In recent years, the presence of metal impurities has become a major issue in the drug-making industry, and thus, the need for its effective removal. The time pressure associated for drug candidates to quickly reach the market has greatly increased the number of metal-catalysed reactions progressing from lead optimization to early scale-up.

For almost two years now, the International Conference on Harmonisation (ICH) has been working on its Q3D guidelines for metal elemental impurities in new drugs and new formulations containing known ingredients. After many revisions and improvements, the final version or the Q3D guidelines was finally accepted and signed off by the ICH Steering Committee in December 2014, hence requiring that the entire manufacturing industry and supply chain follow these regulations. The implementation phase was in January 2016.

Learn more on what do drug manufacturers need to do and how we can help you.
ICH Steps
The guideline proposed by the ICH and other regulatory agencies can be summarized in four steps:

1. Identify potential sources of elemental impurities
2. Determine the possibility of occurrences of elemental impurities in a final drug
3. Evaluate the concentration of elemental impurities according to the established potential daily exposure (PDE)
4. Control by developing a plan to reduce or limit elemental impurities in a final drug

Potential sources of elemental impurities
Potential sources of elemental impurities during a drug manufacturing process are very broad. It could come from an intentionally added element during synthesis or from potentially contaminated water, excipient, equipment or containers, as shown below. Indeed, reaction can be summarized in four steps:

- « The Big Four »
  - Highly toxic across all administration routes. It will be necessary to demonstrate compliance for the removal of these metals in all drugs.
  - Arsenic (As)
  - Cadmium (Cd)
  - Lead (Pb)
  - Mercury (Hg)

- Class 2
  - Generally considered as route-dependent toxicants, this class is divided in two groups which are related to their abundance likelihood in drugs.
  - Relatively high possibility to be present:
    - Cobalt (Co)
    - Nickel (Ni)
    - Vanadium (V)

- Class 2B
  - Reduced possibility of occurrence in the drug product.
    - Gold (Au)
    - Iridium (Ir)
    - Osmium (Os)
    - Palladium (Pd)
    - Platinum (Pt)
    - Rhodium (Rh)
    - Ruthenium (Ru)
    - Selenium (Se)
    - Silver (Ag)
    - Thallium (Tl)

- Class 3
  - Relatively low toxicity by oral administration but need to be considered for inhalation and parenteral routes.
    - Antimony (Sb)
    - Barium (Ba)
    - Chromium (Cr)
    - Copper (Cu)
    - Lithium (Li)
    - Molybdenum (Mo)
    - Tin (Sn)

- Other elements for which a PDE has not yet been established.
  - Aluminum (Al)
  - Boron (B)
  - Calcium (Ca)
  - Iron (Fe)
  - Magnesium (Mg)
  - Manganese (Mn)
  - Potassium (K)
  - Sodium (Na)
  - Tungsten (W)
  - Zinc (Zn)

Which metals need to be evaluated?
Henceforth, twenty-four (24) metals have been implicated and associated with great health risk and are presented in the USP’s Chapter <232>. Inside this new chapter, metals that should be evaluated are subdivided in four groups:

- Class 1
  - Elements that can be easily scavenged
- Class 2A
  - Elements that cannot be scavenged
- Class 2B
  - Elements that can be scavenged
- Class 3
  - Elements that cannot be scavenged

How SiliCycle can help you?
What SiliCycle has to offer is a turnkey solution for rapid, reliable, removal of metal contaminants.
Taking advantage of SiliCycle’s strong expertise in the field of grafting technology is your solution for metal removal.
With over 20 years of research and development on this type of technology, we are today one of the world’s leaders in the industry of functionalized silicas, to purify APIs from metallic residues. We can provide you with the broadest portfolio of multi-functional scavengers (for the removal of ligands and metals), in the widest range of available formats for laboratories to plant scale purifications.

We call it the 65 Solution!
- Safe: very stable material
- Simple: no extra apparatus required, no extra solvent, no complicated calculations, no extra work-up...
- Strength: extreme affinity toward targeted metal
- Selectivity: very specific for the metal, high API recovery
- Speed: quick, one-step process
- Scalable: easily scalable technology from R&D to production scales

We are available to work with your team, step by step:
- from discovery, through development and all the way up to your manufacturing processes.
- If you would like more information on how we can help you with your metal removal challenges, please contact us at support@silicycle.com

You also might be interested by our scavenging solution poster (PN: POS-001).

Call us to get yours:
1.877.745.4292 (North America only)
+1 418 874.0054 (Worldwide)
As a recognized industry leader in the development, manufacturing and commercialization of innovative silica gel products, and with multi-ton manufacturing capability, SiliCycle® is your partner of choice for all your METAL REMOVAL, CATALYSIS, SYNTHESIS, and PURIFICATION requirements.

**METAL & ORGANIC SCAVENGING**

- Removal of:
  - Metals
  - Electrophiles & Nucleophiles
  - Potential Genotoxic Impurities (PGI)

**CATALYSIS & SYNTHESIS**

- Couplings (Suzuki, Stille, Heck, ...)
- Debenzylation & Hydrogenation
- Oxidation
- And Many More Reactions

**ACIDS, BASES & REAGENTS**

- Acids & Bases
- Amide Couplings
- Reductive Aminations
- Other Reactions

**LOW PRESSURE CHROMATOGRAPHY**

- Bulk Silica Gels (Irregular & Spherical)
- Bonded Phases
- TLC Plates
- Prepacked Flash Cartridges

**SAMPLE PREPARATION**

- SPE & Well Plates
- Micro-SPE Tips
- QuEChERS
- SPE Hardware & Manifold

**HIGH PRESSURE CHROMATOGRAPHY**

- Bulk Sorbents
- HPLC & UPLC Columns
- SEC & SFC Columns
- Guard Cartridges & Accessories

**CONSUMABLES**

- Vials & Caps
- Syringe Filters
- Membrane Filters

**EQUIPMENTS**

- Parallel Synthesis Synthesizer - MiniBlock & MiniBlock XT
- TLC Scanner
- Vacuum Manifold

**DESICCANTS & OTHER BULK ABSORBENTS**

- Desiccant
- Activated Alumina
- Molecular Sieve

**R&D SERVICES**

- Scavenging Screening
- Method Development & Optimization
- Impurities Determination
- Custom Column Packing

---

**CONTACT INFORMATION:**

T: 1 418.874.0054   F: 1 418.874.0355
Toll Free: 1 877.SILICYCLE (North America only)
info@SiliCycle.com
SiliCycle.com

SiliCycle Europe
European Office
europe@SiliCycle.com

SiliCycle China
Chinese Office
china@SiliCycle.com

SiliCycle India
Indian Office
india@SiliCycle.com

SiliCycle Inc - Worldwide Headquarters
2500, Parc-Technologique Blvd
Quebec City (Quebec) G1P 4S6
CANADA

Printed in Quebec, Canada, © SiliCycle Inc.
WP-001 V1.3 02/17