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Control of Elemental Impurities A Canadian Pharmaceutical Generic Company Perspective

PQRI/USP Workshop
November , 2017
Rockville MD

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Outline

- Road Map To Compliance
- Governance
- Approach to identification, analysis, evaluation, and Control Strategy
- Life Cycle Concept applied to EI
- Some points that still need clarification

Implementation dates

FDA	Health Canada	EMA
June 1, 2016 – new submissions (ANDA) January 1, 2018 – marketed products	New submissions (ANDS) December 31st 2016 Submission of a new supplemental (A)NDS for a change to a marketed product December 31st, 2016 January 1, 2018 – marketed products	June 1, 2016 – new submissions December 1, 2017 – marketed products

Road Map to EI Control

2013 Program design; start

- Vendor Data Collection
- Equipment purchase, installation, qualification

Jan 2016

- Define project governance
- Develop Project outline
- Project teams
- Continue vendor data collection

June 2016

- Finalize, Approve Protocol
- Project Manager
- Project Governance
- Team Execution (per site)

June 2016

- All filings include EI
- Focus on execution for marketed products

Jan 2018

- High risk and high priority product assessments completed
- Specification updates initiated
- Controls in place assuring Q3D compliance before product release
- Lifecycle management processes established

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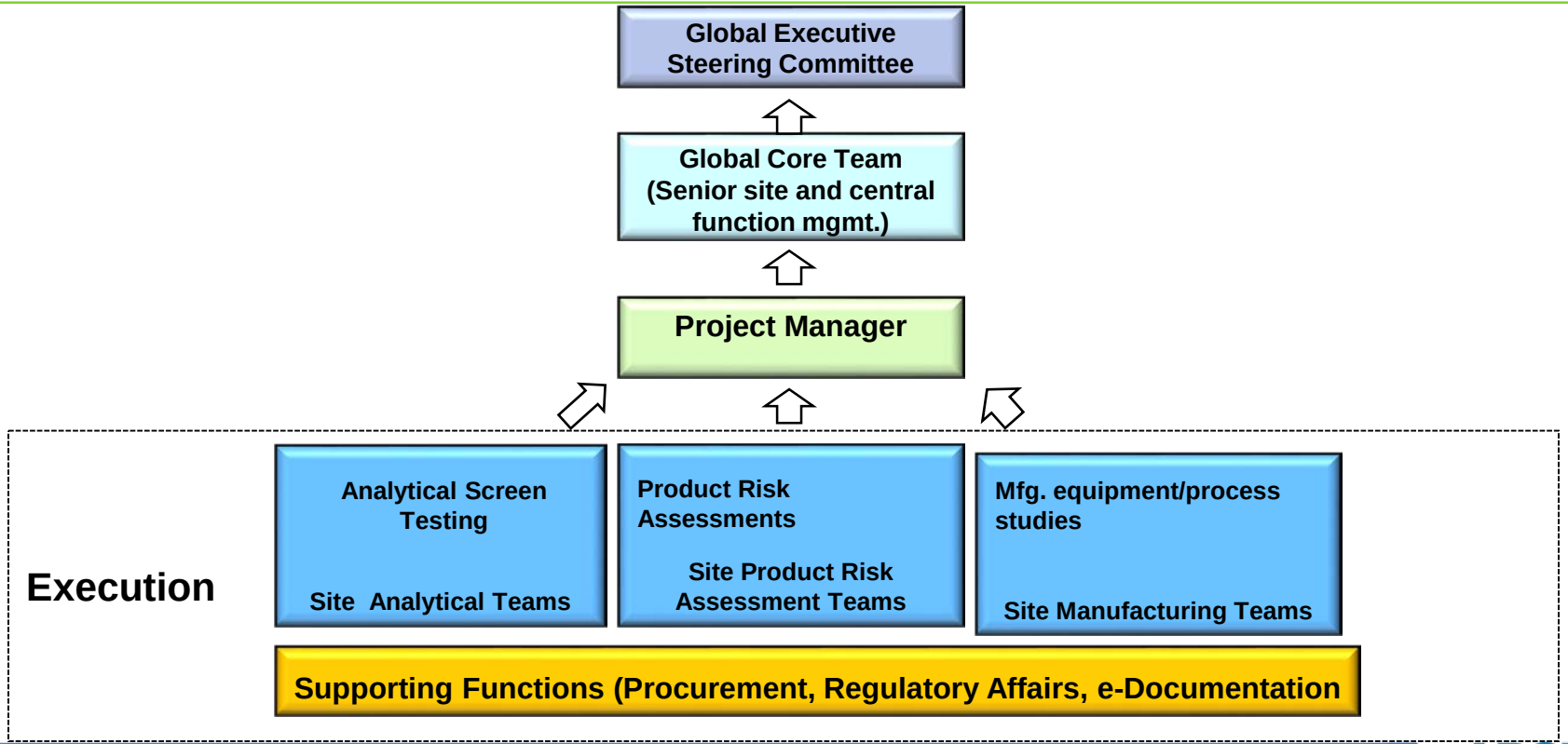
Governance


