ICH Q3D practical implementation challenges - a dual perspective - Manufacturer and excipient supplier

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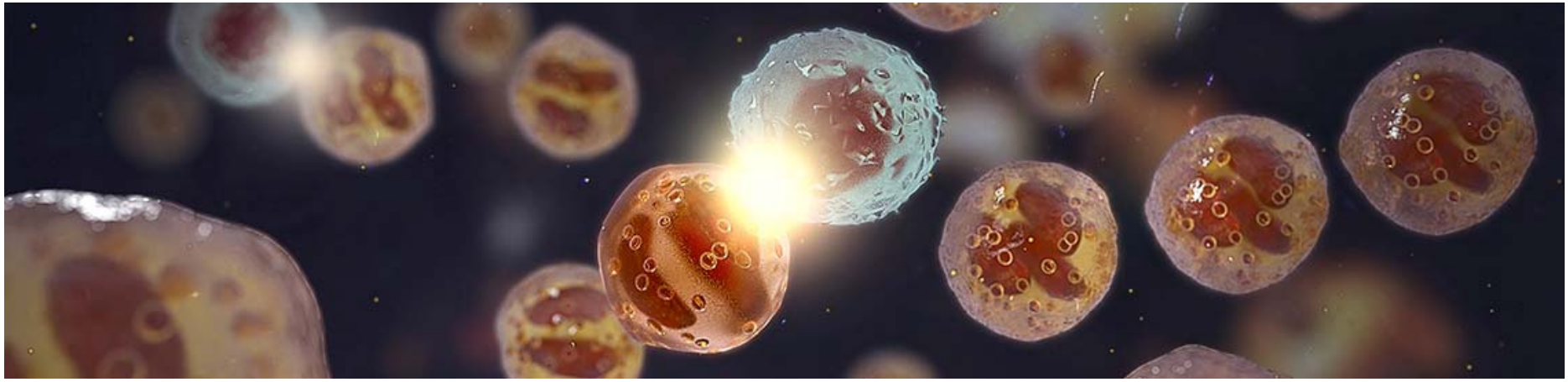
IPEC Europe Excipients Forum

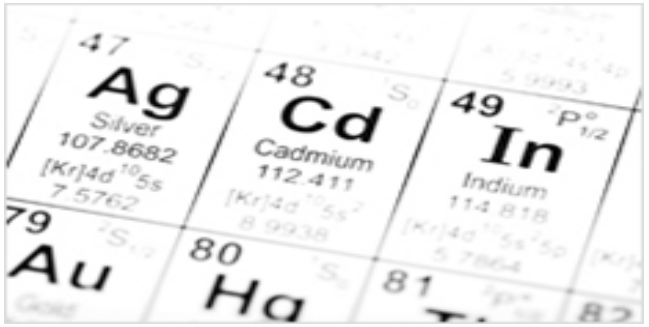


Overview of presentation

- **What is ICH Q3D**
- **What's has changed?**
- **Practical Implementation Challenges**
  - API
  - Manufacturing equipment
  - Utilities
  - Container closure system
  - **Excipients**
- **Database**
- **Conclusions**

What is ICH Q3D

- ICH Q3D is a Guideline for the control of elemental Impurities (EI) in drug products
- It can be viewed as replacing the old “heavy metal” <USP 231> test
- It is effective now (Step 4 - Dec 2014)
- NCEs compliance in EU is expected by June 2016
- All marketed products in ICH regions will need to be ICH Q3D ready by Dec 2017
- Jan 1st 2018 <USP 231> will be retired

