ICH Q3D Industry Perspective and Consequences

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Multiple stakeholders; **one objective.**

International Pharmaceutical Excipients Council

Collaborative solutions for excipient industry stakeholders

Disclaimer

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ICH Q3D

Defines a science and risk based assessment process to identify, evaluate and define controls to limit elemental impurities in drug products:

- **Identify:** Known or suspected sources of elemental impurities with the potential to be included in the finished product
- **Analyze:** Determine the probability of elemental impurity occurrence
- **Evaluate:**Compare actual or predicted elemental impurity levels with PDE's
- **Control:** Develop, document and implement a control strategy

FDA – Elemental Impurities in Drug Products Guidance for Industry August 2020

Manufacturers should then evaluate each elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the established PDE. If the risk assessment fails to show that an elemental impurity level is consistently less than the control threshold (defined as being 30 percent of the established PDE in the drug product), additional controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product. These additional controls could be included as in-process controls or in the specifications of the drug product or components.

Guideline

The PDEs DO NOT apply to excipients or APIs

Excipients and APIs MAY have levels HIGHER than what is in the table

it is the final formulation that MUST comply

An excipient may have 15 ppm of Pb: it is < 10% of the formulation – the level of Pb = FAR < PDE

Then Letters Like These Show Up

The Certificate of Analysis supplied with your product is missing analysis results to demonstrate compliance against the USP Limits of:

- Cd < 0.5 ug/g
- Pb < 0.5 ug/g
- As < 1.5 ug/g
- Hg < 3 ug/g

Reporting of these values is a requirement of the US FDA in our drug product application.

Which came from ICH Q3D using a10 gram dose to show concentration in finished product and option to show each component alone would meet

Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1

The values presented in this table represent permitted concentrations in micrograms per gram for elemental impurities in drug products, drug substances and excipients. These concentration limits are intended to be used when Option 1 is selected to assess the elemental impurity content in drug products with daily doses of not more than 10 grams per day. The numbers in this table are based on Table A.2.1.

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1

We Reply with our Standard Statement

Table 1. Typical content of non-intentionally added elements

Class	Element	Not intentionally added elements Typical content [ppm]	Note
Class 1	As	< 0.1	Below detection limit
	Pb	2	
	Cd	< 0.1	Below detection limit
	Hg	< 0.1	Below detection limit
Class 2A	Co	0.3	
	V	2	
	Ni	1	
Class 2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl		No risk assessment required for non-intentionally added elements
Class 3	Ba, Cr, Cu, Li, Mo, Sb, Sn		Oral routes of administration : no risk assessment required for non-intentionally added elements

Also sold into food and feed meeting the FCC limit of 5 ppm for lead (Pb) by HCl acid leach

We Explain

- Testing confirms lead (Pb) in our product is a function of the Pb in the mineral raw material source
- 2015 – 2017 monthly test data in our products typically about ~2 ppm Pb with the highest value of 2.6 ppm and lowest of 0.9 ppm
- Typical uses for free flow/anti caking are 1% level or less.
- For oral dosage of a 10 gram tablet the "summation" option will be well below the PDE
  - 3 µg/g (ppm) X 1 g/100 g tablet X 10 g/day = 0.3 µg/day (out of PDE oral tablet of 5 ug/day)
  - 0.3 µg/day ÷ 10 g/day = 0.03 µg/g (ppm) (concentration in finished product from excipient)
- Our product can be used in a drug product that complies with the USP 40 < 232 > ELEMENTAL IMPURITIES using the "drug product analysis" option or "summation" option

