ICHQ3D Implementation: An Innovator's experience

Dr. H. Rockstroh, F. Hoffmann-La Roche Ltd, Basel, Switzerland

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Content

Background: ICHQ3D Risk Based Aproach

- Strategy: Reduce the scope, reduce need for testing

Component Approach

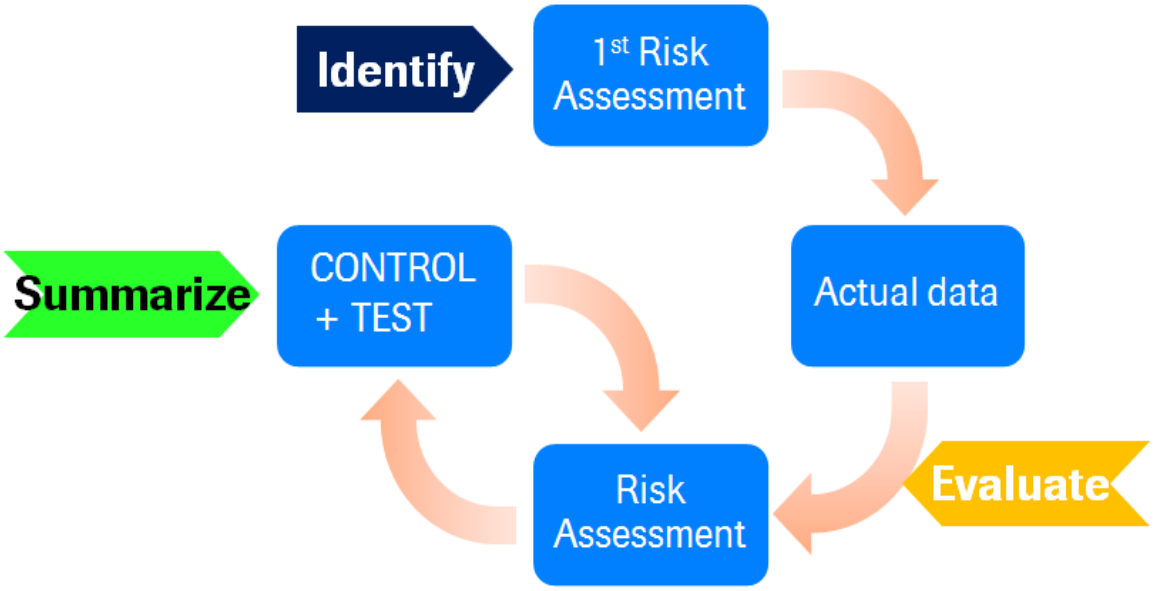
ICH Q3D: Paradigm Change

Proactive iterative *Risk Based Approach*

Identify → **Evaluate** → **Summarize/Control**

Strictly speaking **Q3D limits apply to Drug Products:**

- The limits do **NOT** apply to Substances for Pharmaceutical Use
- **Component approach** (2b)
  allows “mix“ of low/high EI content material



Risk Based Approach: Where to start

The challenge is to find a means to identify and categorize risk.

- Otherwise you will test everything (all potential sources / all 24 EIs) or simply default to Option 3
- Option 3 (End Product testing) ⇒ Discouraged!
- Test everything then decide where your risks are ⇒ Discouraged!