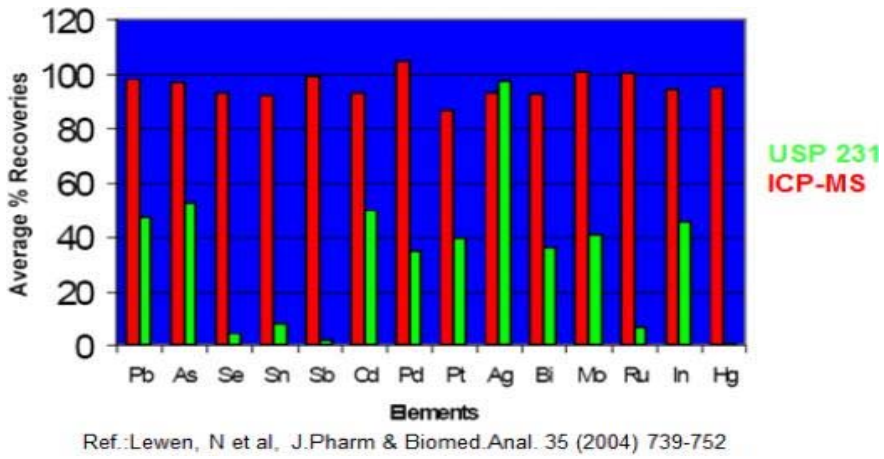


What is ICH Q3D and what's changing

- <USP 231> is a colorimetric limit test
- <USP 231> is not specific
- <USP 231> has a 10 ppm sensitivity limit
- ICH Q3D introduces a risk based approach to control of EI's in the final product
- Focusing on all potential sources of impurities
- Testing needs to be specific and sensitive (~0.1 PPM)

ICH Q3D requires a change in analytical technique

- During the late 90's and early 00's ICP became more prevalent
- Comparisons between USP<231> and ICP spiking data started to become published
- USP<231> non - selective
- USP<231> was shown to be inferior to ICP in spiking studies
- This was the beginning of the end for USP<231>, consensus it had become an uninformative compliance test



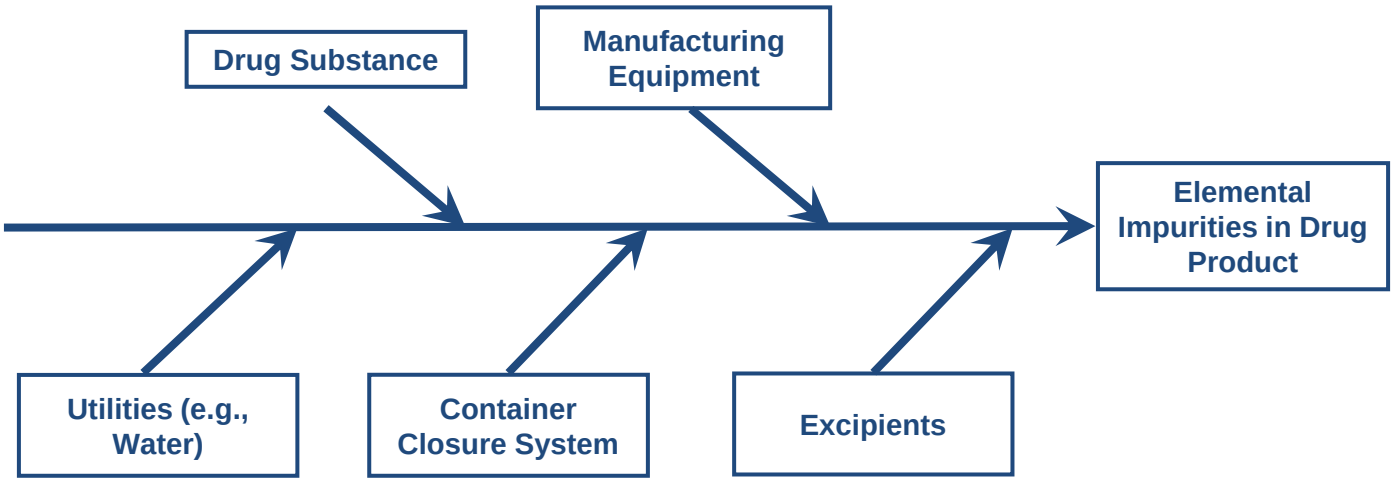
Ref.:Lewen, N et al, J.Pharm & Biomed.Anal. 35 (2004) 739-752