Global Executive Steering Committee
Global Core Team (Senior site and central function mgmt.)
Project Manager
Execution
Analytical Screen Testing
Site Analytical Teams
Product Risk Assessments
Site Product Risk Assessment Teams
Mfg. equipment/process studies
Site Manufacturing Teams
Supporting Functions (Procurement, Regulatory Affairs, e-Documentation

Implement a control strategy to limit elemental impurities in the drug product

Identify

- Identify known and potential sources of elemental impurities that may find their way into the drug product

Analyze

- Determine the probability of observance of a particular elemental impurity in the drug product

Evaluate

- Compare the observed or predicted levels of elemental impurities with the established PDE

Control

- Document and implement a control strategy to limit elemental impurities in the drug product

Implement a control strategy to limit elemental impurities in the drug product

Identify metals that can be present (class 1 included by default)

- Components
- (solvents)
- Manufacturing Equipment
- Packaging materials

Calculate the acceptable metal impurity limits based on PDE using calculation options 1-3

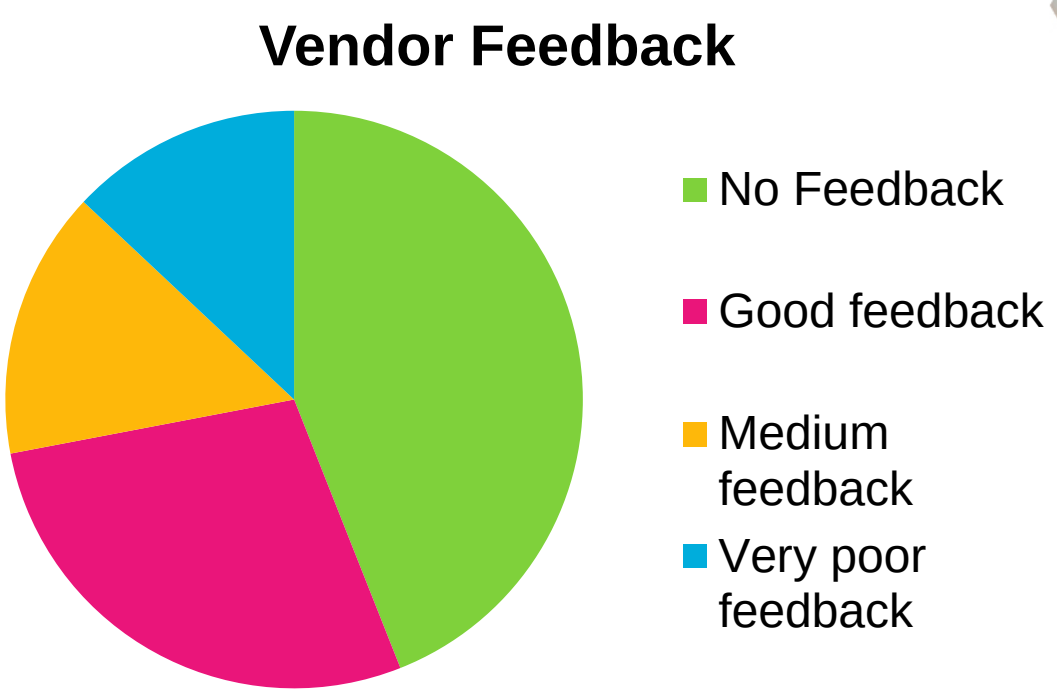
- Evaluate and compare levels observed with PDE

