ICH Q3D Guideline

Elemental Impurity Risk Assessment

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ICH Q3D – Basics - Classification of elements

CLASS 1

- There are four elements defined within this class, Arsenic (As), Mercury (Hg), Cadmium (Cd) and Lead (Pb).
- These are defined based on their toxicity, lack of general use in manufacturing processes and high natural abundance.
- Specific reference is made to the potential risk of presence in mined excipients,
- What is required in terms of assessing the risk of the 'big 4' is often misinterpreted – the guideline that the risk posed by the four elements must be assessed irrespective of route of administration
    - **IT DOES NOT SAY TESTED**

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CLASSIFICATION OF ELEMENTS

- **CLASS 2**
- Class 2 is actually divided into 2 further sub-classes based on natural abundance:
- **Class 2A** – this includes those elements considered to present a risk based on their relatively high natural abundances, the elements concerned are Cobalt (Co), Nickel (Ni) and Vanadium (V).
- **Class 2B** – This relates to elements that are generally considered to be of low natural abundance.

- Class 2B elements need only be considered where deliberately added to the manufacturing process typically as a **catalyst**.
- The elements concerned are Silver (Ag), Gold (Au), Iridium (Ir), Osmium (Os), Palladium (Pd), Platinum (Pt), Rhenium (Re), Ruthenium (Ru), Selenium (S Thallium (Tl).

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ICH Q3D - Safety Assessment of Potential Elemental Impurities - Basics

- Using this approach limits were established for 24 elements in total;
- The individual assessments are described in detail in Appendix 3 of the guideline.
- Appendix 2 describes the actual individual limits, limits being provided for Oral, Parenteral and Inhalation routes of administration.
- These are reproduced and shown opposite

Also within the table Elements are classified

Element	Class	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	[illegible]
Sb	3	1200	90	[illegible]
Ba	3	1400	700	[illegible]
Mo	3	3000	1500	[illegible]
Cu	3	3000	300	[illegible]
Sn	3	6000	600	[illegible]
Cr	3	11000	1100	[illegible]

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Classification

Table 5.1: Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
					on
Cd	1	yes			
Pb	1	yes			
As	1	yes			
Hg	1	yes			
Co	2A	yes			
V	2A	yes			
Ni	2A	yes			
Tl	2B	yes			
Au	2B	yes			
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	ye
Mo	3	yes	no	no	
Cu	3	yes	no	yes	
Sn	3	yes	no	no	
Cr	3	yes	no	no	

For Parenterals only need to

Consider Lithium, Antimony and

Copper

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Risk assessment - Process

- The guideline describes the risk assessment process in 3 Stages:

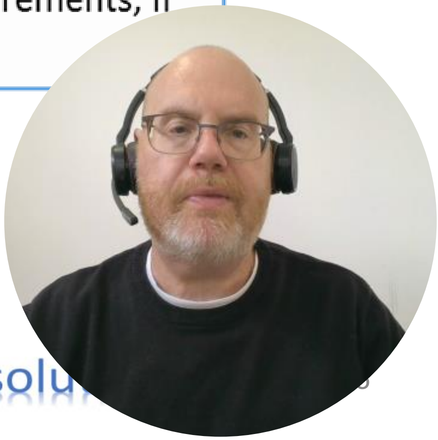
  - Identify
  - Evaluate
  - Summarize Control

Identify
- Review API, excipient, drug product manufacturing process and container systems to identify known and potential sources of Elemental Impurities

Evaluate
- Collect predicted and/or observed levels of elemental impurities
- Compare data with the established Permitted Daily Exposure

Summarize Control
- Summarize and document the risk assessment
- Identify additional control requirements, if required, to ensure PDE is met

- This process is often an iterative process that may involve repeated re-iterations of some of the steps as knowledge and understanding are continuously developed



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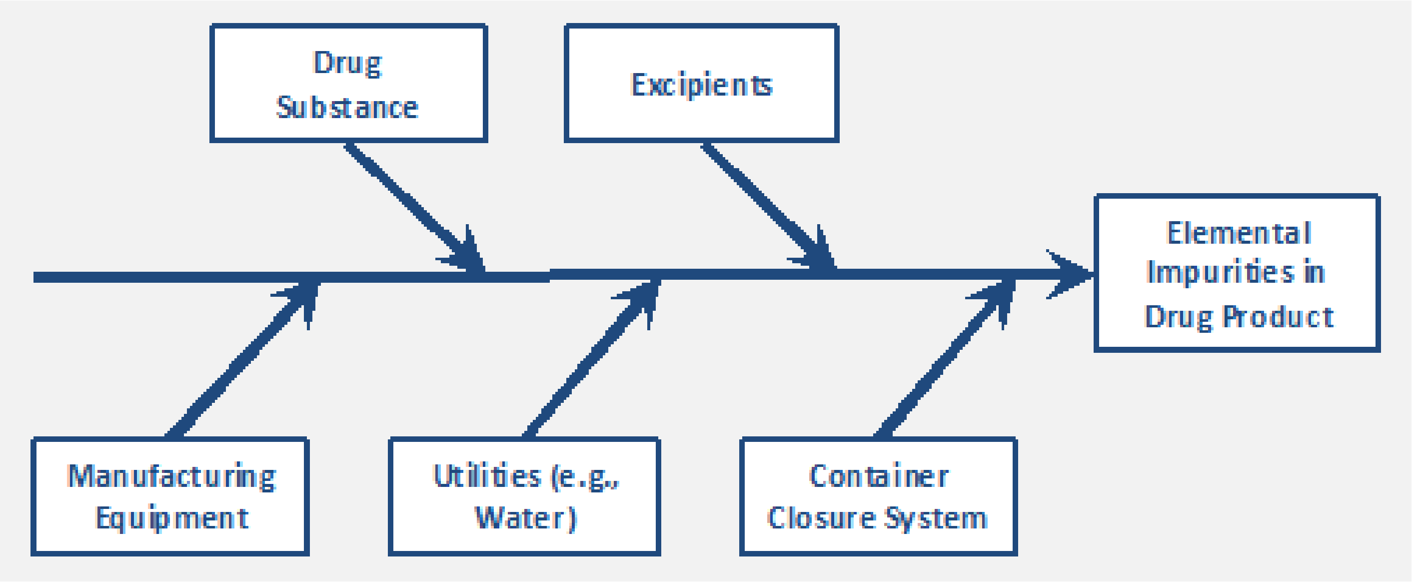
IDENTIFY