Guideline

Two approaches to risk assessments

- Drug Product Approach
- Component Approach

Gather information about known or potential Elemental Impurities

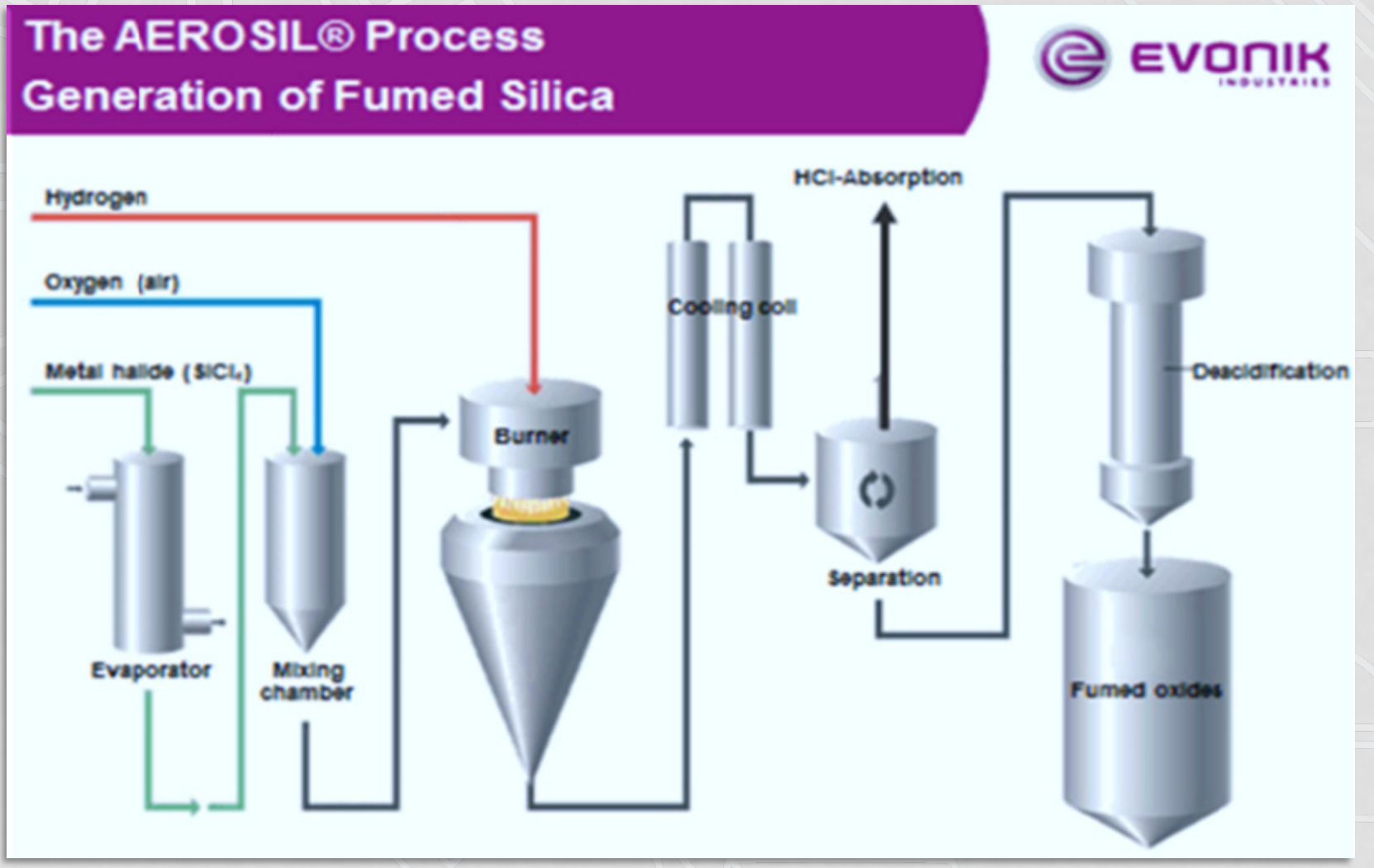
- **Remember NOT all Elemental Impurities need to be considered in the risk assessment**