Practical Implementation ICH Q3D

- A **risk based** approach starts with element selection
- **24+ elements** are in scope for assessment
- These are divided into classes 1, 2a, 2b and 3; based on toxicity and natural abundance
- Class 1 and 2a are always in scope for oral DP
- Class 2b and 3 depend on intentional addition or non-oral route of administration
- If a good risk assessment is established, based on a good understanding of the product and processes used to make it, then potentially no extra controls or commitments to on-going testing can be filed

Practical Implementation ICH Q3D

- The risk assessment focuses on all inputs in to the drug product
- A fish bone diagram is provided to assist in selecting ingoing components to focus on

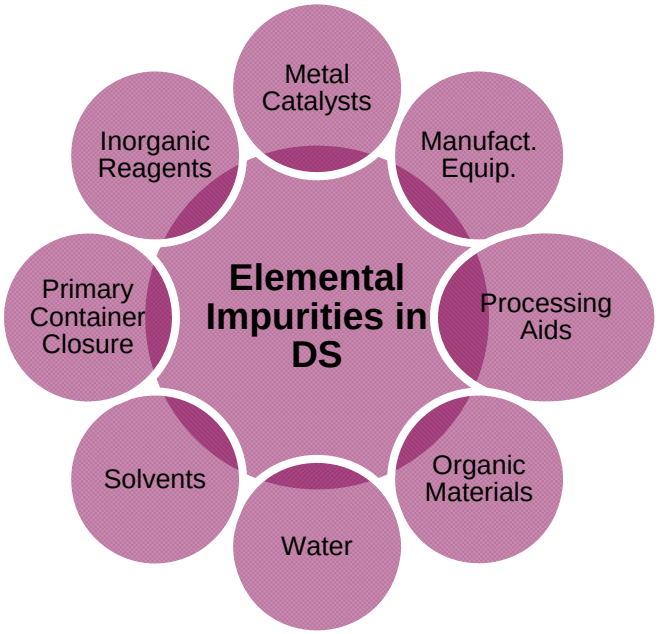


Practical Implementation ICH Q3D – API possible risk

API is an important component of any drug product

- Manufacture Equipment
  - GMP / inspection/ experimentation
- Processing aids / Organic materials
  - Unlikely to contain significant EI
- 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
- Inorganic Reagents / Metal Catalysts
  - High risk of being in final API especially if introduced in late stages of synthesis

Factors to consider



Many of these points equally relevant in assessing Excipient Manufacture

Practical Implementation ICH Q3D – DP manufacturing equipment – possible risk

- Almost all DP will be manufactured using metal equipment
- Key considerations... what metal is used? Possible risk of 2A metals
  - e.g. 316L stainless steel (contains approximately 10% w/w Ni nickel)
- DP manufacturing processes include – Blending, granulation, particle size reduction, tableting and coating.

How to assess the risk?

- Understand the metals used
- Understand material compatibility
- Visual inspection; corrosion or metal reduction
- Overall risk is low

Where is the risk?

- High energy process e.g. particle size reduction for solids
- Corrosive liquids, high/low pH

AGAIN - Many of these points equally relevant in assessing Excipient Manufact

Practical Implementation ICH Q3D – Utilities

- Utilities are such low risk they are almost out of scope
- **Water.** *"The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process(es)."*
- **Air.** "*Air is not likely to present a substantive risk; furthermore, air quality can also be managed through proper GMPs via use of HEPA filtered air, etc. No specific assessment is therefore generally required*."

- If you are using correct grade of water, manufacturing under GMP the risk from utilities is extremely low

Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Container Closure Systems (CCS)

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?