Risk assessment - Process



- The guideline provides a useful framework to use for conducting the initial stage of the ri assessment;
- This is illustrated in the Fish Bone dia
- Each of the components needs to be considered

Risk assessment – drug substance

- In respect of the drug substance arguably the first question to address is *where in the process should the assessment start?*

- Manufacturing processes for some drug substances are long/ complex syntheses
  - Some syntheses to exceed 20 chemical steps.

- In general it would seem reasonable to instigate the risk assessment from either the registered starting material or from late stages (2 to 3 steps) from the API.

- Most of the catalysts are heterogeneous in nature, i.e., 5% PD on charcoal and in these cases, purging wi isolation, at the point of use.

- May be differences in interpretation betwee – *more of a concern for EMA?*

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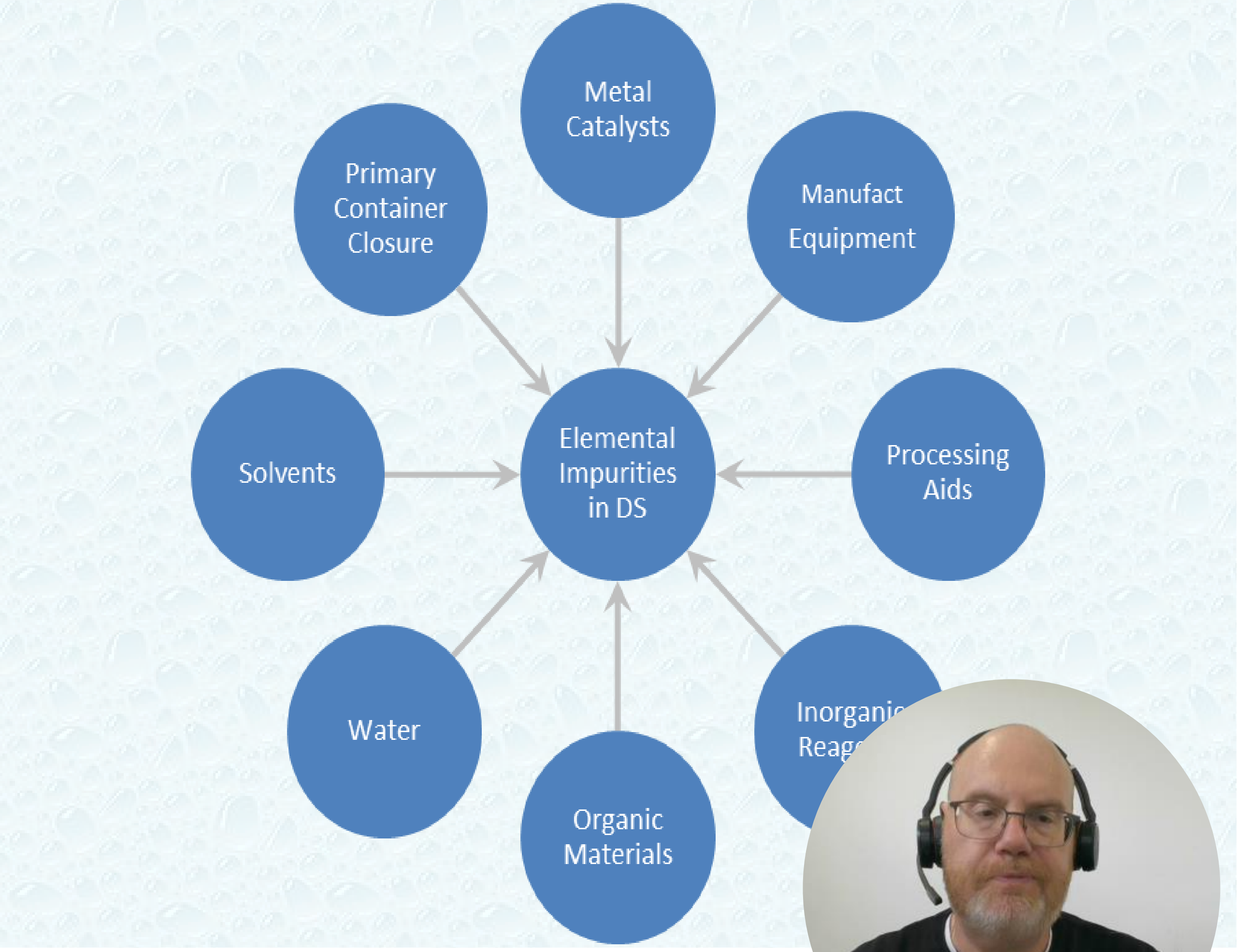
RISK ASSESSMENT – DRUG SUBSTANCE

- In respect to the Drug Substance there are multiple potential sources of EIs.

- Metal Catalysts - The most likely source of EIs in drug substance is the use of intentionally added metals in the form of a metal catalyst.

- The advent of the EMA guideline implemented in 2008 has meant that many organizations have started to build up a significant level of knowledge in terms of catalyst levels in drug substance, including an understanding of purging under typical process conditions.