Control strategy

- Projected levels found below the Control Threshold
  - Document in risk assessment
- Projected Levels exceed Control Threshold or too much variability (below the PDE)
  - include in specifications (routine control)
  - Exceed PDE- investigate source and develop adequate Control Strategy*

Identify- Components API:

- Vendor information:- verify
- No vendor input or input inadequate- full metal scan
    - Commitment to provide by December 2017



Example of good feedback

Worst case

Based on option 1

Actual batch data

Elemental Impurity	Parenteral specification	Target limit[a]	Batch 10401620033	Batch 10401620034	Batch 10401620035
Ag	1	0.30	<0.09	<0.09	<0.09
Al [b]	150	45	<13.5	<13.5	<13.5
As	1.5	0.45	<0.14	<0.14	<0.14
Cd	0.2	0.06	<0.02	<0.02	<0.02
Co	0.5	0.15	<0.05	<0.05	<0.05
Cr	110	33	<9.9	<9.9	<9.9
Cu	30	9	<2.7	<2.7	<2.7
Fe [b]	150	45	<13.5	<13.5	<13.5
Hg	0.3	0.09	<0.03	<0.03	<0.03
Mn [b]	150	45	<13.5	<13.5	<13.5
Mo	150	45	<13.5	<13.5	<13.5
Ni	2	0.60	<0.18	<0.18	<0.18
Pb	0.5	0.15	<0.05	<0.05	<0.05
Sb	9	2.7	<0.81	<0.81	<0.81
Se	8	2.4	<0.72	<0.72	<0.72
Ti [b]	150	45	<13.5	<13.5	<13.5
V	1	0.30	<0.09	<0.09	<0.09
W [b]	150	45	<13.5	<13.5	<13.5
Zn [b]	150	45	<13.5	<13.5	<13.5
Zr [b]	150	45	<13.5	<13.5	<13.5

[a] 30% of the parenteral specification

[b] These elements are not described in ICH Q3D guideline and are considered as of low toxicological concern. It is taken as specification the value of the element less restrictive (Molybdenum: 150ppm)

Reports of Limited usefulness:

Element	ICH Q3D Class	Intentionally Added (Yes/No)	Element considered for Risk Management (Yes/No)	Results observed
Cadmium	1	No	Yes	Absent
Lead	1	No	Yes	Absent
Arsenic	1	No	Yes	Absent
Mercury	1	No	Yes	Absent
Cobalt	2A	No	Yes	Absent
Vanadium	2A	No	Yes	Absent
Nickel	2A	No	Yes	Absent
Thallium	2B	No	No	N/A
Gold	2B	No	No	N/A
Palladium	2B	No	No	N/A
Iridium	2B	No	No	N/A
Osmium	2B	No	No	N/A
Rhodium	2B	No	No	N/A
Ruthenium	2B	No	No	N/A
Selenium	2B	No	No	N/A
Silver	2B	No	No	N/A
Platinum	2B	No	No	N/A
Lithium	3	No	No	N/A
Antimony	3	No	No	N/A
Barium	3	No	No	N/A
Molybdenum	3	No	No	N/A
Copper	3	No	No	N/A
Tin	3	No	No	N/A
Chromium	3	No	No	N/A

Reports on the 7 and provides information on class 2B

No information re: number of batches tested

No numerical information

No clarity re: route of administration

Helps with understanding relevance

[1] 'Absent' signifies that the levels are observed 30% below the ICH Q3D Option 1 limit for the individual element or the maximum observed levels for individual element is reported as 'Maximum level ≤ 'X' ppm.

Reports of No usefulness:

Elemental Impurity	Class	Element Intentionally Added? (Y/N)	Likely to be Present (Y/N)	ICH Q3D Option 1 Limit (µg/g)	Meets Option 1 Limit		If available, please provide analytical test results (ug/g)	Analytical Method Used (and Limit of Detection if Available)	Comments including Testing Plan (frequency)
Arsenic (As)	1			1.5 (O)	Yes ☐	No ☐			
				1.5 (P)	Yes ☐	No ☐			
				0.2 (I)	Yes ☐	No ☐			
Cadmium (Cd)	1			0.5 (O)	Yes ☐	No ☐			
				0.2 (P)	Yes ☐	No ☐			
				0.2 (I)	Yes ☐	No ☐			