THINK first, **THEN TEST**

Component Approach (Option 2b): Use logic to simplify / exclude

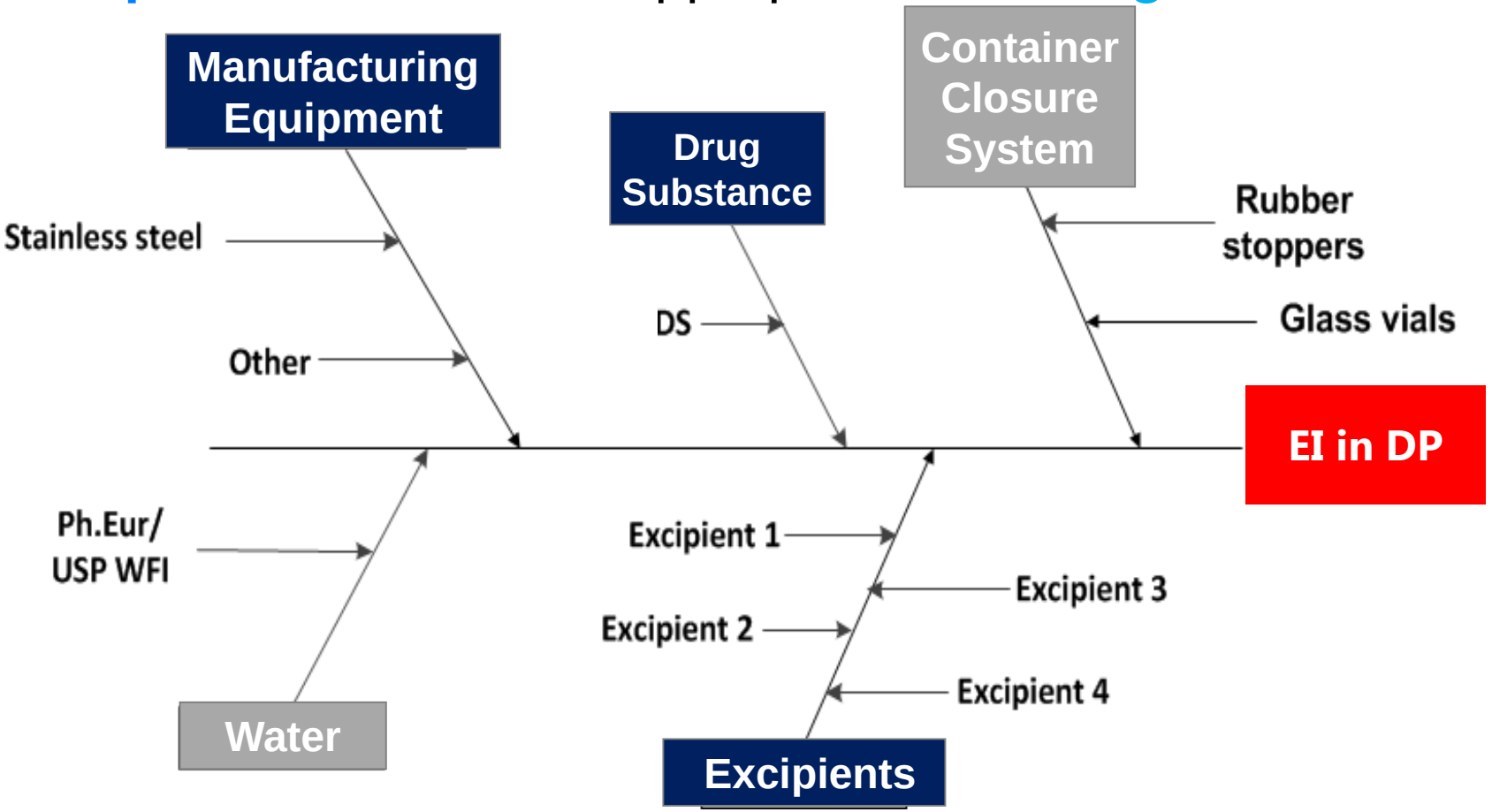
How do you do this? What role will data play in this?

- Test data or
- Literature *(testing has already been done for you)*
- Data sharing *(testing has already been done for you)*

Q3D Risk Based Approach and Control Strategy

Component Approach

Group / Exclude where appropriate: **Use Logic!**



EI in Scope

Reduce Scope:
DP is Solid / Liquid / Inhalational?

Are the EIs intentionally added?