Risk assessment – drug substance

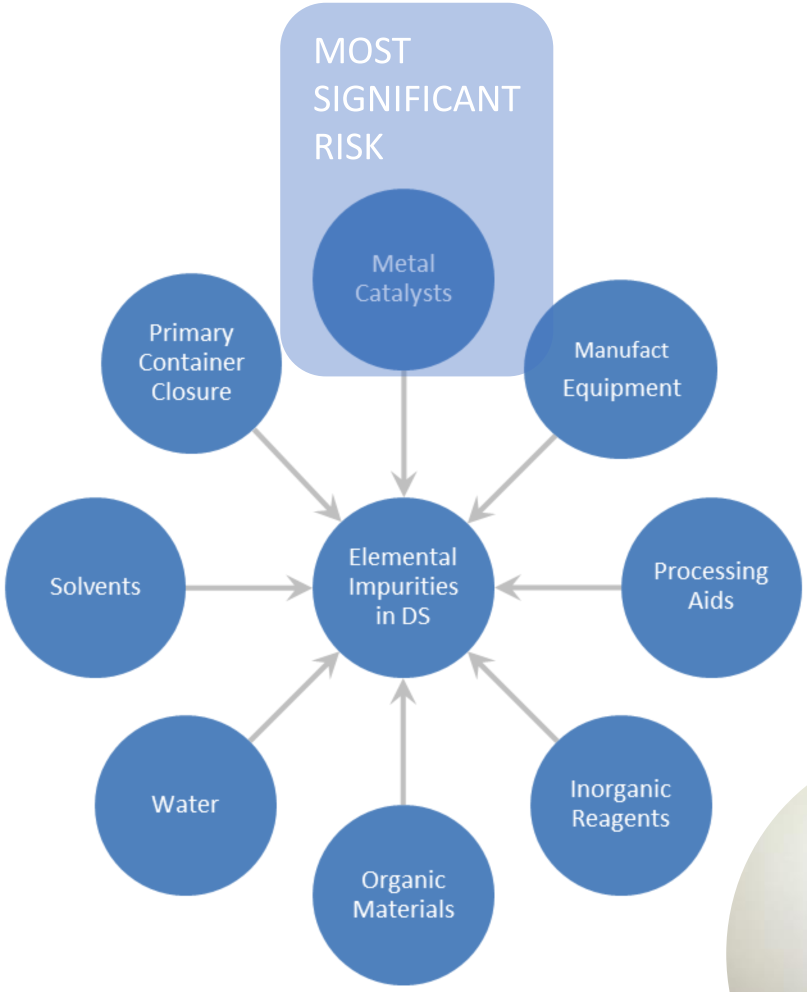
Equipment

- The guideline states that the risk associated with manufacturing equipment is generally higher when related to the manufacture of the active due to the typically more aggressive conditions employed in the synthetic process (by comparison to typical drug product manufacturing processes.)

- While generally true it is important to consider the key role played by **GMP** when assessing such risks:
  - Running processes in unsuitable/incompatible equipment simply **makes no sense,** either in terms of impurity concerns or cost (replacing damaged equipment). GMP will typically involve assessment of equipment compatibility as part of the process accommodati
  - Such studies are deliberately designed to show that elemental impurities are not l from manufacturing equipment into the process liquors and therefore drug substa

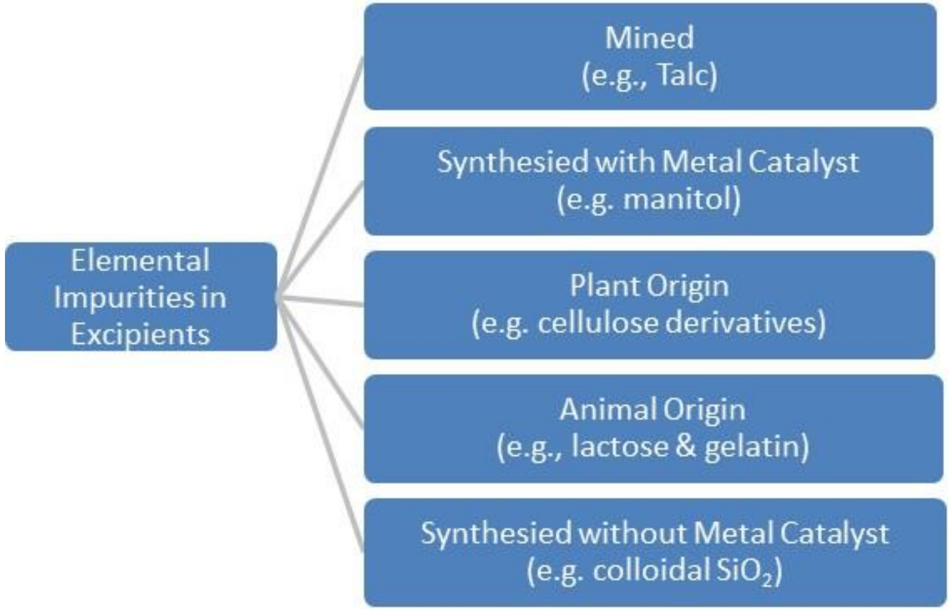
Risk assessment – drug substance

- Other factors
- Processing aids / Organic materials
  - Unlikely to contain significant Elemental Impurities
- Water
  - If high quality USP grade, out of scope
- Solvents
  - Few utilise metals deliberately in manufacture. (Many are distilled).
- Primary Container Closure
  - Little evidence of contamination
  - Low level metals
  - Solid – Solid – No clear mechanism



Risk assessment – excipients

- Considered by many to be the most likely source of risk; excipients come in a range of forms.
- Mined excipients <u>considered</u> the most likely to contain EIs at elevated levels



Perceived Increased Risk of Contributing Elemental Impurities

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Risk assessments – water

- Water is used widely in the manufacture of both the drug substance and the drug product.
- In parenteral formulations, especially large volume parenterals (LVPs) it is the major component of the final drug product. It is therefore clearly a potential source of risk.
- The risk is directly related to the quality of water used.
- As with processing equipment **GMP** is an integral part of the overall managem of this specific risk.
  - As part of standard GMP, water quality should be routinely monitored and the purifi system and storage of the water should not re-introduce elemental impurities.