If levels are ≤ 30% of PDE – no further actions are needed

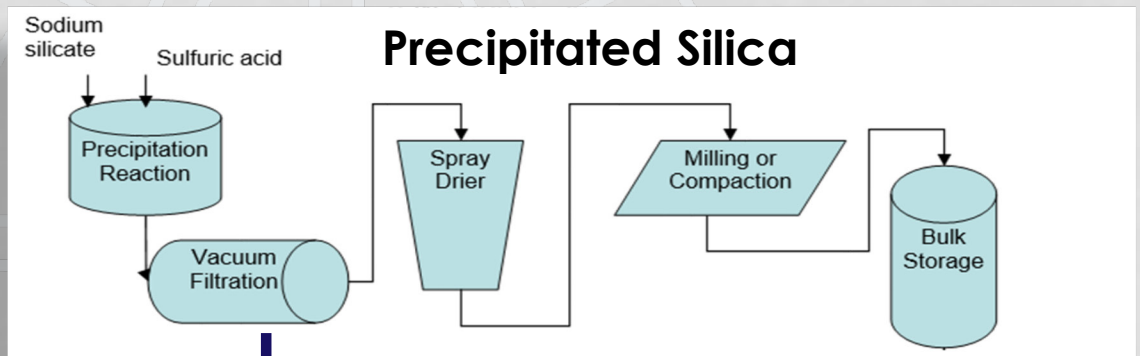
Levels above the threshold **MAY** want to include in control strategy

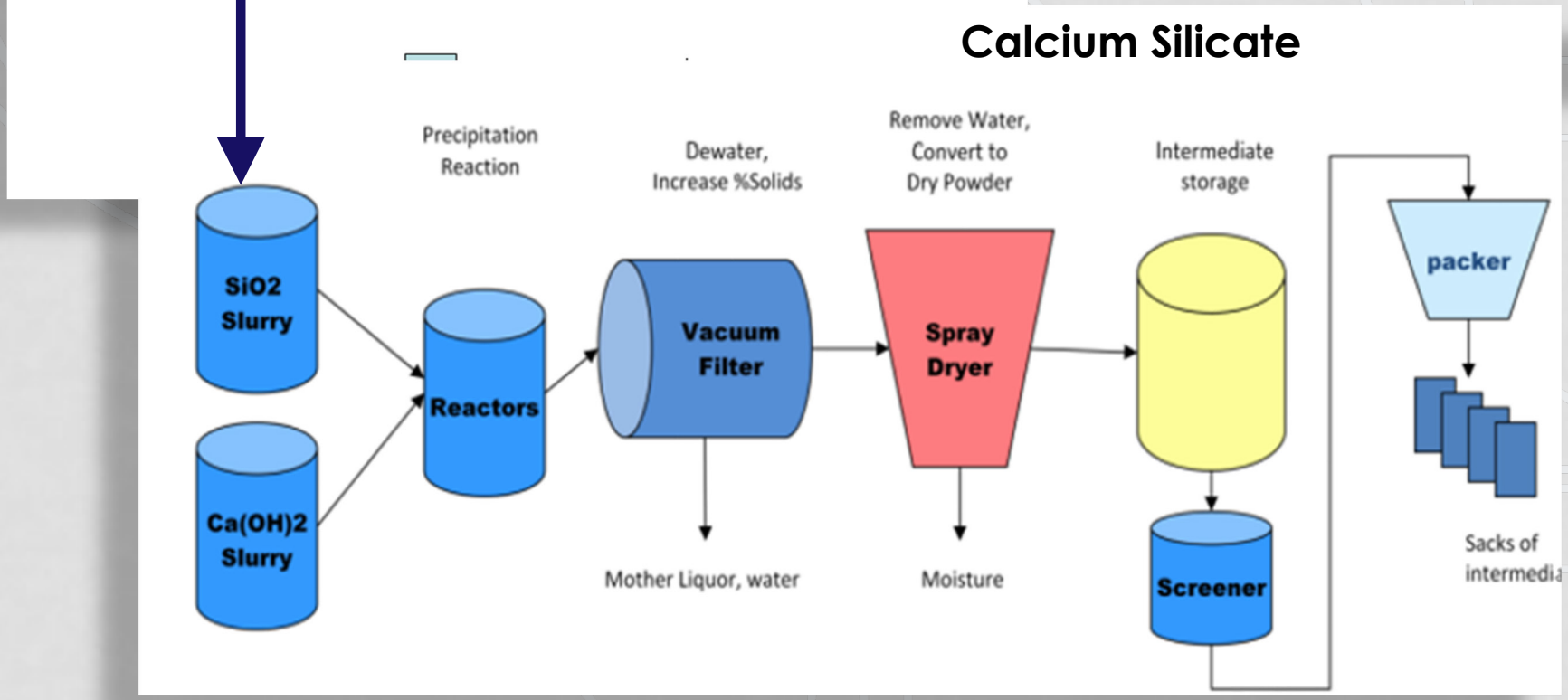
Potential for Presence of Elemental Impurities in Excipients