NOT APPLICABLE

Elemental Impurity	Class	Element Intentionally Added? (Y/N)	Likely to be Present (Y/N)	ICH Q3D Option 1 Limit (µg/g)	Meets Option 1 Limit		If available, please provide analytical test results (ug/g)	Analytical Method Used (and Limit of Detection if Available)	Comments including Testing Plan (frequency)
Mercury (Hg)	1			3 (O)	Yes ☐	No ☐			
				0.3 (P)	Yes ☐	No ☐			
				0.1 (I)	Yes ☐	No ☐			
Lead (Pb)	1			0.5 (O)	Yes ☐	No ☐			
				0.5 (P)	Yes ☐	No ☐			
				0.5 (I)	Yes ☐	No ☐			
Cobalt (Co)	2A			5 (O)	Yes ☐	No ☐			
				0.5 (P)	Yes ☐	No ☐			
				0.3 (I)	Yes ☐	No ☐			
Vanadium (V)	2A			10 (O)	Yes ☐	No ☐			
				1 (P)	Yes ☐	No ☐			
				0.1 (I)	Yes ☐	No ☐			
Nickel (Ni)	2A			20 (O)	Yes ☐	No ☐			
				2 (P)	Yes ☐	No ☐			
				0.5 (I)	Yes ☐	No ☐			

NOT APPLICABLE

Thank you for NOTHING!!!

ICH Q3D Guideline for Elemental Impurities, Dec. 16, 2014. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf
*Always include Class 1 and Class 2A in assessment, as outlined in the document above.

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Identify; Components, Excipients

- **Vendor input**
- **Prior Knowledge (literature, publications)**
- **Internal screening**
  - **Low risk (vegetable and synthetic)**
    - For each of the excipients used we established the maximum daily intake
    - So far, none exceed 10g/day
    - Screening is done against CT , option 1.
  - **High risk (minerals, mined materials)**
    - Several do not meet option 1 limits
    - These are considered to be included on the CofA for routine testing with an acceptance criteria PDE based

Identify: Manufacturing Equipment

- Evaluate unit operations with respect to probability of contamination
  - Low risk
  - High risk (temperature, friction, solution,)
- Equipment inventory and composition
  - Typically, test for (Class 1 and 2A; + 2B if applicable)

Identify: Manufacturing Equipment

Korsch PH 800 : Collect samples of 100g after compression for each of the tooling used																					
Elements to be Tested 'If not intentionally added'							Elements to be Tested 'if intentionally added' (Elements contained in Product Contact Surface of the Equipment)														
Cd	Pb	As	Hg	Co	V	Ni	Tl	Au	Pd	Ir	Os	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
✓	✓	✓	✓	✓	✓	✓												✓		✓	✓	✓	✓

Encapsulators																							
Elements to be Tested 'If not intentionally added'							Elements to be Tested 'if intentionally added' (Elements contained in Product Contact Surface of the Equipment)																
Cd	Pb	As	Hg	Co	V	Ni	Tl	Au	Pd	Ir	Os	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
✓	✓	✓	✓	✓	✓	✓														✓	✓		✓

For Tablet Products																							
Elements to be Tested 'If not intentionally added'							Elements to be Tested 'if intentionally added' (Elements contained in Product Contact Surface of the Equipment)																
Cd	Pb	As	Hg	Co	V	Ni	Tl	Au	Pd	Ir	Os	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
✓	✓	✓	✓	✓	✓	✓												✓		✓	✓	✓	✓

For Capsule Products																							
Elements to be Tested 'If not intentionally added'							Elements to be Tested 'if intentionally added' (Elements contained in Product Contact Surface of the Equipment)																
Cd	Pb	As	Hg	Co	V	Ni	Tl	Au	Pd	Ir	Os	Rh	Ru	Se	Ag	Pt	Li	Sb	Ba	Mo	Cu	Sn	Cr
✓	✓	✓	✓	✓	✓	✓														✓	✓		✓

Identify Packaging

- **For solid dose low risk**
- **For liquids/solutions high to medium risk**
  - Prior Knowledge (literature, publications, Compendia)
  - Vendor information- no feedback