Risk assessment – water

- GMP requires the use of a minimum of <u>WHO standard potable</u> water for stages up to the isolated drug substance and for the final isolation compendial quality e.g. USP purified water.
- Similarly manufacture of the drug product requires similar exacting standards.
- The overall issue of the impact of water quality on the EIs was discussed in a USP stimuli article.

Risk assessment – water

- Alert from PF43(2) - USP General Chapter <1231> Water for Pharmaceutical Purposes
  - Contains the following very important statement

Water that meets US EPA National Primary Drinking Water Regulations or WHO Drinking Water Guidelines that has been purified by conventional technologies used to produce Water for Injection can comply with chapter ⟨232⟩ for LVP.

Risk assessment – manufacturing equipment – drug product

- In general the risk associated with the manufacture of the drug product is lower than that associated with the drug substance:

  - Conditions used are, less chemically aggressive, avoiding the extremes often seen in drug substance manufacture i.e. extremes of pH and/or high temperature and highly reactive reagents.

  - Drug Product manufacture of the drug product may still involve the use of solvents or liquid formulations.

  - In addition, conditions can also be physically aggressive leading to abrasion of manufacturing equipment, e.g. tablet punch wear.

  - <u>Furthermore unlike the manufacture drug substance there is usually no eff mechanism to remove any potential</u>

Risk assessment – container closure system

THEORETICAL RISK

- Especially in the case of liquid formulations there is risk of metals leaching out of CCS into the formulation

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 fo is minimal and does not require further consideration in the risk assessment*

Risk assessment container closure system

- Jenke et al publication summarized literature data for a number of common packaging materials.

  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;

  - Trace levels present within the component material, for example cadmium and lead levels up to 100 ppm were reported in polyvinyl chloride (PVC).
  - NB – This relates to DIGESTION

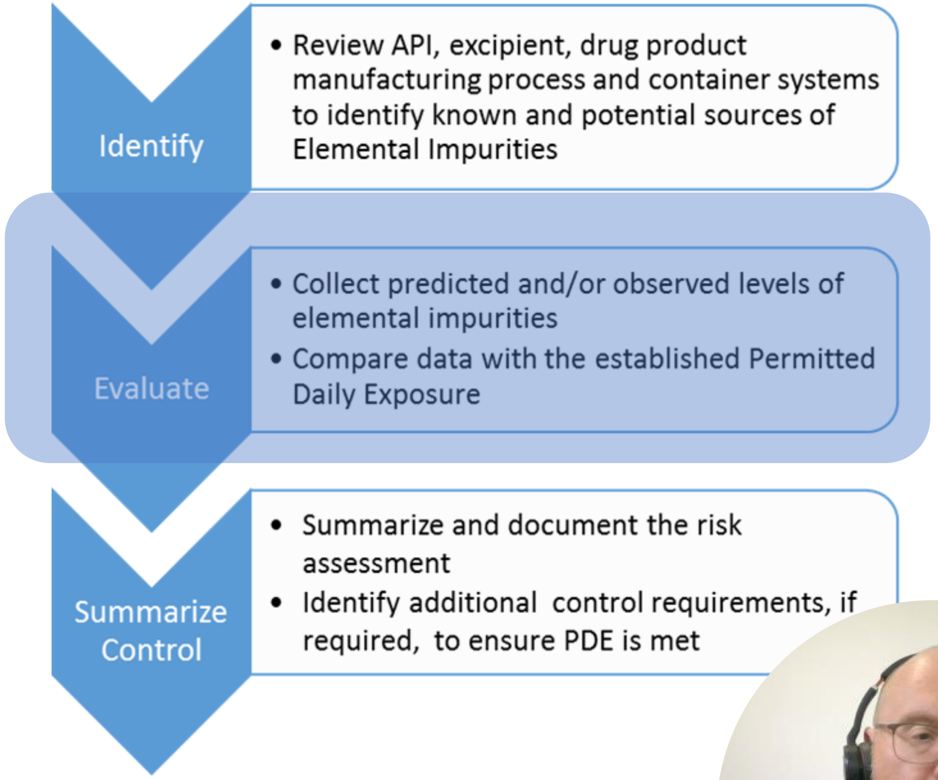
- However effective ‘availability’ of the elemental impurity needs to be considered.
  - Typically <u>extraction</u> level <u><0.1% </u>of that observed following digestion.

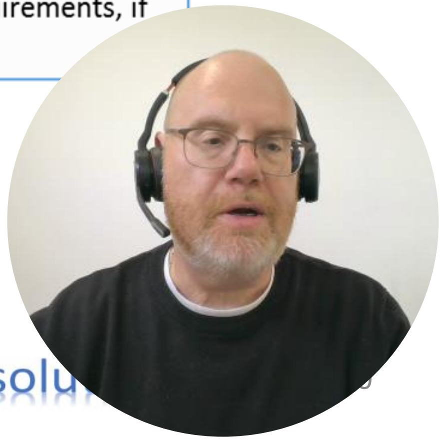
- Therefore, even when trace levels of certain elements are found in the component the available elemental impurity concentration may represent an <u>extremely low sa</u>

Risk assessment – Evaluate

- Once potential risk sources have been identified next stage is to evaluate the risk.

- *How likely are the sources of risk likely to result in Elemental Impurities at levels of concern ?*





Risk assessment - evaluate

- Not necessarily a simple case of test everything.
- **Screening every component for 24 elements is not a risk assessment**

- Evaluation can include a combination of:

1. Evaluation of risk at a first principles level
   - Equipment – GMP
   - Container closure systems – especially solid dose forms
   - Purified water.
2. Use of existing data (will examine through case study)

3. Analysis- NB – this is screening analysi specification test.

Excipients

In many ways this was the trigger for development of ICH Q3D.