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;

Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Container Closure Systems

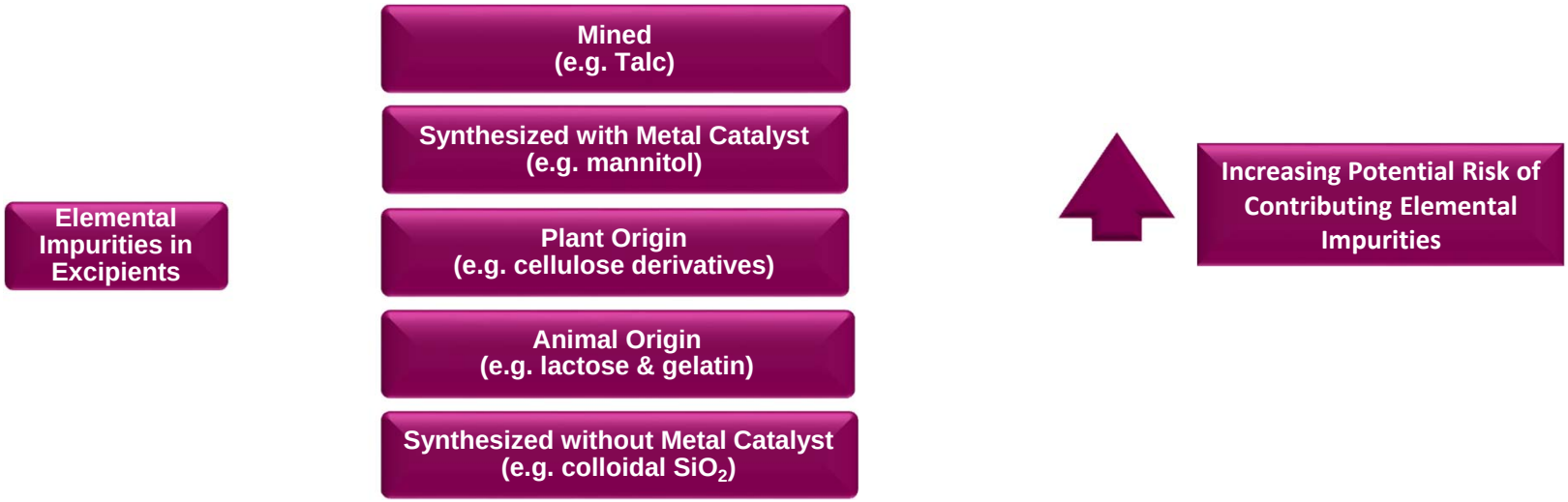
- Publication summarized literature data for a number of common packaging materials.
- Trace levels present within the component material, for example cadmium and lead levels up to 100 ppm were reported in polyvinyl chloride (PVC).
- NB - DIGESTION
- However effective ‘availability’ of the elemental impurity needs to be considered.
    - Typically extraction level <0.1% of that observed following digestion.
- Therefore, even when trace levels of certain elements are found in the component material, the available elemental impurity concentration may represent an extremely low safety risk.

Practical Implementation ICH Q3D – Excipients

- Many see excipients as the primary concern
- Is this justified?
  - Commonly the major component(s) in DP
  - Many excipients are mined
    - Variation? Homogeneity?
  - The area of least control
  - Current CoA isn't relevant to ICH Q3D
  - Many suppliers don't carry out routine full testing on each batch

Practical Implementation ICH Q3D – Excipients

- Perceived probability of EI content



- *Is there any evidence to support the perceived risk?*

Practical Implementation ICH Q3D – Excipients

FDA Studies (J Kauffmann)

Study involved:

- Some 200+ samples
- Examined 24 elements

RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Elemental Impurities in Pharmaceutical Excipients

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Summary of results

- **Little evidence of substantial levels of even the 'big 4/Class 1' (ubiquitous?) in mined excipients**
  - Pb seen in TiO2 but levels <10ppm, variability not significant.
  - Pb also seen in Zn Stearate.
  - Cd levels in Magnesium hydroxide / Calcium carbonate exceed Option 1 limits – levels need to fail to an option 2 limit before serious concern

Practical Implementation ICH Q3D – Excipients

Summary of results continued

- Metals seen where might be expected…
  - Class 2a metals seen at appreciable levels in some mined excipients
    - Ferric Oxide – V ,Ni, Co levels approx. 100 ppm
    - Ferric Carbonate – elevated Ni levels
  - NB - Such excipients unlikely to represent a major % of overall DP composition.

