Utilisation of Data as part of an Integrated EI Risk Assessment Process

Role of Industry Collaboration /FDA-IPEC Excipient Study Data

Andrew Teasdale

PQRI/USP Workshop on Elemental Impurity Requirements in a Global Environment – Next Steps?

March 31 – April 1, 2015
USP Meeting Center
Rockville, Maryland
Elemental Impurities – Practical Implementation of ICH Q3D

Areas Covered

✓ Overview - Utilisation of Data as part of an Integrated EI Risk Assessment Process

✓ Practical Implementation Considerations

✓ Potential Sources of Elemental Impurities in the Finished Product
  ✓ API
  ✓ Equipment
  ✓ Container-closure system
  ✓ Excipients

✓ Data sharing - Elemental Impurities Pharma Consortium

✓ Conclusions
Elemental Impurities – Practical Implementation of ICH Q3D

Basic Principles – What to include in a risk assessment

• ICH Q3D clearly predicates a risk based approach to evaluation of Elemental Impurities (EIs)

• Focus is on final product – fish bone diagram seeks to assist by advising components for consideration.
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk?

If you like certainty then Q3D is going to worry you!!

• The fundamental challenge is to find a means to categorise risk.

• Without this then you will test everything (all potential sources / all 24 EIs) or simply default to Option 3 – End Product testing.

• How do you do this? What role will data play in this?
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – API

- The active is obviously an important component of the risk assessment

**Factors for consideration**

*How can data assist in classifying risk?*

- **Purified water** – Monitoring

- **Equipment** – GMP / inspection / experimentation

- **Container closure** - Little evidence of contamination
  - Limited use of catalysts
  - Low level metals
  - Solid – Solid – No clear mechanism

- **Solvents** – Few utilise metals deliberately in manufacture. Many are distilled.

- **Primary Risk – Deliberately added metal catalysts**
  - Even here future understanding of fate / purge – data may help assess actual risk aka. mutagenic Impurities
What is a risk? – API

- We already have data
- Most if not all API specifications have included USP <231> or equivalent.
- Non-specific test – yet provides some supporting evidence.
- Has anyone ever seen a failure? Not in Elemental Impurities Pharma Consortium
- Is the test so flawed it would have missed routine contamination? Can this be used as part of a weight of evidence argument that processing equipment is a minor risk?? - ASK THE QUESTION OF OURSELVES
- Data derived from instrumental testing of API mirrors this.
  ✓ Where metals are seen they relate to catalysts.
Elemental Impurities – Practical Implementation of ICH Q3D

How to decide what is a risk? – API Conclusions

• Drug substance manufacturing often involves a complex series of processes, however:

• Simple scientific principles can be applied to ensure that elemental impurity levels in the final drug substance are controlled to appropriate levels.

• The application of a risk-based control strategy, involving:
  ✓ an understanding of the manufacturing process and key sources of elemental impurities, focusing on critical later stages.
  ✓ appropriate equipment selection/qualification,
  ✓ adoption of suitable GMP processes/procedures, and the selection and application of appropriate control options will typically result in the manufacture of drug substances with elemental impurity levels well below ICH Q3D.

• Overall low risk status, certainly for oral treatment, is supported by the emerging dataset from ICP-optical emission spectrometry (OES) and ICP-mass spectrometry (MS) screening of a wide range of drug substances plus the significant body of historical heavy-metals test data.
what is a risk? – Product Manufacturing Equipment

- Manufacturing for products encompasses a large variety of processes:
  - solid mixing (blending), granulation, tableting (compression), coating, and particle size reduction.
  - for liquid product manufacture, dissolution or suspension of solid excipients and drug substance (DS) is often carried out in metallic equipment.

IS THERE A RISK?

- Theoretical risk associated with Class 2A metals such as V, Ni etc., since these elements are commonly found in manufacturing equipment;
  - for example, e.g. 316L stainless steel (contains approximately 10% w/w Ni nickel).

HOW CAN THIS BE ASSESSED?

- Understand construction of materials
- What processes may represent a risk? High kinetic energy (solids) or corrosive liquids?
<table>
<thead>
<tr>
<th>Unit operation</th>
<th>Kinetic energy</th>
<th>Aggressive conditions</th>
<th>Recommended routine cGMP controls</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing/granulation</td>
<td>Low</td>
<td>Dry = No</td>
<td>NA</td>
<td>e.g., Low equipment rotation/translation speed</td>
</tr>
<tr>
<td></td>
<td>High (Shear)</td>
<td>Wet = Yes</td>
<td>Periodic visual inspection of the equipment for abrasion and/or corrosion.</td>
<td>Although the likelihood of a potential elemental impurity contribution is increased when moving from low shear mixing to high shear mixing, the overall risk of a significant elemental impurity contribution remains low.</td>
</tr>
<tr>
<td>Tableting</td>
<td>High</td>
<td>NA</td>
<td>Periodic visual inspection, as above.</td>
<td>Normal wear on dyes/punches is unlikely to release any appreciable amount of elemental impurities into the product.</td>
</tr>
<tr>
<td>Encapsulation</td>
<td>High</td>
<td>NA</td>
<td>Periodic visual inspection as above.</td>
<td>--</td>
</tr>
<tr>
<td>(Liquid) Filling, Lyophilisation</td>
<td>Low</td>
<td>Product specific</td>
<td>For aggressive, e.g., high pH conditions, regular visual inspection of the equipment for corrosion.</td>
<td>Effect of actual corrosion, as with tablet punch erosion, unlikely to result in substantive release of elemental impurities at levels of concern into the product.</td>
</tr>
<tr>
<td>Coating</td>
<td>Low</td>
<td>Low</td>
<td>Covered by routine cGMPs, e.g., for maintenance, cleaning.</td>
<td>--</td>
</tr>
<tr>
<td>Particle Size Reduction</td>
<td>High</td>
<td>Very high</td>
<td>Despite the high energy it is not expected that the particle size reduction process will lead to the need for routine drug product testing requirements for elemental impurities associated with the materials of construction of the mill. In the vast majority of cases, routine cGMP will be sufficient.</td>
<td>Although the possibility of metal transfer during this process is high due to abrasion, the risk of levels approaching the limits defined in ICH Q3D is extremely low. Such a risk may be evaluated through a mathematical assessment, evaluating the theoretical maximum level of metal possibly transferred during the process, this to permitted limits. Practical evaluation through comparison of the elemental impurity profile of the ingoing material to that of the outgoing material may also be performed. Such an assessment may also take into consideration historical knowledge of similar processes and substances. Such approaches may be used to determine if further controls other than cGMP are required.</td>
</tr>
</tbody>
</table>
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Product Manufacturing Equipment