- Anticipated that excipients were potentially a major source of elemental impurities

The reality is very different

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Risk assessment evaluate

EXCIPIENTS

- Knowledge of the extent of the risk started to become clearer.
- Studies conducted by the FDA proved illuminating.
- The studies involved over 200 samples, spanning a range of excipient types, including plant derived, synthetic and mined excipients.
- Overall results showed little evidence of substantial levels of even the 'big 4' (ubiquitous?) elements in mined excipients.
- Detectable levels of Pb were seen in titanium dioxide but levels <10ppm are very unlikely to a threat in typical formulations
  - titanium dioxide is typically used in aqueous film coating applied at about 3%w/w

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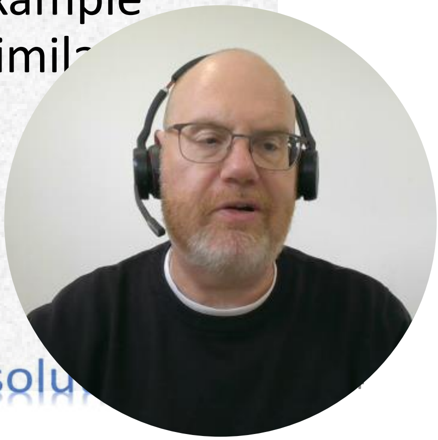
Risk assessment evaluate

EXCIPIENTS continued:

- Variability (batch to batch or supplier to supplier) was <u>not</u> significant.

- In terms of other Class 1 elements: Cd levels in magnesium hydroxide and calcium carbonate were seen to exceed Option 1 limits
  - Concluded that it was highly unlikely these levels would adversely impact on the overall quality of a typical drug product

- Generally metal impurities were found where they might be expected.
  - Class 2A metals were detected at appreciable levels in some mined excipients, for example ferric oxide samples were seen to contain V, Ni, Co at approximately 100 ppm, and simil ferric carbonate contained elevated Ni levels.
  - <u>In all these cases the level at which the excipient would be used becomes important</u>



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Risk assessment - evaluate

EXCIPIENTS – CONTINUED

- **<u>Other data</u>** - Elemental Impurities Pharma Consortium
  - Borne out of discussions during a JPAG EI meeting October 2013.
  - Agreed the value of pooling data
- <u>Aims</u>
  - Build a database
  - Share data collected on non-IP substances tested (excipients)
  - Plan to interpret data and summarise key findings – compare / contrast with FDA study

Elemental Impurities Data Sharing Consortium

Takeda

polpharma

APOTEX
ADVANCING GENERICS

abbvie

gsk GlaxoSmithKline

Bristol-Myers Squibb

Qualiphar

NOVARTIS

Pfizer

Roche

SANOFI

MSD

ucb

AstraZeneca

B|BRAUN
SHARING EXPERTISE

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Boetzel et al Publication

- The purpose of this publication was to show how an elemental impurities excipient database can be used in assisting the execution of a drug product elemental impurities risk assessment as required by the ICH Q3D guidelines.
- This demonstrated that the database, used in conjugation with other sources of information, is a credible source of elemental impurity levels in excipients therefore, a valuable source of information in completion of drug product risk assessments.
- This collection of data helps to reduce the burden of analytical testing for elemental impurities in excipients.

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ELSEVIER

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

ICH Q3D Drug Product Elemental Risk Assessment: The Use of An Elemental Impurities Excipients Database

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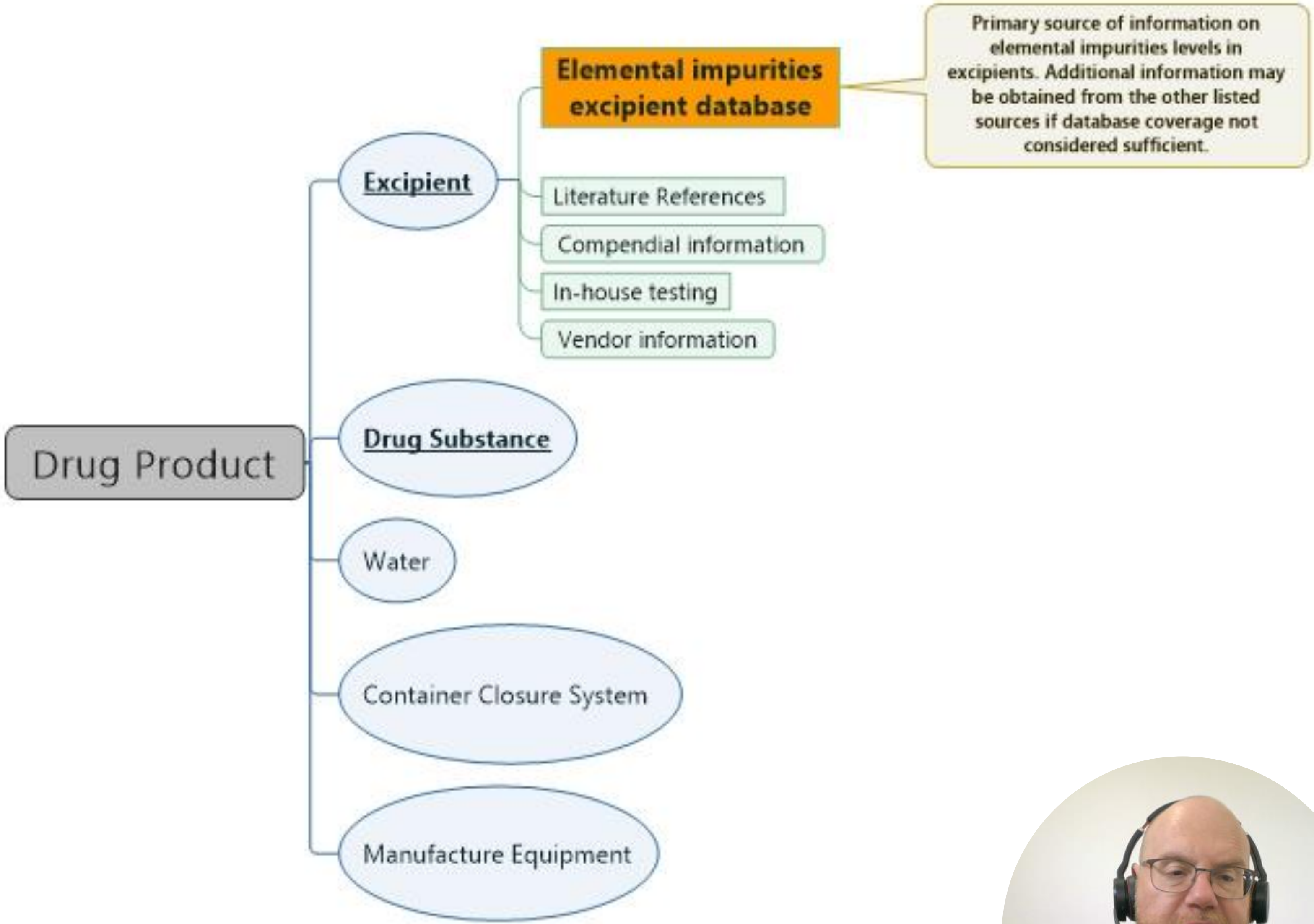
Boetzel et al