- Very little evidence of presence of Class 2b metals – unless deliberately used
  - Select silicones found to contain Pt up to 8 ppm, when added as catalyst.

- Several excipients contained Class 3 metals such as Cr, Mo, Sn, Ba
  - NONE exceeded Option 1 limits.

Data shows overall risk of ICH Q3D limit failure from excipients is low
  - Unless the excipient is used in DP with an atypically high daily intake.

Practical Implementation ICH Q3D – Excipients

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

Practical Implementation ICH Q3D – Excipients

Current status

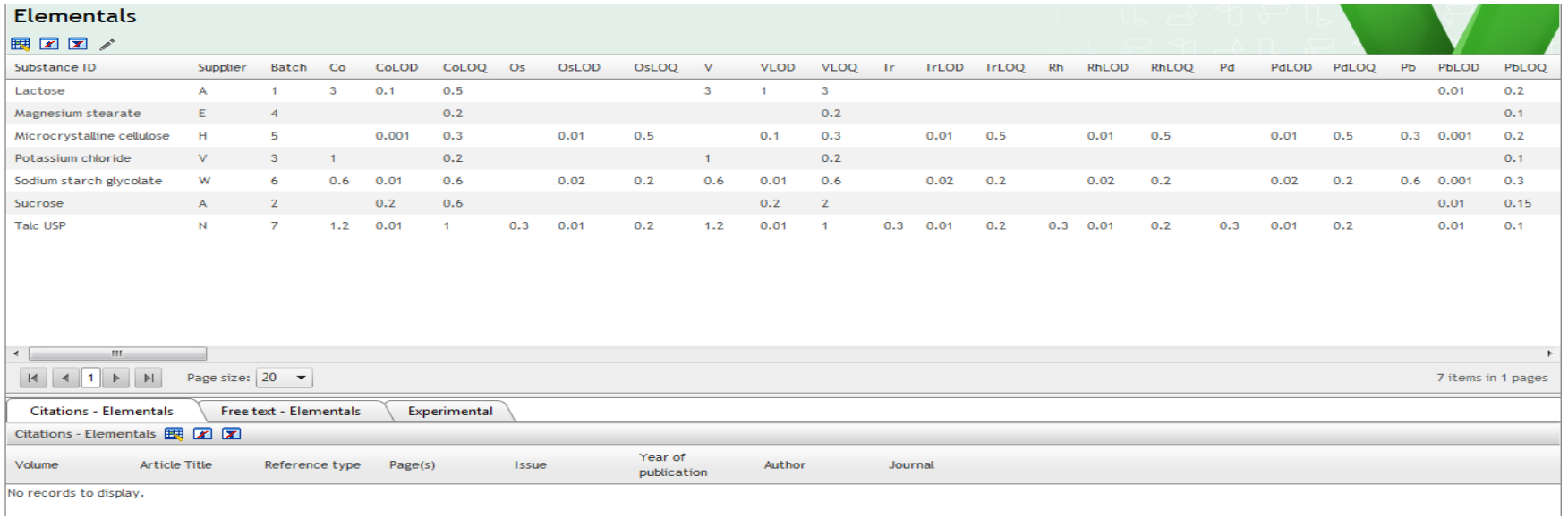
- 8+ big pharma companies
- Cursory knowledge of each members data
- To date no evidence of substantive issues associated with any of the excipients examined to date
- Lots of data on some common materials
  - E.g. Colours, Lactose , Microcrystalline Cellulose
- Data collated by individual members was seen to provide little evidence of gross metal contamination
  - Metals were detected in some materials e.g. V in tablet colouring
  - Mirrors findings of the FDA study.

