aqpa – Vereinstreffen
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Q3D – Guideline for Elemental Impurities

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ICH-Richtline Q3D – Allgemeines

- **Veröffentlichung** – Dez. 2014
- **Übergangszeit**
  - Neue Zulassungen: Juni 2016
  - Bestehende Zulassungen: Dez. 2017
- **Allgemeine Vorbemerkungen**
  - Umfangreich und komplex (68 Seiten)
  - Risikobasierte Vorgehensweise
  - PDE (Permitted daily exposure) ersetzt die Grenzwert-Testungen
  - Genauere Testmethoden (z.B. ICP - Inductively coupled plasma) werden klassische „Naßchemie“ ersetzen
    „Pharmacopoeial procedures or suitable alternative procedures „
  - Herausforderung für pharmazeutische Unternehmen

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ICH-Richtline Q3D - Umfang

This guideline **does not apply** to herbal products, radiopharmaceuticals, **vaccines**, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or **blood derivatives** including plasma and plasma derivatives, dialysate solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit.

This guideline **does not apply** to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as **advanced therapy** medicinal products.

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ICH-Richtline Q3D – Safety Assessment

- **Principles of the Safety Assessment**
  - Elements evaluated in this guideline were assessed by reviewing the **publicly available data** contained in scientific journals, studies, guidance, …
  - The available information was reviewed to establish the oral, parenteral and inhalation PDEs (Permitted daily exposure).
- **Element Classification**
  - **Class 1:** The elements, As, Cd, Hg, and Pb, are human **toxicants** that have **limited or no use** in the manufacture of pharmaceuticals.
  - **Class 2:** Elements in this class are generally considered as **route-dependent human toxicants** (A, B: Probability of occurrence in the drug product)
  - **Class 3:** The elements in this class have relatively **low toxicities by the oral route** of administration (high PDEs, > 500 µg/day) but may require consideration in the risk assessment for inhalation and parenteral routes.

ICH-Richtline Q3D – PDE

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

Element	Class[2]	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	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

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ICH-Richtline Q3D – Mögliche Quellen

Figure 1: Sources of elemental impurities in finished drug products.