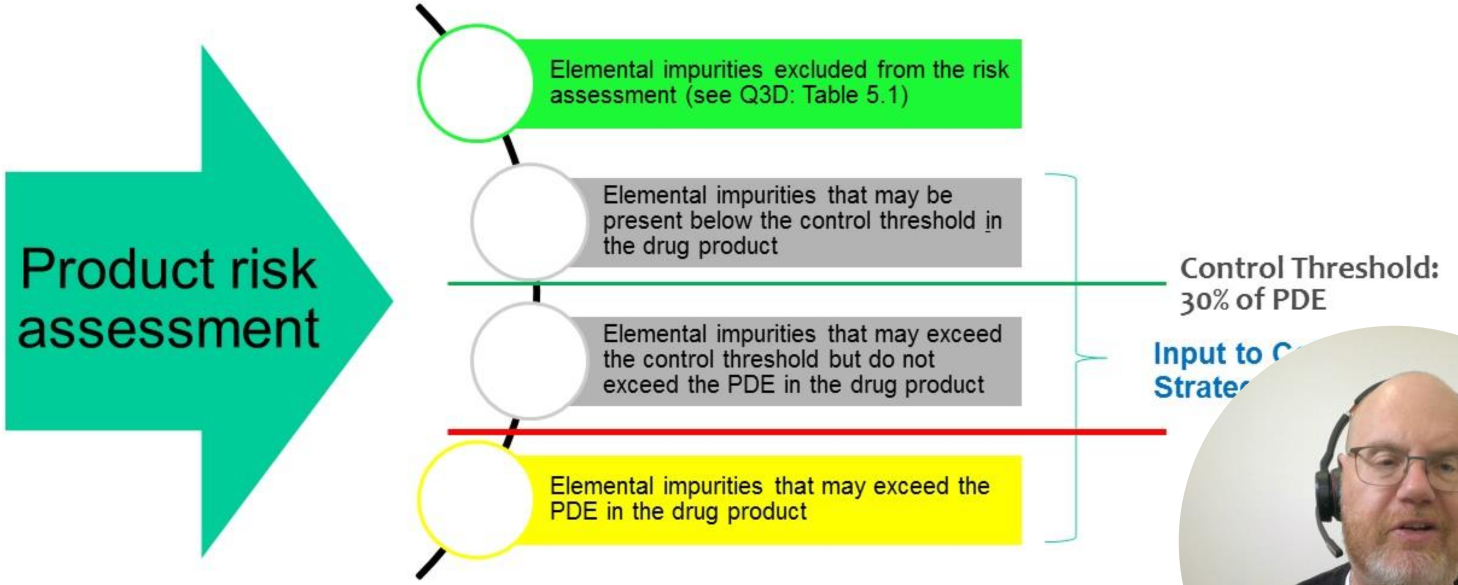
Key Findings

- The studies mirror the findings from the 2015 FDA study (200 samples)
- Overall results show no evidence of substantial levels of even the 'big 4' (ubiquitous?) elements in mined excipients.
- Detectable levels of Pb were seen in some excipients such as titanium dioxide but levels <10ppm are very unlikely to pose a threat in typical formulations
  - titanium dioxide is typically used in aqueous film coating applied at about 3%w/w.
- CRITICALLY - DATA COLLECTED OVER A 3 YEAR PERIOD ACROSS THE INDUSTRY HAS TO FIND ANY EVIDENCE TO SUPPORT THE VIEW OF SUBSTANTIVE RISK OR VARIATI EVEN WITHIN MINED EXCIPIENTS

EVALUATE

Evaluate

- The next stage in the risk assessment process involves the evaluation of the risks taking into account any specific data obtained through either analytical screening, supplier information and/or other sources e.g. literature data.
- The IWG training module, specifically module 5, describes the risk assessment output in terms of a series of options, 4 in total.