Practical Implementation ICH Q3D – Excipients

Building a database

- 3rd party selected to host and blind data
- Data Integrity also important
  - We want data on excipients NOT suppliers
  - There is no intent to use this to compare suppliers, data will be blinded via a third party.
  - Want to see where the real risk is before formulation development starts

Practical Implementation ICH Q3D – Database



Elementals

Substance ID	Supplier	Batch	Co	CoLOD	CoLOQ	Os	OsLOD	OsLOQ	V	VLOD	VLOQ	Ir	IrLOD	IrLOQ	Rh	RhLOD	RhLOQ	Pd	PdLOD	PdLOQ	Pb	PbLOD	PbLOQ
Lactose	A	1	3	0.1	0.5				3	1	3											0.01	0.2
Magnesium stearate	E	4			0.2						0.2												0.1
Microcrystalline cellulose	H	5		0.001	0.3		0.01	0.5		0.1	0.3		0.01	0.5		0.01	0.5		0.01	0.5	0.3	0.001	0.2
Potassium chloride	V	3	1		0.2				1		0.2												0.1
Sodium starch glycolate	W	6	0.6	0.01	0.6		0.02	0.2	0.6	0.01	0.6		0.02	0.2		0.02	0.2		0.02	0.2	0.6	0.001	0.3
Sucrose	A	2		0.2	0.6					0.2	2											0.01	0.15
Talc USP	N	7	1.2	0.01	1	0.3	0.01	0.2	1.2	0.01	1	0.3	0.01	0.2	0.3	0.01	0.2	0.3	0.01	0.2		0.01	0.1