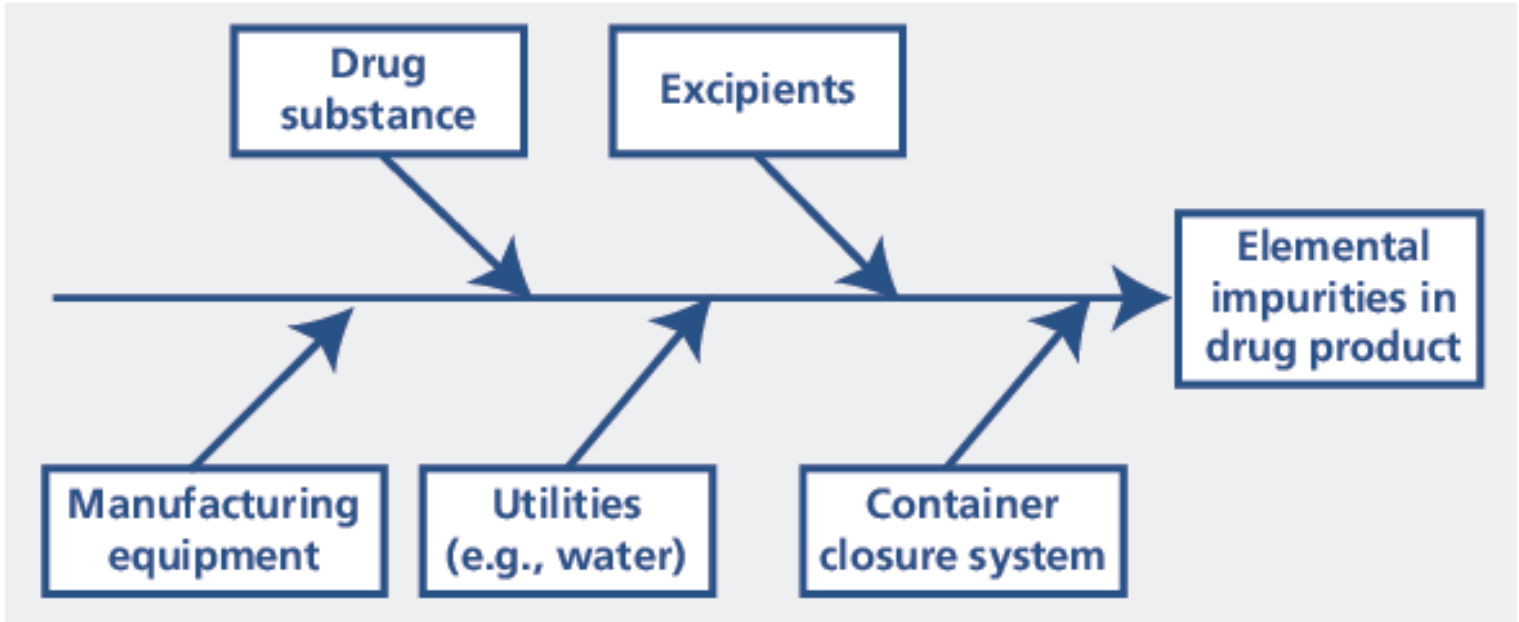

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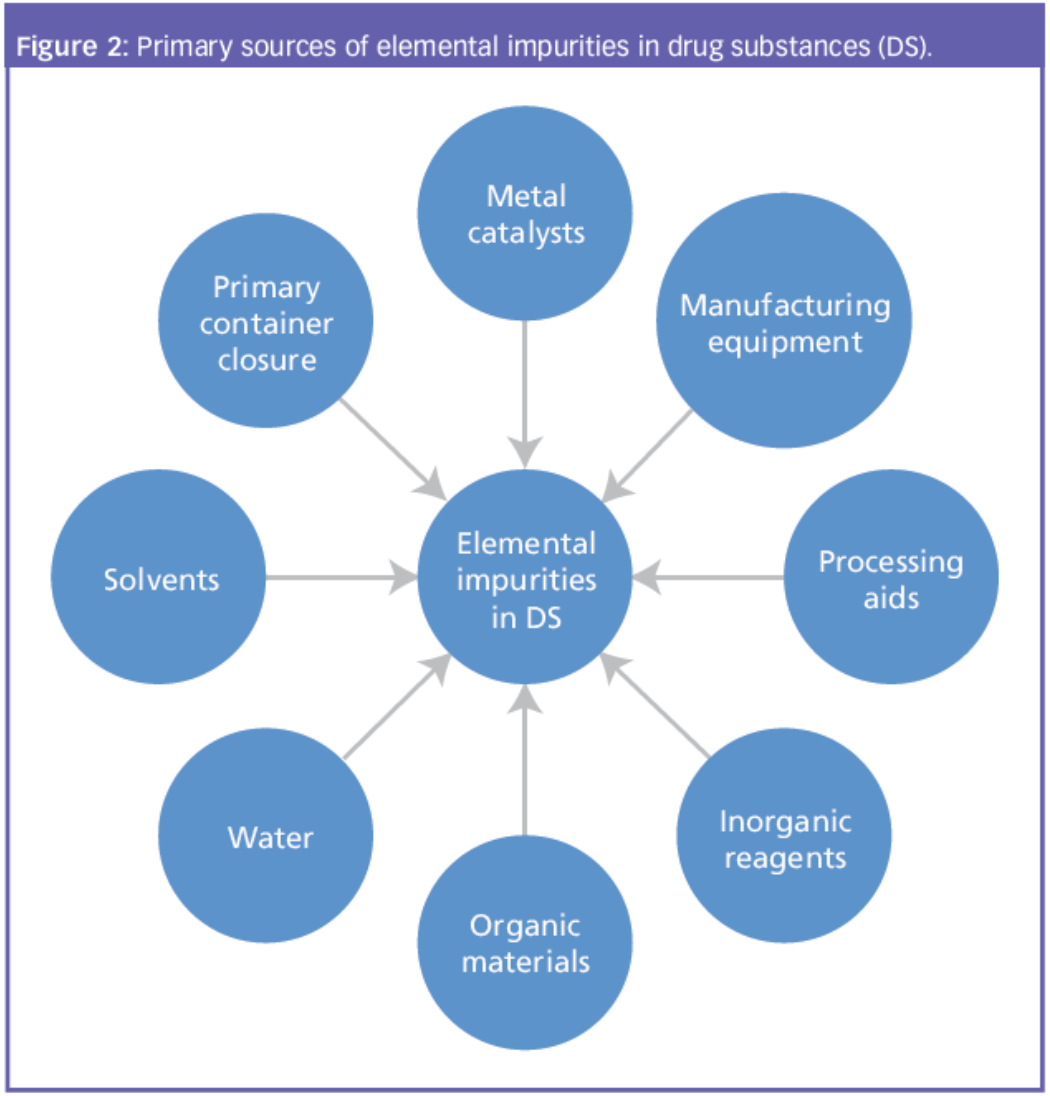
Figure 2: Primary sources of elemental impurities in drug substances (DS).