*) ≤ 0.2% in 316L Steel

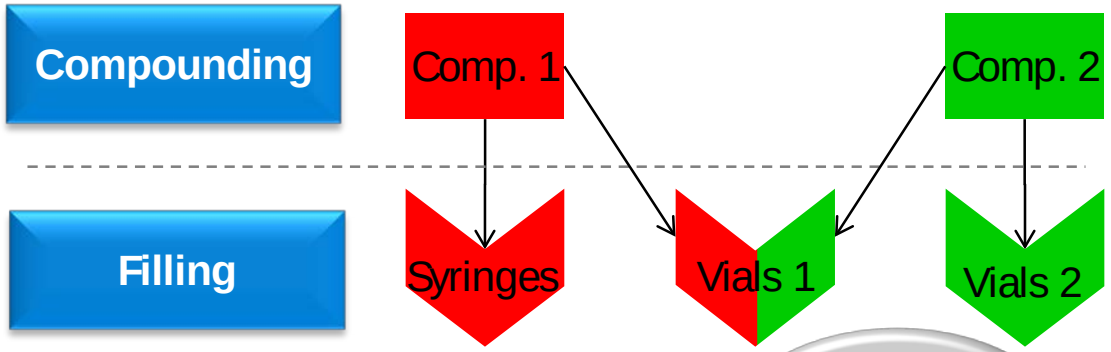
§) ≈11% Ni in 316L

Elements / Class		PDE in [ug/d]			Conc. in [ug/g]			
		Oral	Paren-teral	Inhala-tional	Oral	Paren-teral	Inhala-tional	
As	1	15	15	2	1.5	1.5	0.2	
Cd	1	5	2	2	0.5	0.2	0.2	
Hg	1	30	3	1	3	0.3	0.1	
Pb	1	5	5	5	0.5	0.5	0.5	
Co	2A	50	5	3	5	0.5	0.3	* § *
Ni	2A	200	20	5	20	2	0.5	
V	2A	100	10	1	10	1	0.1	
Ag	2B	150	10	7	15	1	0.7	
Au	2B	100	100	1	10	10	0.1	
Ir	2B	100	10	1	10	1	0.1	
Os	2B	100	10	1	10	1	0.1	
Pd	2B	100	10	1	10	1	0.1	
Pt	2B	100	10	1	10	1	0.1	
Rh	2B	100	10	1	10	1	0.1	
Ru	2B	100	10	1	10	1	0.1	
Se	2B	150	80	130	15	8	13	
Tl	2B	8	8	8	0.8	0.8	0.8	
Ba	3	1400	700	300	140	70	30	
Cr	3	11000	1100	3	1100	110	0.3	
Cu	3	3000	300	30	300	30	3	
Li	3	550	250	25	55	25	2.5	
Mo	3	3000	1500	10	300	150	1	
Sb	3	1200	90	20	120	9	2	
Sn	3	6000	600	60	600	60	6	

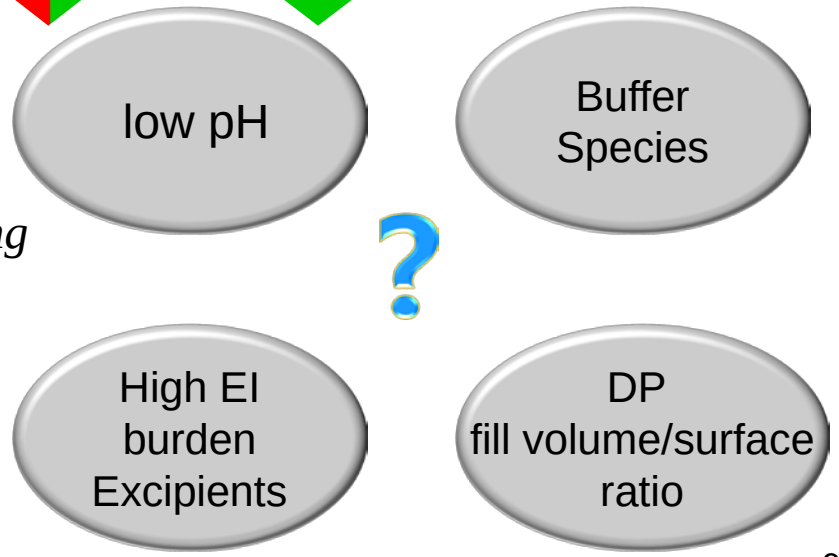
Drug Product

"Platform Approach"

Identify a representative worst-case Product per platform:



Platforms can be defined based on different combinations of products, dosage strengths, compounding approaches / processes, and filling line / equipment combinations.



