches and dies.	

5. UTILITIES:

The general GMP policies, processes and procedures ensure that the contribution of elemental impurities to drug products is low.

5.1 Water:

Purified water complying with Pharmacopoeial claim, BP/USP is used for manufacturing of product and cleaning of equipments & accessories used for manufacturing of product.

Purified water is generated using potable water complying with the drinking water standards and same is evaluated through testing as per specification on regular basis.

Purified water is generated using RO, DM & Ultra-filtration generation system and stored in storage tank of MOC SS 316L. Purified Water is distributed using a sanitary distribution loop of MOC SS 316L at ambient temperature. The purified water distribution loop is always maintained at positive pressure.
The Ultraviolet sanitization system is provided at the start of distribution loop immediately after the sanitary distribution pump.

The return of the loop is provided with the spray ball with 360° coverage. The distribution system is provided with the conductivity meters / TOC meters / controllers coupled with the recirculation system. Return header consisting of Flow Transmitter, TOC Sensor, Temperature element and Temperature transmitter and Conductivity sensor with Conductivity transmitter, Pressure Indicator.

Purified Water loop is integrated with an automatic hot water sanitization process with the help of steam supplied at PW tank. The sanitization frequency is once in week for 60 minute at 80ºC.
All the wetted parts are made of SS 316L. All the gaskets are made of inert materials like Silicone.

The entire system is designed to produce and distribute Purified Water meeting chemical specifications laid down in USP / B.P. monograph with conductivity not more than 1.3 µS/cm and return water flow velocity at the return of the loop is maintained more than 1.0m/sec, and TOC as NMT 500 ppb.
The Purified water system is controlled and monitored continuously through a PLC for critical parameters like conductivity, TOC and return velocity.

The quality of purified water is tested on daily basis as per specification .

As purified water produced under GMP controls are used for manufacturing and cleaning of equipment and accessories. Use of compendia grade purified water reduces the potential contribution of elemental impurities.

Data show very low EI risk

5.2 Compressed Air

Air compressors are designed to produce compressed air at 7.0 bar pressure and are catered for use in utility, service and process areas.
Compressed air is generated from ambient air and air compressor is passed through air drier for getting moisture free air.
The compressed air is passed through a series of filters, 40 micron, 20 micron, 5 micron, 1.0 micron and finally it is provided to the process area through terminal 0.2 micron filter.
The compressed air system has been qualified against chemical and microbial limit.

Data show very low EI risk

5.3 Air

The HVAC is designed to maintain area classification as class 100,000 (Grade D) by providing terminal high-efficiency particulate air (HEPA) filters of 0.3 µ Rating and 99.97% Efficiency.
Validation is done to confirm the area classification and verification is done on early basis to ensure compliance.

The Air Handling Systems are designed to maintain the temperature between 15- 25°C and humidity between 40 to 60% RH in the production area.
The positioning of supply and extract grilles provides effective room flushing. Low-level return air grilles provided in the area.

The areas of different criticality levels are separated with minimum 15-pascal pressure differential. The air flows from production corridor to the processing areas. The processing areas have been provided with minimum 20 air changes per hour. The air from the processing area is sucked through the low level return risers fitted with 20 µ filters and fed back to the Air Handling unit.
Airlocks are provided as appropriate to maintain pressure cascade systems and also to limit cross-contamination

Dust extractors are provided at suitable points where dust is generated. Such dust is immediately extracted and removed from the working environment through the dust extraction system.
Dust extraction ducting is designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting.
Dust extraction systems are interlocked to the air-handling systems to prevent failure to interlock fans could result in pressure cascade imbalances.

Planned preventive maintenance programme, procedures and records for the HVAC system is maintained and records are kept for a sufficient length of time.

Air quality is monitored through GMPs controls hence no specific assessment is therefore generally required. Air is not likely to present a substantive risk;

Data show very low EI risk

Section: B- Following elements to be evaluated during initial Risk assessment. (Elements to be considered in risk assessment as per ICH Q3D)

Route of administration	Recommended class of elements	Elements
Oral	Class 1	Cd and Pb
	Class 2A	Ni
	Class 2B	#Not applicable
	Class 3	#Not applicable

As per ICH Q3D Class 3 elemental impurities which are not intentionally added need not to be considered for further risk assessment.

Section C: Based on section A and section B of drug product following total elements consider for risk assessment.

Components	Intentionally added	Potential elemental impurities with a relatively high abundance and/ or are impurities in Excipients	Potential Elemental impurities from manufacturing equipment	Potential Elemental impurities from container closure system	Target elements*
Magnesium Stearate	Information Not available	Pb, Cd, Ni	Information Not Available	Not Available	Cd, Pb & Ni
Povidone K-30	Information Not available	Pb	Information Not available	Not Available	
Sodium Starch Glycollate	Information Not available	Ni	Information Not Available	Not Available	
Pre-gelatinized Starch	Information Not available	Fe	Information Not Available	Not Available	
Maize Starch	Information Not available	Fe	Information Not available	Not Available	

* As per ICH Q3D Class 1 elemental impurities which are not intentionally added need not to be considered for further risk assessment.