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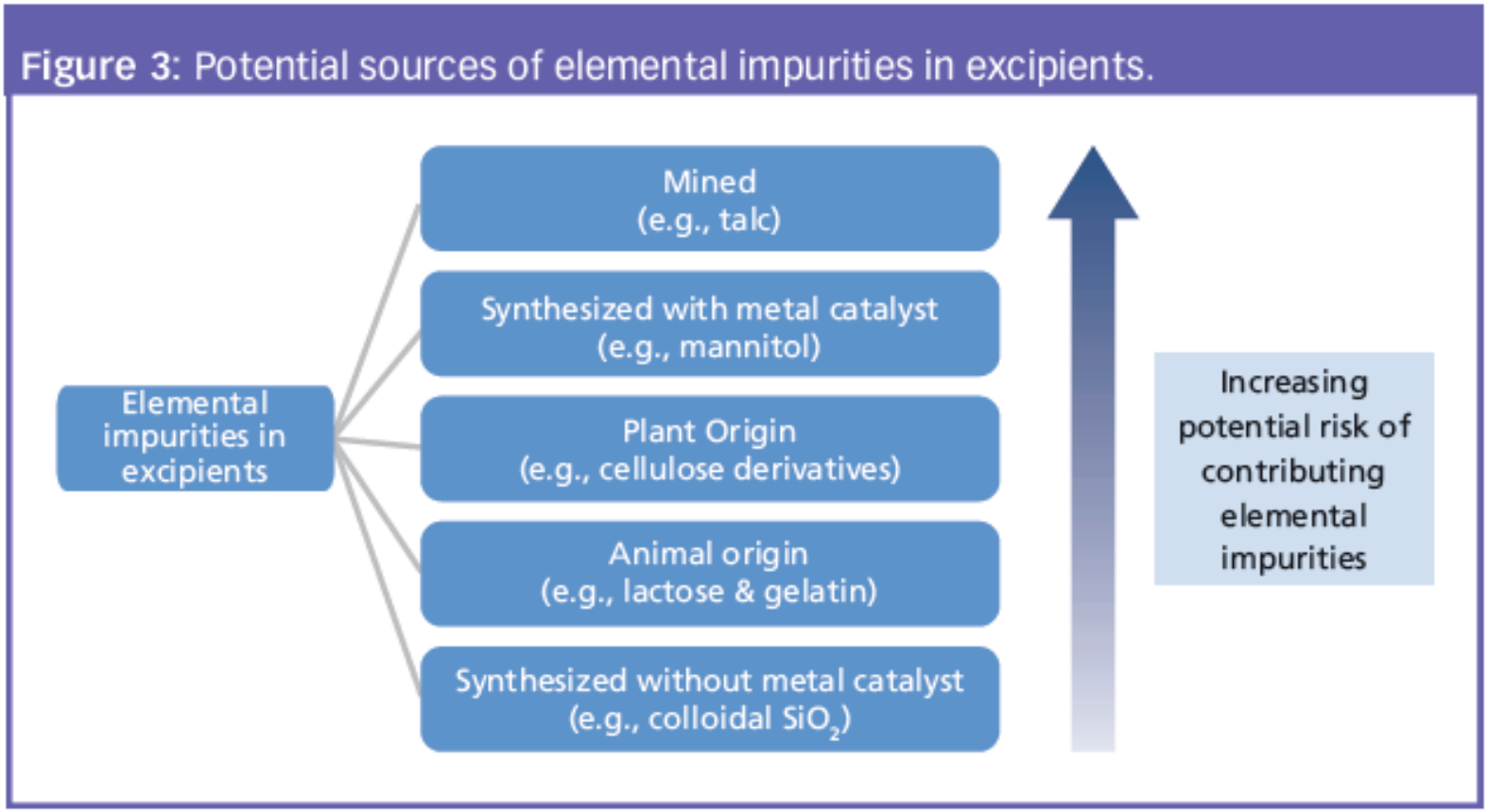

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ICH-Richtline Q3D – Control Strategy

- **Generals**
  - A **control threshold** is defined as a level that is **30% of the established PDE** in the drug product.
  - Data from **three (3) representative production** scale lots
- **Approaches**
  - Modification of the steps in the **manufacturing process**
  - Implementation of **in-process or upstream controls**
  - Establishment of specification **limits for materials**
  - Establishment of specification **limits for the drug substance**
  - Establishment of specification **limits for the drug product**
  - Selection of appropriate **container closure systems**

ICH-Richtline Q3D – Control Strategy

Fragen, Kommentare oder Erfahrungen?

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