Simplify: Use existing Materials / Data

Water Feedwater meets WHO Drinking Water standards PLUS

- Water meets compendial water quality requirements PLUS
- Controls in place

DS Intentionally added metals / EI are main concern

- Information may be proprietary

CCS Jenke et al, PDA J Pharm Sci Technol Vol. 69(1), p 1-48 (2015)
PDA J Pharm Sci Technol Vol. 67(4), p 645-57 (2013)

Overview article: A. Teasdale et. al , Pharmtech Europe, 2015(3), p12ff

ICH Training Modules (Module 8 Case studies)

CCS Container Closure Systems

First example of a data sharing initiative

THEORETICAL RISK:

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

WHAT DOES THE DATA SAY?

Jenke et al:
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*

Courtesy of A. Teasdale, AZ, 2017

CCS

Container Closure Systems (2)

Extraction Study for Type 1 Glass Tubing

Glass supplier extraction study: V_A= 35.2 cm²; Fill: 10ml; Rel: 3.52 cm²/ml

- Worst Case: Any CCS with a relative surface < 3.52 cm²/ml is covered
- All Q3D elements were < 0.01ppm in the extract.

Extrapolation to smaller volumes (larger rel. surface) is easy:

$$c_{glass}[ppm] = \frac{Rel.Surface \times 0.01}{3.52}$$

So we're looking at really small contributions!!

Example: Liquid filling line: ICH Case Study 3 (Old; "Before Jenke")

- *"It was assumed that the entire EI content of the glass container had leached into the DP. Where no information was available, the EI was tested in the DP.*
- *The expected contributions from As and Pb were close to their respective control thresholds. Actual levels "found" were <0.05 pppm*

Equipment

Reductio ad Absurdum

Worst-Case assumptions: "Ridiculous erosion levels" ⇒ Easy to refute

Example: 316L Hammermill used to make a solid oral DP

- 316L Steel: ≈17% (w/w) Cr, ≈11% Ni. Surface 1.43 m^2, ρ = 8 g/cm^3
- Equipment is 3000 lots (20yrs at 150 lots)
- Batch size 300kg assumed MDD of 10g DP/Day
- PDEs: 11000µg/day for Cr, and 200 µg/day for Ni,
- **Total lifetime erosion: 510/14mm** before PDEs of **Cr/Ni** are exceeded

Example: Liquid filling line: ICH Case Study 3

- *"It was assumed that the most rigorous cleaning conditions used…, would incur an erosion of not more than approx. 10 nm" (10nm=passivation layer)*
- *With a surface area of 1265 m^2, a total contribution of e.g. 0.3ppm Ni was predicted for the equipment train* ⇒ ***Negligible!***

Drug Substance

Synthetic **Small Molecule DS**

- Main concern: Intentionally added EIs – reagents / catalysts
  - Effective removal has been a quality requirement even before Q3D
  - Organic solvents → Low risk
  - EI removal is validated

Recombinant **Biotech DS** are <u>low risk</u>

- All our Biotech DS have been subject to a risk evaluation + verification (baseline) testing.
- DP: Compounding risk has been assessed → Also low risk
- (Q3D Sec 5.7) *"Potential elemental impurity sources included in drug product manufacturing (e.g., excipients) and other environmental sources should be considered"*

Excipients

Data Sources

Data Sharing

Q3D Sec. 5.5: “The data that support the risk assessment can come from:

- Published literature, data (Someone else has already done it → Data sharing
- Supplier Information; However: Suppl. qualification is required (cGMP)
- Testing of components of the drug product, testing the DP

Data sharing FDA/IPEC/Industry 2015:

- Li et al., J.Pharm.Sciences, Sept. 2015, DOI 10.1002/jps.24650
  - 24 Elements, 205 excipients samples, > 4900 determinations
  - Overall low EI levels. Some Pb, Cd, As in mined/marine derived excipients

Data sharing Consortium (founded 2015)

- 200 Excipients, >1700 datapoints
- Data anonymised and checked by Lhasa
  https://www.lhasalimited.org/research-and-collaboration/Elemental-Impurities.htm
  http://www.lhasalimited.org/
- *Data sharing greatly reduces “anxiety” associated with small sample sets*
  Methods have been validated.