Page size: 20 — 7 items in 1 pages

Citations - Elementals | Free text - Elementals | Experimental

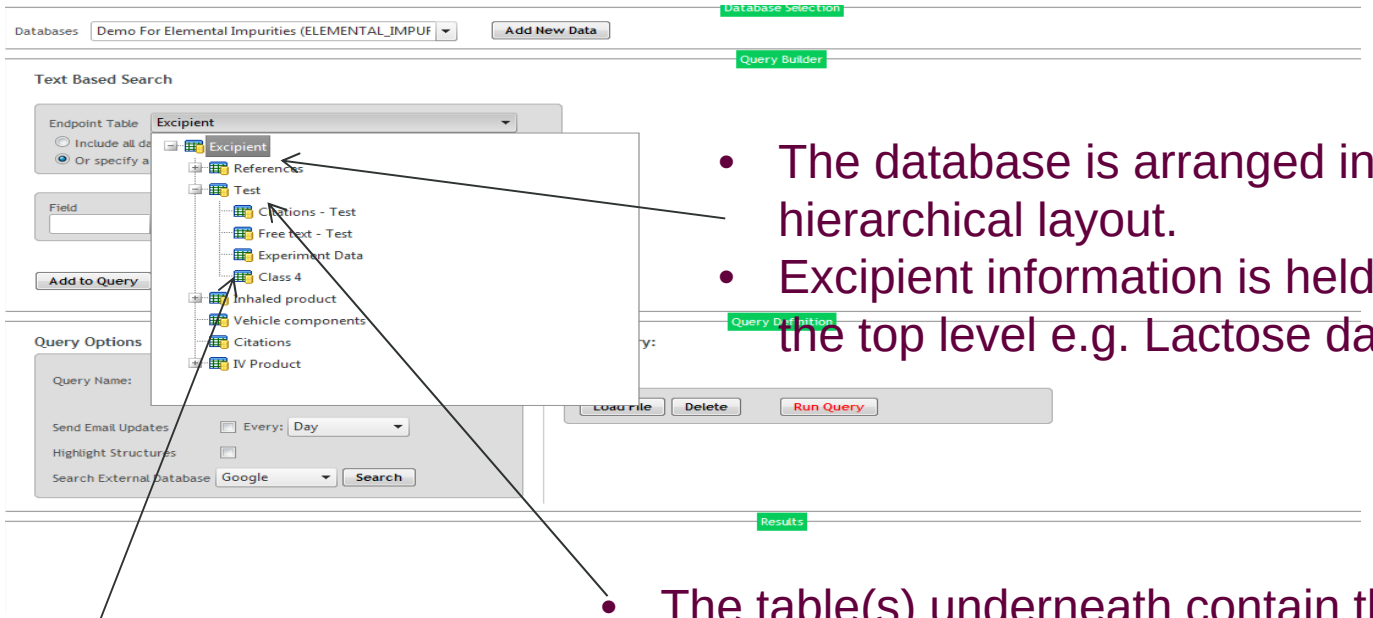
Citations - Elementals

Volume	Article Title	Reference type	Page(s)	Issue	Year of publication	Author	Journal

No records to display.

- Database will show... - Excipient name, supplier (blinded), batch (blinded), method LOD or LOQ and result

Practical Implementation ICH Q3D – Database



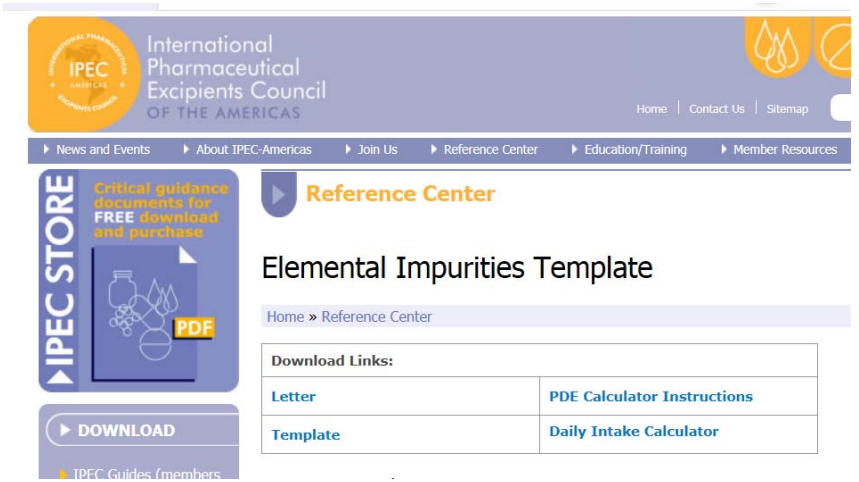
- The database is arranged in hierarchical layout.
- Excipient information is held at the top level e.g. Lactose data
- The table(s) underneath contain the study information.
- It is also possible to add further layers, e.g. shown here a third laver.

Practical Implementation ICH Q3D – Engagement

- Practical Implementation of ICH Q3D requires the sharing of knowledge, this requires effective communication between all parties.

- To facilitate this IPEC + Coalition input generated a questionnaire.

- Other tools such as calculator are accessible .



This is not about demanding option 1 limits be applied without thought

Practical Implementation ICH Q3D – Conclusions

- There is most likely not the smoking gun that was perhaps anticipated before ICH Q3D
- Risk assessments need to be rational,
  scientific and focus controls on highest risk areas

- Overall risk of reaching ICH Q3D limits is low
  - If GMP processes are followed
  - If material compatibility is understood
  - Risks associated with each component understood

Practical Implementation ICH Q3D – Conclusions

- The more data we can generate and share, the more this will help with a practical rational implementation
- It is a risk based approach not testing for certainty
- Only real risk areas are likely to be...
  - If you have a solid oral product with an atypically high daily intake (e.g. >10 g) and a high wt% of a mined excipient in the DP (e.g. >40wt%).
  - If you have large volume liquid product with low pH manufactured and held in metal for a long time.

- Overall the content of EI in drug product is likely to be extremely low, in the vast majority of cases.

Practical Implementation ICH Q3D – Further information

- Link to pharm tech article http://www.pharmtech.com/implementation-ich-q3d-elemental-impurities-guideline-challenges-and-opportunities

- If you would like to become involved in the database and data sharing contact pass on your details or contact
- Andrew.teasdale@astrazeneca.com

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