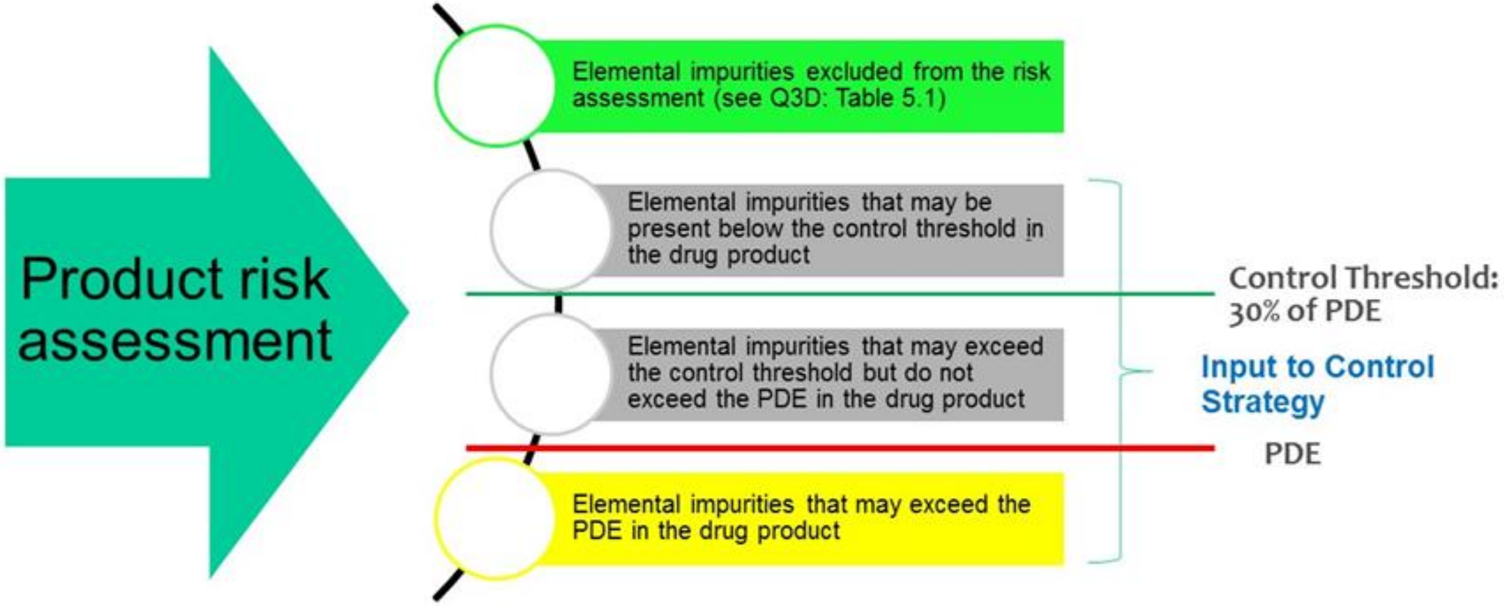
Evaluate

The risk assessment must be formally documented and comprehensive enough to provide a complete description of the risk assessment process outlining:

- the contributory factors considered,
- associated data and
- ultimate conclusions of the impact on the final drug product.
- It should identify any significant risks and the subsequent controls required to manage this linking directly to the overall control strategy.

The guideline provides a benchmark level
30% of the PDE for an individual eleme
basis for defining significance and the
routine control.

Control



- Although this illustrates a series of outcomes of the evaluate phase, in reality and experience to date there are **two outcomes,** either
- no significant risk is identified or a risk is identifi
specific control is required.

CONTROL

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Control Options

Option 1

<u>Common</u> permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than <u>10 grams</u>

Option 2a

<u>Common</u> permitted concentration limits across drug product components for a drug product with a specified daily intake:

Generally the preferred option

Option 2b

Permitted concentration limits of elements in individual components of a product with a specified daily intake:

$$\mathrm{PDE}(\mu g/\mathrm{day}) \geq \sum_{k=1}^{N} C_k \cdot M_k$$

k = an index for each of N components in the drug product

C_k = permitted concentration of the elemental impurity in component k (μg/g)

M_k = mass of component k in the maximum daily intake of the drug product (g)

Option 3

- Finished Product Analysis:
- Recent finalised EMA guideline c concerns over this approach.

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Option 2B

- The **total dose** of the elemental impurity in the drug product should comply with the PDEs given in the guideline.
- Critically the guideline makes clear that if the risk assessment has determined that a specific element is not a potential impurity in a specific component, there is no need to establish a quantitative result for that element in that component (<u>it can be assumed to be zero for the purposes of the calculation</u>).
- This option is particularly useful for evaluating analytica data following the identify/analyze stages of the risk assessment, or for setting tailored specifications f components of the drug product

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Option 3

- This option involves measurement of the concentration of each element in the final drug product.
- While apparently the simplest option this does not effectively align with the core risk assessment principles of the guideline and when used in isolation represents little more than quality by testing.
- A **major flaw** with option 3 is that were the drug product to fail it would give no indica
as to the route cause.

Control

- Even if the risk assessment concludes that there is no substantive risk and all elemental impurities are controlled below 30% PDE, there is still a need to maintain effective control through the overall quality system,
  - Aligned to the principles outlined in ICH Q10
  - Including appropriate use of standard cGMPs and change control.

- This needs to also take into consideration other factors such as:
  - Security of external supply chain along with a quality history (e.g., audit history /levels of complaints / recalls, etc.) for each vendor.
  - Control of current vendor elemental impurity specifications and elemental impurity reporting on ingr certificates of analysis.

- Of particular importance during the lifecycle of the product is change control

Control overall

In reality, most companies are likely to encapsulate aspects of each option into their risk assessment processes.