Standardize:

Rationale

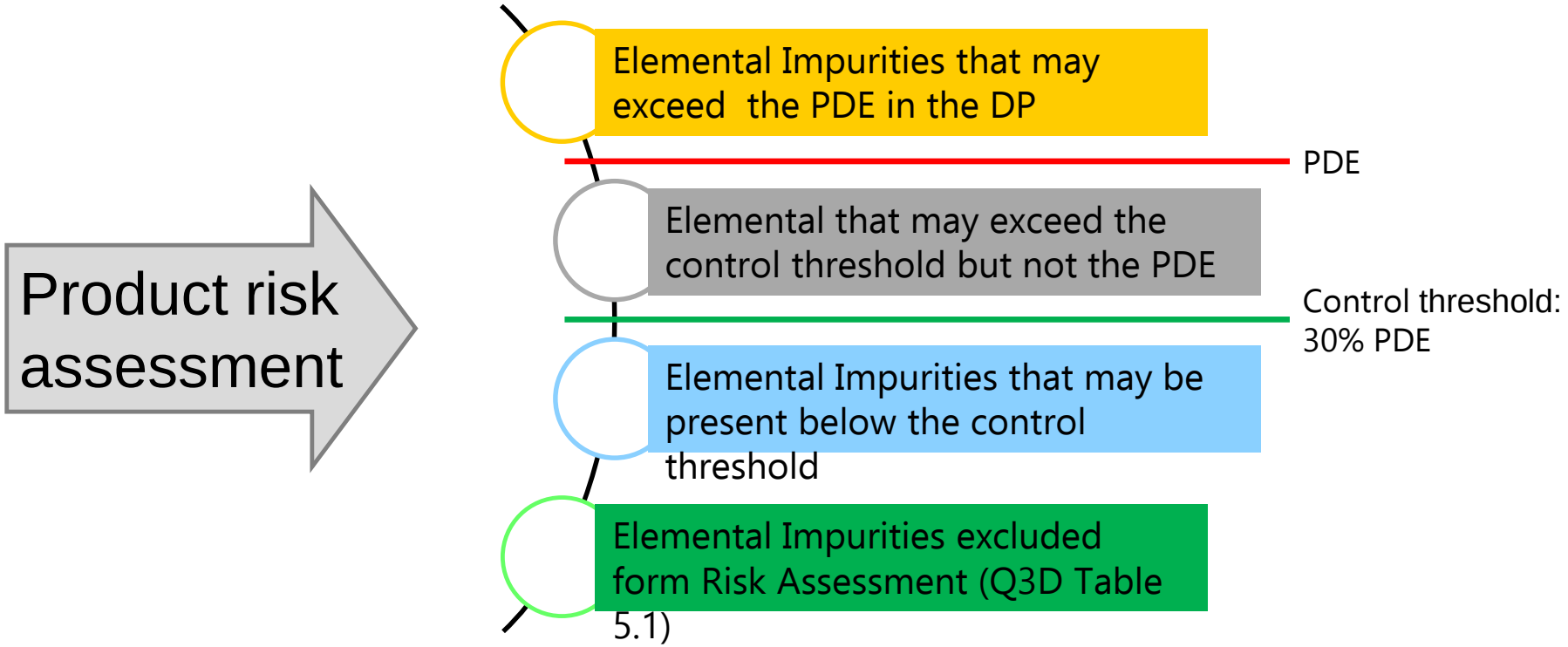
Technical Rationale for predictive calculations to support Elemental Impurities Risk assessments for Sterile Drug Products