This Process has no Source for Metals



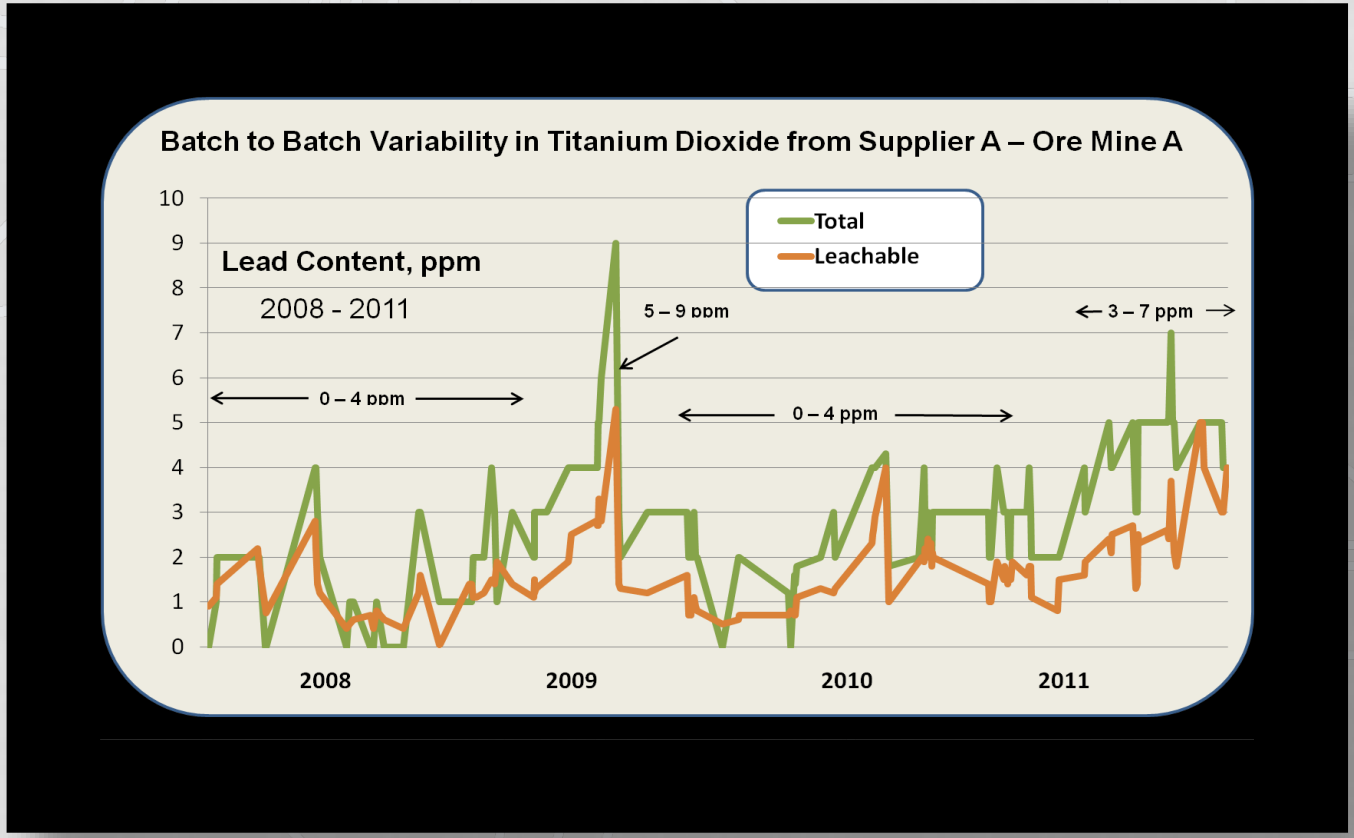
This Process Does





Validated Potential Normal Variation

- Many metal impurities are naturally present (e.g. lead) in **mined excipients** and cannot be further processed out; therefore, it is important to understand the actual levels present
- Normal variation can be expected from **excursions** that occur in the raw material source



Lead is present in Natural Minerals

Total vs. Leached Elemental Impurities in Natural Mineral Absorbants (ppm)								
	Acid Activated Clay		Bentonite		Diatomaceous Earth		Perlite	
	Total	Leached	Total	Leached	Total	Leached	Total	Leached
As	0.9	0.6	1.6	1.2	12.7	2.1	0.4	ND
Pb	14.3	8.70	21.6	9.95	8.0	0.03	14.5	0.28
Cd	0.04	0.01	0.10	0.02	0.08	ND	0.07	ND
Co	0.6	0.1	1.9	1.0	4.8	ND	0.4	ND
Mo	1.0	ND	1.7	1.2	7.7	4.6	1.3	0.1
V	5.2	0.5	9.4	ND	1.0	20.6	ND	ND

Presence of EI Does Not Automatically Equal Risk to Patient

- These excipients, particularly clays, do typically contain the highest content of EI, for instance, Pb
- They DO NOT represent the highest potential risk to the patient in oral dosage when the EI are bound in mineral complexes that are not soluble in the digestive process.