Analysis :ICH Q3D limit options

Option	Components	Intermediates	Product	Benefits	Negatives
1	Risk assessed/tested assuming common concentrations and 10 grams daily intake	Risk assessed to confirm contamination (or the lack thereof) from most aggressive processing steps	No need for product testing	Facilitates risk assessment; i.e. components can be mixed in any proportions (<10g/day) Can significantly reduced routine testing	High Initial investment Relies heavily of vendor's input
2a	Risk assessed/tested assuming common concentrations for a product with a specified daily intake	Risk assessed to confirm contamination (or the lack thereof) from most aggressive processing steps	No need for product testing	Same as above	Same as above
2b	Risk assessed/tested assuming uncommon component concentrations set at levels that would ensure the PDE is met in the final product	Risk assessed to confirm contamination (or the lack thereof) from most aggressive processing steps	No need for product testing	Facilitates risk assessment, but need to know the composition of the drug product and have additional knowledge regarding the content of each elemental impurity in the components of the drug product.	It can be Product Specific
3	Knowledge is limited	No knowledge available	A must	Limited knowledge of components; equipment contaminants have to be included in drug product testing	Batch tested at release, Strongly discouraged by regulators

Analyze: Analytical Procedure (s)

- Analytical Procedure- USP <233>
  - Validated* for all class 1 and class 2A (system)
  - Verification (run including accuracy (recovery)) material/product specific with protocol defined acceptance criteria (USP) to accept/reject results

* *expanded*

Analytical Procedure Validation Scheme

MV Parameters	USP <233>	USP <233> Alternate Limit Test	USP <233> Alternate Quanti-tative Test	EQ. Manuf's Recommen dation	FDA Food	General	Verification
Drift: NMT 20%	x	x	x	x			x
Recovery: 70-150%			x	x			x
Stability Check (std 0.25J) 6 runs							
Precision: 6 Prep at J		x	x	x		x	
Intermediate Precision(Ruggedness)			x	x		x	
Calibration blank					x	x	x
Std1 (0.25J)						x	x
Std 2 (0.5J)	x		x	x	x	x	x
Std (0.8J)		x					
Spike 1 (0.25J)						x	x
Spike 2 (0.5J)							
Spike 3 (1.5J)					x	x	x
Std (1 J)		x	x				
Std 3 (1.5J)	x		x	x	x	x	x
Check-1 Std 3 (1.5J)					x	x	x
Reagent Blank (Matched Matrix)	x				x	x	x
Sample 1,	x					x	x
Run any subsequent samples							x
Check Std every 10 sample						x	x
Specificity							

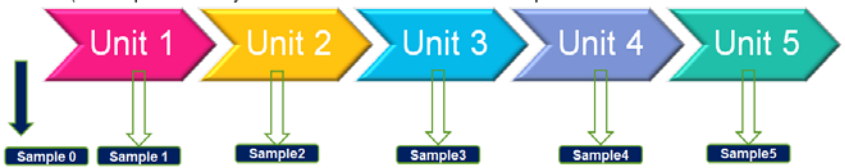
Testing

- API
  - Verification: 3-5 lots
  - Full assessment: 3-5 lots
- Excipients:
  - Low risk: 3-5 lots
  - High risk: as needed (NLT 5)
- Manufacturing equipment: varies
- Packaging for liquids, solutions:
  - Included in the stability program

Analyze: Risk Evaluation for metal impurity contamination for Solid Dose

Low risk Analysis

1. Test Sample "0" and sample "5". If results indicate that there is no increase in metal impurity content stop testing. This will support conclusion of no contamination for unit 1 to unit 5
2. If results show increase in one or two of the metal impurities continue testing backwards up to the sample where result show no change.
3. Evaluate in increase with respect to significance and adopt appropriate Control Strategy. (this step if necessary will need to be further assessed for impact.