For example target levels to frame analysis of a generic excipient may be calculated using Option 1 limits,

Levels measured in individual drug product components may be compared to the PDE using an Option 2A or Option 2B approach, and

During the development phase Option 3 testing of any
risk drug products may be preferred to component
and results fed back into the overall risk assessme
the risk assessment and define the long-term con

Option 2B

- ➢ The coalition for rational implementation of elemental impurity guidelines, has in partnership with IPEC Americas developed a calculation tool to facilitate the Option 2B calculations (Accessible through IPEC Americas website).
- ➢ Also included on the website concerned is an instruction manual how to use the simple tool.
- ➢ Included within the tool are both blank templates and pre-defined templates illustrating a wide range of formulation types ranging from simple tablets to large volume parenterals.

	Category	Quantity (mg/tablet)	Dose "x" tablets (mg/day)	Arsenic in component ug/g		As ug in daily dose of formulation		Lead in component ug/g		Pb ug in daily dose of formulation		Mercury in component ug/g		Hg ug in daily dose of formulation		Cadmium in component ug/g		Cd
		x =	2	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	Total	Bio Acc	To
	Synthetic	100	200	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0
	Synthetic	120	240	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0
ate	Mineral	65	130	0.11		0.01	0.00	0.02		0.00	0.00	0.00		0.00	0.00	0.03		0
ch	Plant derived	10	20	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0.00	0.00	0.00		0
	Plant derived	10	20	0.00		0.00	0.00	0.09		0.00	0.00	0.00		0.00	0.00	0.00		0
rate	Synthetic	3	6	0.02		0.00	0.00	0.01		0.00	0.00	0.00		0.00	0.00	0.00		0
de	Mineral	2	4	0.03		0.00	0.00	2.41		0.01	0.00	0.01		0.00	0.00	0.04		0
	Mineral	1	2	0.17		0.00	0.00	0.19		0.00	0.00	0.01		0.00	0.00	0.00		0
ycol	Synthetic	1	2	0.00		0.00	0.00	1.00		0.00	0.00	0.00		0.00	0.00	0.00		0
ed	Mineral	0.1	0.2	0.66		0.00	0.00	0.37		0.00	0.00	0.00		0.00	0.00	0.00		0
r*		NA																
ight		312.1	624.2															
t				As		0.02	0.00	Pb		0.02	0.00	Hg		0.00	0.00	Cd		0

ision Process stimuli "Elemental Impurities in Pharmaceutical Waters" excludes analysis of compendial water meeting monograph conductivity requirements

	As	Pb	Hg	Cd
its	As	Pb	Hg	Cd
	Q3D	Q3D	Q3D	Q3D
	15	5	30	5
DE	15	5	3	2
	2	5	1	2

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ICH Q3D Overall Summary

Initial concerns over potentially significant levels of Metals in excipients, especially mined excipients has proven to be LOW risk.

For most dosage forms risk assessments can actually be performed based on existing data

- Process compatibility – DS manufacturing equipment
- Excipient database

A formal control strategy, including specific testing, is RARELY needed.

ICH Q3D(R2): Cutaneous PDEs and revisions Summary of cutaneous PDEs

Establishing The Cutaneous PDE (for systemic toxicity)

Cutaneous PDE = Parenteral PDE x CMF

PDE for EIs (other than Tl and As)

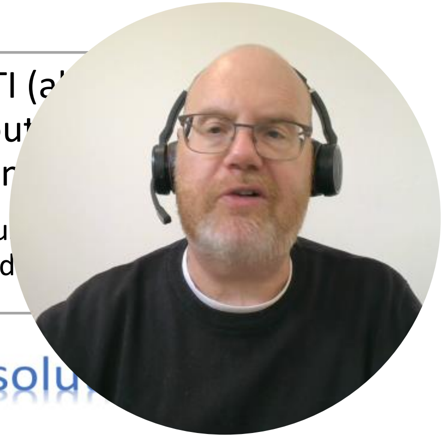
- Cutaneous PDE = Parenteral PDE x 10 (CMF = 10)

PDE for As (absorption is approximately 5%)

- Cutaneous PDE = 15 µg/day x 2 = 30 µg/day (CMF = 2)

PDE for Tl (a
is high, but
data are n

- Cutaneou
1 = 8 µg/d



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ICH Q3D(R2): Cutaneous PDEs and revisions Summary of cutaneous PDEs

- Cutaneous and Concentration Limits (CTCL) for Ni and Co
  - The CTCL in addition to the PDE is warranted for Ni and Co to reduce the likelihood of eliciting skin reactions in already sensitized individuals.
  - The dermal concentration limit of 0.5 µg/cm^2/week (EU directive) is applied to set a CTCL of Ni
    - Application of 0.5 g dose to a skin surface area of 250 cm^2

0.5 µg/cm2/week = 0.07 µg/cm^2/day

0.07 µg/cm2/day x 250 cm^2 = 17.5 µg/day

17.5µg/day/0.5 g = 35 µg/g/day

  - Recent report suggested Co shows a similar limit to Ni

ICH Q3D(R2): Cutaneous PDEs and revisions Summary of cutaneous PDEs

- Product Risk Assessment

- Product assessments for cutaneous drug products should be prepared following the guidance provided in Q3D Section 5.
- For Ni and Co, the concentration (µg/g) in the drug product should be assessed relative to the CTCL, in addition to the PDE
- The total Ni and Co level (µg/day) is at or below the PDE, and their respective concentrations does not exceed the CTCL
- “Control threshold” approach is also applied to the CTCL
- Evaluation of the retention during ty
conditions of use is important, be
removing or rinsing from the ar
dermal drug application.

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ICH Q3D(R2): Cutaneous PDEs and revisions Conclusions

- Develop a new appendix for "Limits for Elemental Impurities by the Cutaneous and Transcutaneous Route"
- This appendix does not apply to drug products intended for mucosal administration, topical ophthalmic, rectal, or subcutaneous and subdermal routes of administration
- Establish the cutaneous PDE of all EIs for systemic toxicity
- Establish the CTCL for Ni and Co for sensitized patients
- The total Ni or Co level is at or below the cutaneous PDE, and their respective concentrations does not exceed t

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