Section D: Risk assessment as per Option -1 (ICH Q3D)

Maximum Daily dose: 8 Tablets (4.0 g)
Maximum Daily intake of components of Drug Product

S.No.	Components	Daily intake (g)- a	Max Daily intake (g)-b
1.	Paracetamol BP	0.500	4.00
2.	Pre-gelatinized Starch	0.0175	0.52
3.	Maize Starch	0.0450	0.0189
4.	Povidone (K-30)	0.0080	1.000
5.	Sodium Starch Glycollate (Type A)	0.00517	0.200
6.	Magnesium Stearate (Ligamed MF 2V)	0.00433	0.024
	Drug product	**0.580**	**5.7629**

Maximum daily intake of Drug product: 5.7629 gm

Calculation for Identified Permitted Elemental Impurities as per ICH Q3D Option 1:

For maximum permitted concentration (µg/g) = $\frac{\text{PDE µg / day}}{\text{Daily amount of drug product g / day}}$

Element	Pb	Cd	Ni
PDE µg/day	5	5	600
Daily amount of drug product g/day	10		
Maximum permitted concentration (µg/g)	**0.5**	**0.5**	**60**

Permitted concentration for Product from above table
(Assuming uniform concentration and 10 gm daily intake)

Component	Max. daily intake (g) (b)	Maximum Permitted concentration level – (c)			For Maximum daily intake in each component (b×c)		
		Pb	Cd	Ni	Pb	Cd	Ni
Paracetamol	4.0	0.5	0.5	60	2.0000	2.0000	240.000
Pre-gelatinized Starch	0.52	0.5	0.5	60	0.2600	0.2600	31.200
Maize Starch	0.0189	0.5	0.5	60	0.00945	0.00945	1.1340
Povidone (K-30)	1.000	0.5	0.5	60	0.5000	0.5000	60.000
Sodium Starch Glycollate (Type A)	0.200	0.5	0.5	60	0.1000	0.1000	12.0000
Magnesium Stearate (Ligamed MF 2V)	0.024	0.5	0.5	60	0.0120	0.0120	1.4400
Maximum Daily Intake (µg)					**2.88145**	**2.88145**	**345.774**
PDE (µg/day)					5	5	600

Maximum Daily Intake: Maximum Permitted concentration (c) x Maximum daily intake of Drug component (b)

Conclusion: This calculation demonstrates no elemental impurities exceed their PDE's. Thus, if these concentrations in each component are not exceeded, the drug product is assured to not exceed the PDE's for each identified Elemental impurities.

Section E: **Risk assessment as per Option -2a (ICH Q3D)**
Maximum Daily intake of components of Drug Product

S.No.	Components	Daily intake (g)- a	Max Daily intake (g)-b
1.	Paracetamol	0.500	4.0
2.	Pre-gelatinized Starch	0.0175	0.52
3.	Maize Starch	0.0450	0.0189
4.	Povidone (K-30)	0.0080	1.00
5.	Sodium Starch Glycollate (Type A)	0.00517	0.200
6.	Magnesium Stearate (Ligamed MF 2V)	0.00433	0.024
	Drug product	**0.580**	**5.7629**

Maximum daily intake of Drug product: 5.7629 gm

Calculation for Identified Permitted Elemental Impurities as per ICH Q3D Option 2a:

For maximum permitted concentration (µg/g) = $\frac{\text{PDE µg / day}}{\text{Daily amount of drug product g / day}}$

Element	Pb	Cd	Ni
PDE µg/day	5	5	600
Daily amount of drug product g/day	**5.7629**		
Maximum permitted concentration (µg/g)	**0.87**	**0.87**	**104.11**

Calculation for maximum Permitted concentration in Product (Assuming uniform concentration in product with a specific daily intake)

Component	Max. daily intake (g) (b)	Maximum Permitted concentration level – (c)			For Maximum daily intake in each component (b×c)		
		Pb	Cd	Ni	Pb	Cd	Ni
Paracetamol	4.0	0.87	0.87	101.44	3.48	3.48	405.760
Pre-gelatinized Starch	0.52	0.87	0.87	101.44	0.4524	0.4524	52.7488
Maize Starch	0.0189	0.87	0.87	101.44	0.01644	0.0164	1.9172
Povidone (K-30)	1.00	0.87	0.87	101.44	0.870	0.870	101.44
Sodium Starch Glycollate (Type A)	0.200	0.87	0.87	101.44	0.174	0.174	20.288
Magnesium Stearate (Ligamed MF 2V)	0.024	0.87	0.87	101.44	0.0208	0.0208	2.4345
Maximum Daily Intake (µg)					**5.01364**	**5.0136**	**584.588**
PDE (µg/day)					5	5	600

Maximum Daily Intake: Maximum Permitted concentration (c) **X** Maximum daily intake of component (b)

Conclusion:

Based on review of risk assessment for option 1 and option 2a , class 1 and 2A elemental impurities are identified potential impurities for drug product “Paracetamol 500 mg Tablet” .These calculation demonstrates no elemental impurities exceed their PDE’s. Thus, if these concentrations in each component are not exceeded, the drug product is assured to not exceed the PDE’s for each identified Elemental impurities.

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