Excipients Example 0.5mg Tablet
Sources: CoAs + Own test results

		Material [mg/U]									
		DS	Starch Pregl.	Corn-starch	Lactose mh	Talc	FeO	Mg-Ster.			
El	30%CT at MDD	CoA Contents [ppm]							Sum Conc.	Cornst. Actual	2-Sum Conc.
As	0.75	0.6	1.5	1.5	0.45	0.1	1	0.2	1.21		
Cd	0.25	1.9	0.5	0.5	0.15	0.04	1	0.03	0.41		
Hg	1.5	1.8	3	3	0.9	0.02	0.5	0.04	2.42		
Pb	0.25	1	0.5	0.5	0.15	1	5	0.13	0.42		
Co	2.5	1.2	5	5	1.5	0.6	10	0.07	4.05		
Ni	10	1.8	20	20	6	7.3	70	0.19	16.23		
V	5	2.4	10	10	3	4.3	10	0.7	8.09		

Evaluate - Summarize

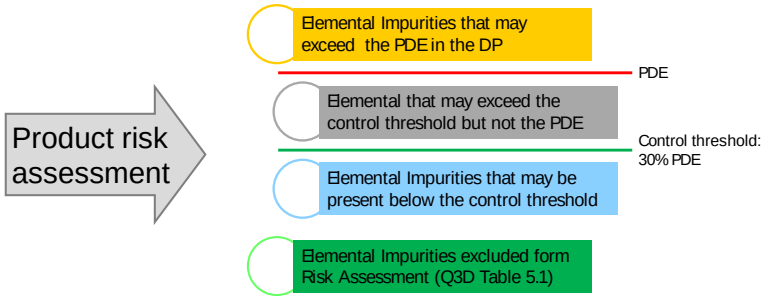
Express Risk(s) as expected contamination



Courtesy of M. Schweitzer, Novartis, 2017

Q3D Risk Based Approach and Control Strategy

Risk categories follow PDE



Default C+T Strategy Option
Accept on certificate/CoA/questionnaire. Reduced or no monitoring
As above with (reduced when justifiable) monitoring - Risk based approach enables you to leverage grouping / matrixing
Qualify (Initial Baseline Testing) representative Lots (≥3). Define (periodic) testing frequency as appropriate.
If >PDE, material not ok. Proceed to mitigate.

Summarize

Standardized Report

Technical Plan / Report

Quality Risk Management (QRM) Preliminary Hazard Analysis (PHA) Plan for ICHQ3D

DOC NO **TEC-0108939** VERSION **3.0** STATUS **Approved** APPROVED DATE

Conclusions / Summary

The implementation of **ICH Q3D provides an opportunity** to put into practice a **risk and science based approach** to control of EI

- Leveraging of “worst-case” approach and
- pre-existing knowledge / data / cGMP controls
- Enables reduction of testing

The observed **EI content** of most products is significantly below the control threshold (i.e. **<30% PDE**) for all elements, with few exceptions

- Perceived risk is higher than actual risk of EI contamination

Data sharing: Benchmarking of own results against peers

- “Safety in numbers”
- Offers Cross-check of own RA results and test data
- Has helped in simplification of our own approach

THANKS

Stephanie Knueppel, F. Hoffmann-La Roche Ltd, CH

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The colleagues in the Datasharing Consortium

The folks at Lhasa, especially Crina Heghes and Wiliam Nye

And a host of others…

Backup:

EI contributions from WFI

Production of WFI

- High Quality purified water used
- Distillation, ionic exchange resins
- Filter
- CO_2- Degassing
- Reverse osmosis
- Ozonization

Control mechanisms for WFI

•Monitoring for PW and WFI quality

•Aerobic microorganisms (daily)

•Bacterial Endotoxin (weekly)

•Conductivity (Inline)
•TOC (Inline)
•Appearance, clarity, colour, odour, Nitrate (monthly)
•Particles ≥10µm und ≥25µm (monthly)
•Warning levels below acceptance criteria established (safety margin)
•Data Trending shows constant quality over years (conductivity and TOC data constantly 10-6 times below acceptance limit)

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Q3D Control Options:
Component Approach is preferred

Option 2b

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

Option 2a

Common permitted concentration limits across drug product components for a drug product with a specified daily intake:

Option 1

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

Option 3

Finished Product Analysis

EMA guideline confirms concerns over this approach

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

2b: Generally the preferred option

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)

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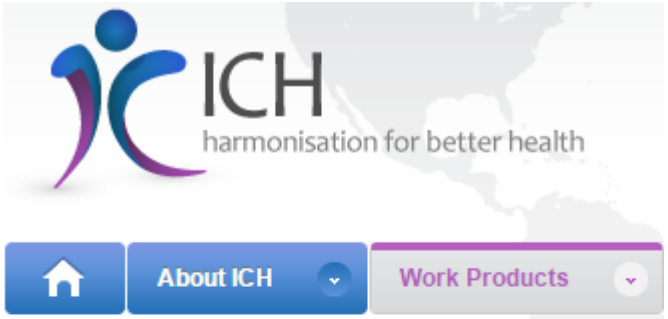
ICH Training Materials



Training Module 0: Introduction

Training Module 1: Other Routes of Administration

Training Module 2: Justification for Elemental Impurity Levels Higher than an Established PDE

Training Module 3: Acceptable Exposures for Elements without a PDE

Training Module 4: Large Volume Parenteral Products

Training Module 5: Risk Assessment and Control of Elemental Impurities

Training Module 6: Control of Elemental Impurities

Training Module 7: Converting between PDEs and Concentration Limits

Training Module 8: Case studies

1a: Solid oral dosage form (submission+internal), 2: Parenteral product, 3: Biotechnological product

Training Module 9: Frequently Asked Questions

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Ph.Eur.9.3 5.20

Replacement of the EMA guideline on metal catalysts and metal reagents by the principles of the ICH Q3D guideline

No verbatim reproduction to avoid introducing a “Ph. Eur. Copy” of the guideline. The enforceable text is the version as published by EMA. Only introduction and scope of Q3D will be reproduced in 5.20

- *The …Ph. Eur. applies this guideline to all (human) medicinal products via the general monograph Pharmaceutical preparations (2619) unless excluded from the scope of the guideline*
- *Unless otherwise prescribed, tests for elemental impurities are not mentioned in individual monographs*
- *….manufacturers …shall assess and control elemental impurities in the medicinal product using the principles of risk management*.

Pheur 29(4): Removal of specific limits from individual monographs

Regulatory expectations

FDA: Submission of product specific RA reports (summaries)

- Legacy: Integration into Annual Report 2018, even if no changes
- Analytical procedures to follow USP <232> <233>

EMA: Summary of the RA required. CTD (Module 2 and Module 3).

- Full RA at site (Inspections)
- Legacy: Submission of RA report only required if adaptation of product control strategy due to Q3D
- Re-assesment for changes + periodic (unplanned changes)

CAN: Statement of ICH Q3D-compliance has to be contained in every Drug Product Specification from January 1st, 2018

- Module 3.2.P.5.6 Justification of Specifications
- The RA should be documented and available for inspection and any controls should be implemented
- Legacy: Notification of any Q3D driven changes

Full View Excipients Example 0.5mg Tablet

		Material [mg/U]									
		DS	Starch Pregl.	Corn-starch	Lactose mh	Talc	FeO	Mg-Ster.			
El	30%CT at MDD	CoA Contents [ppm]							Sum Conc.	Cornst. Actual	2-Sum Conc.
As	0.75	0.6	1.5	1.5	0.45	0.1	1	0.2	1.21	0.2	0.31
Cd	0.25	1.9	0.5	0.5	0.15	0.04	1	0.03	0.41	0.03	0.08
Hg	1.5	1.8	3	3	0.9	0.02	0.5	0.04	2.42	0.04	0.37
Pb	0.25	1	0.5	0.5	0.15	1	5	0.13	0.42	0.07	0.12
Co	2.5	1.2	5	5	1.5	0.6	10	0.07	4.05	0.3	0.79
Ni	10	1.8	20	20	6	7.3	70	0.19	16.23	0.3	2.59
V	5	2.4	10	10	3	4.3	10	0.7	8.09	0.3	1.37

Validated spreadsheet!

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Doing now what patients need next