- Vanderbilt Minerals bioavailability studies have shown no increase in EI when consumed to remove toxins from moldy grain

Vanderbilt provides Bioavailability Data

Vanderbilt Contributes Bioavailability Data

Patent Application 20080008763

- Clays used to absorb toxins from moldy grains.
- 3 grams per day dosage in humans.
- no elevated heavy metals during 3 month study in Africa.

TABLE 9

Analysis of non-nutritional minerals in serum samples of study subjects: Baseline levels vs. High Dose of NS at the end of the trial

Minerals	Before Trial	After Trial
Ag (Silver) (µg/L)	0.23 ± 0.03	0.26 ± 0.27
Al (Aluminum) (µg/L)	132.08 ± 71.92	130.17 ± 73.56
As (Arsenic) (µg/L)	8.83 ± 1.45	8.63 ± 1.63

Vanderbilt Chemicals, LLC

Vanderbilt Contributes Bioavailability Data cont'd…

Patent Application 20080008763

TABLE 9-continued

Analysis of non-nutritional minerals in serum samples of study subjects: Baseline levels vs. High Dose of NS at the end of the trial

Minerals	Before Trial	After Trial
Ba (Barium) (µg/L)	80.07 ± 15.23	115.92 ± 32.89*
Be (Beryllium) (µg/L)	1.11 ± 0.06	1.11 ± 0.12
Cd (Cadmium) (µg/L)	0.70 ± 0.38	0.71 ± 0.39
Hg (Mercury) (µg/L)	5.57 ± 0.30	5.60 ± 0.60
Li (Lithium) (µg/L)	22.30 ± 1.15	22.37 ± 2.44
Pb (Lead) (µg/L)	16.13 ± 8.55	15.03 ± 9.25