Case Study: extreme example – visible loss

Visible abrasion of nozzles

Key questions:
• Level of metal lost?
• Batch Size?

• Level of metal = 1.0g
• Batch Size = 500Kg (assumed all in 1 batch)
• Level of metal = 2ug/g of product
• Level of Mo = 60ng/g (3% level in SS)
• ICH Q3D limit for Mo = 10ug (Inhaled)
• Conclusion - even is this extreme case levels are << permitted levels.
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?**

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.
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

• Seen by many as the primary concern.

• Is this justified?

• Points for consideration
  ✓ May form a large part of the overall drug product (this should of course be assessed).
  ✓ Many excipients are mined – anticipated variability
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

- Mined (e.g. Talc)
- Synthesized with Metal Catalyst (e.g. mannitol)
- Plant Origin (e.g. cellulose derivatives)
- Animal Origin (e.g. lactose & gelatin)
- Synthesised without Metal Catalyst (e.g. colloidal SiO₂)

What does the evidence show?

Increasing Potential Risk of Contributing Elemental Impurities

Elemental Impurities in Excipients
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

FDA Studies (J Kauffmann) – Key Learning

Study involved:
• Some 200+ samples,
• Examined 24 elements,
• LODs 1ppt.

Results
• Little evidence of substantial levels of even the ‘big 4’ (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 – BUT need to take into consideration level (% composition) in the DP.
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

FDA Studies (J Kaufmann) – Key Learning

Results – continued

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

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

- **Several excipients contained Class 3 metals such as Cr, Mo, Sn, Ba**
  - NONE exceeded Option 1 limits.
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

Elemental Impurities Pharma Consortium

• Borne out of discussions during a JPAG EI meeting October 2013.

• Circumstantially - 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 that found in FDA study.

• To date no evidence of substantive issues associated with any of the excipients examined to date.

• Agreed the value of pooling data
Elemental Impurities – Practical Implementation of ICH Q3D

What is a risk? – Excipients

SOME CAUTION IS NEEDED:

✓ At this stage we have only cursory knowledge relating to the level of variability.

✓ The limited number of samples tested cannot as yet represent what types of excursions may be possible, especially for mined excipients.

✓ This will only really be known after much more testing of excipients over a period of time.

✓ How much data is needed?

✓ The data generated to date is encouraging
Data Sharing

• Key to data sharing is establishment of principles upon which data will be shared;

• **Quality is critical**
  - Minimum Standards for methods including validation.
    - Detailed proposals drafted.

• **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.
Elemental Impurities – Practical Implementation of ICH Q3D Data Sharing

This would be blinded and visible only to the organisation maintaining the database.

Results donated would be recorded for all metals tested – colour coded to flag any levels > Option 1 limit

These data will be used to inform NOT as the formal basis of a risk assessment.

• Do provide supportive data
Elemental Impurities – Practical Implementation of ICH Q3D

Data Sharing

• Current status
  ✓ 8 companies involved
    • 7 Major Pharmaceutical Companies

• Data on over 500 samples covering ~100 different materials

• Substantive data on some materials
  ✓ E.g. Colours
  ✓ Lactose
  ✓ Microcrystalline Cellulose

• Anticipate rapid growth of data.

• Plan once established to interpret data and summarise key findings cf FDA study data
  ✓ Similarities / differences etc.
Elemental Impurities – Practical Implementation of ICH Q3D

Conclusions

• While understandable that ICH Q3D is predicated on examining all potential sources of EIs; any assessment should be **risk based and data driven**.

  The more data we can collate and interpret the closer we can get to achieving practical implementation differentiated and focused on actual rather than perceived risk.

• **Overall risk of EIs in the final drug product going to be low, in most cases**’

Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 2 Kingdom Street, London, W2 6BD, UK, T: +44(0)20 7604 8000, F: +44 (0)20 7604 8151, www.astrazeneca.com
Acknowledgements

Data Sharing team members

Cyrille C. Chéry, Lance Smallshaw UCB Pharma

Graham Cook, Laurence Harris, Carlos W. Lee, Samuel Powell Pfizer

John Glennon, Phil Nethercote, Laura Rutter, Mike James GSK

Nancy Lewen BMS

Sarah Thompson, Vicki Woodward AZ

Helmut Rockstroh Roche

Katherine Ulman Dow Corning

Darragh Norton, Patrick Drumm, Mark Schweitzer Novartis