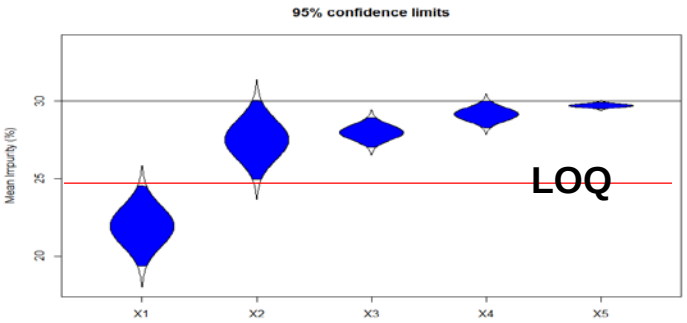


High risk Analysis

- Unit operations of high risk are evaluated individually (heat, high shire, temperature)

1. Test input and output sample. If results indicate that there is no increase in metal impurity content will support conclusion of no contamination
2. Evaluate in increase (if) with respect to significance and adopt appropriate Control Strategy. (this step if necessary will need to be further assessed for impact)

Control Strategy: All levels <30% of PDE, no routine testing necessary
95% confidence



MDI	%	PDE ppm	CT (ppm)
1g or less	45	5ppm	1.5
1-2g	68	2.5ppm	0.75
2-3g	82	1.7ppm	0.51
3-4g	87	1.25ppm	0.38
4-5g	90	1ppm	0.3
10g	100	0.5ppm	0.15

- 1-sided 95% CI for the mean:

$$(-\infty, t_{\alpha,n-1} * SEM)$$

S.E.M*.: $\mathrm{Var}(\bar{X}) = \frac{Var(Batch)}{n_{batch}} + \frac{Var(Analytical)}{n_{batch} * n_{rep}}$

Control threshold

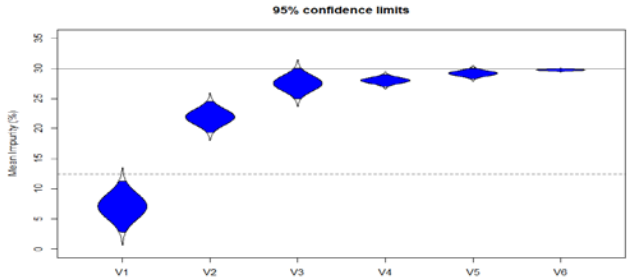
- Guidance 95% confidence
  - Sample to sample
  - Analytical procedure (MU)- SD
  - How far from the threshold
    - (limit test at PDE?)

- Increasing n_{batch} has a direct effect on lowering total variability of $\bar{X}$
- Increasing n_{rep} has an effect only on one portion of the total variability of $\bar{X}$

- * Standard Error of the Mean

Control Strategy: All levels <30% of PDE, no routine testing necessary
95% confidence

5g/day



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- Control threshold
  - Guidance 95% confidence
    - Sample to sample
    - Analytical procedure (MU)- SD
    - How far from the threshold
      - (limit test at PDE?)
- Increasing n_{batch} has a direct effect on lowering total variability of $\bar{X}$
- Increasing n_{rep} has an effect only on one portion of the total variability of $\bar{X}$

* Standard Error of the Mean

Control Strategy- summary

- Essentially for >90% materials (samples; API, Excipients, Product, etc.) meet the “Below LOQ “ criteria therefore no further testing or control is necessary
- Remaining 10%
  - Typically antibiotics
  - Products with wide range of strengths (ug to mg)
  - Some minerals Eg. (CaCo3)
- These are being assessed and decisions made on case by case basis to ensure PDE is met

Control Strategy justification*

(this table needs to be created for each product to demonstrate compliance)