Vanderbilt Chemicals, LLC

A Minerals Excipient Maker's Perspective, PQRI Elemental Impurity Workshop, November 3, 2017

USP Removed < 231 >

- We updated our CoA System and removed the heavy metals test to align with USP-NF monograph.
- Some customers complained that they had not changed their specifications and still require heavy metals <30 ppm as lead (Pb) to be reported.
- What?? – it is gone from USP and that was the method we used – so is your next request for us to validate our non-USP method for heavy metals?
- We did this change over a year ago and you just now noticed it was missing!

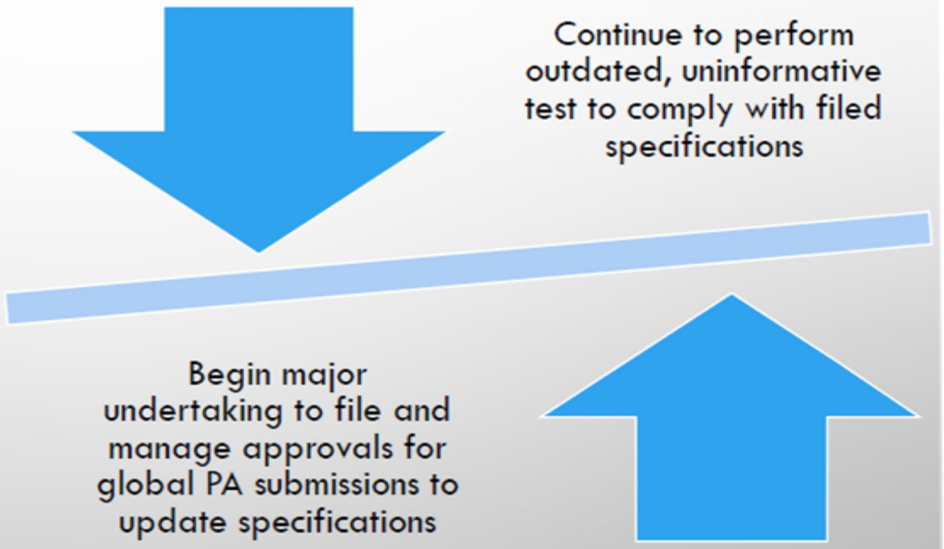
Explanation

ADAPTATION- THE PRESENT AND THE FUTURE

COMPENDIAL CHANGES AND SUPPLIER TESTING (CONT.)

THE REGULATORY QUANDARY:

- Most MOW markets would need prior approval to remove the obsolete <231> from specifications without replacing with another assay
  - Many suppliers notify of intention to <231> testing
  - Some suppliers may not recognize the need to communicate intent because of the obsolete nature of the chapter
- **All license holders are then left with two options:**



From May 2020 NJPQCA presentation by Elisabeth Corbett, Merck

The Reality

- **Adoption is NOT universal**
- Majority of countries outside US/EU/Japan are **NOT** on board
- Retention of heavy metals test still expected

Adding Element Concentration Limits to Monographs for select Excipient

- Why limits for excipients – I thought ICH Q3D intent was to focus on PDE for patient…
- Natural minerals will have variation in trace element compositions as current sources are consumed and new ones found.
- Levels common today may be unattainable tomorrow.
- We could end up with no excipient available that meets the monograph.

Adding Element Concentration Limits to Monographs for select Excipient

- If an elemental impurity is commonly found in an excipient does it need to be in the monograph?
- Already established that
  - drug maker should do the risk assessment to determine controls for finished product
  - The quantity of excipients vary in formulation
  - Elemental impurity levels change over time in excipients made from mineral and plant sources
- Where a substance is marketed as different grades depending on source and elemental impurity levels, having a limit could be helpful – BUT limits should be based on reasonable safe levels and **NOT** point in time measurement of what is currently for sale

THANK YOU