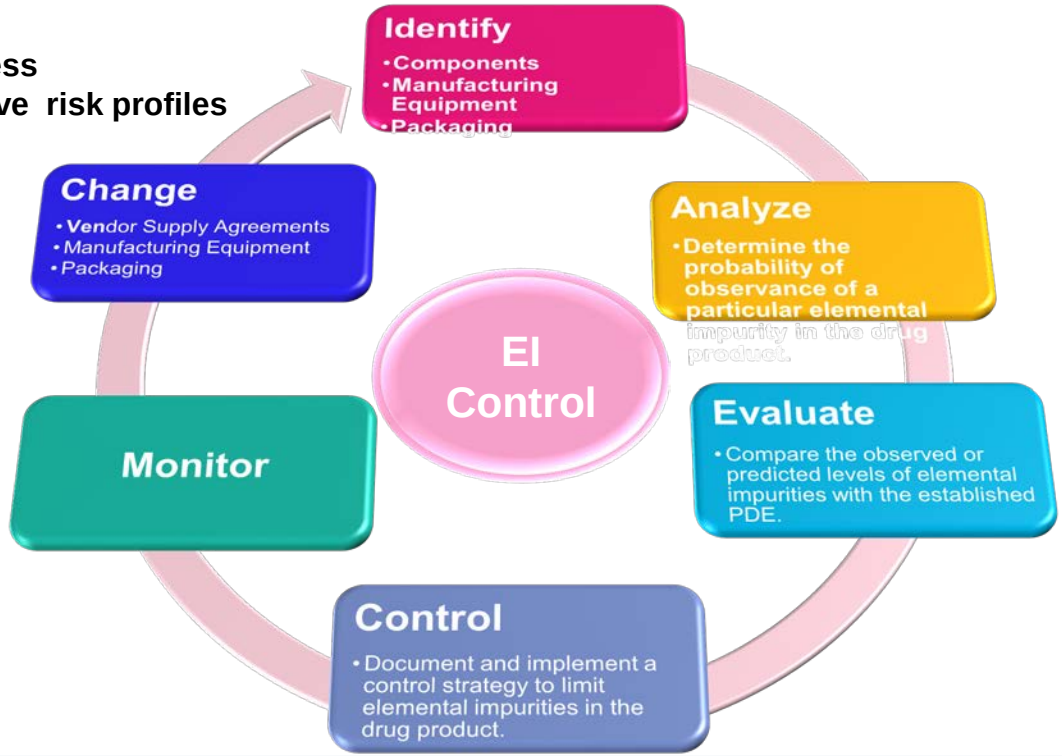
Table A4.1. Calculation of concentrations assuming uniform concentrations in any product whose mass does not exceed 10 grams.

Component	Daily Intake (milligrams)	Maximum Permitted Concentration (ug/g)						
		Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	200	0.5	1.5	0.5	5	10	10	200
MCC	1100	0.5	1.5	0.5	5	10	10	200
Lactose	450	0.5	1.5	0.5	5	10	10	200
Ca Phosphate	350	0.5	1.5	0.5	5	10	10	200
Crospovidone	265	0.5	1.5	0.5	5	10	10	200
Mg stearate	35	0.5	1.5	0.5	5	10	10	200
HPMC	60	0.5	1.5	0.5	5	10	10	200
Titanium Dioxide	25	0.5	1.5	0.5	5	10	10	200
Iron Oxide	15	0.5	1.5	0.5	5	10	10	200
Maximum Daily Intake (ug)	**2500 mg**	**1.25**	**3.75**	**1.25**	**12.5**	**25**	**25**	**500**
PDE (ug/ day)	**PDE (ug/day)**	**5**	**15**	**5**	**50**	**100**	**100**	**2000**

Control Strategy: All levels <30% of PDE, not routine testing necessary

Control of EI linked to the Lifecycle concept

An ongoing risk review process is initiated once the respective risk profiles have been created
Clear quality agreement (ICH 9, 10) and good relationship with the vendor, manufacturer's GMP site is critical.



Risk Evaluation for metal impurity contamination - Change

- Feed back from manufactures
  - Supplier agreements
  - Equipment equivalency; Equipment that from a “process equivalency” perspective are determined as interchangeable. Are they also interchangeable from ICH Q3 D
- Changes Manufacturing Process
- Site Changes

Up to date experience with Filings in Canada

- ANDS
  - approvals- no additional questions re: EI
  - Deficiency responses (filings before June 2016)- currently under review
- Some supplemental filings under review
- So far no comments, observations or deficiencies received

RD to Commercial

Once all process path evaluations are complete, it will be incorporated in the risk assessment at the submission time

Currently, is incorporated in the scale up/process validation

Some items that require further clarification / attention

- USP Monograph or ICH Q3D? (Calcium Carbonate As, 3ppm, 20g/day, PDE 15ug, USP 60ug)
- Class 2B- catalysts tend to be on the CofA and tested routinely for years now
  - Acceptance criteria at times a fraction of the PDE (below CT)
  - Historical data available on several, at times hundreds of batches
  - According to ICH Q3D these should not be routinely monitored
  - Is there a simplified regulatory pathway to accomplish this?
- Dialog with API and Excipient vendors
  - Supply agreements, Supplier driven changes:
    - Clarity regarding changes that can affect the EI
  - Risk Assessment documentation- to be available for audit

Acknowledgements

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Thank you for your attention

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