



Recent experience with global implementation of the principles of ICH Q3D

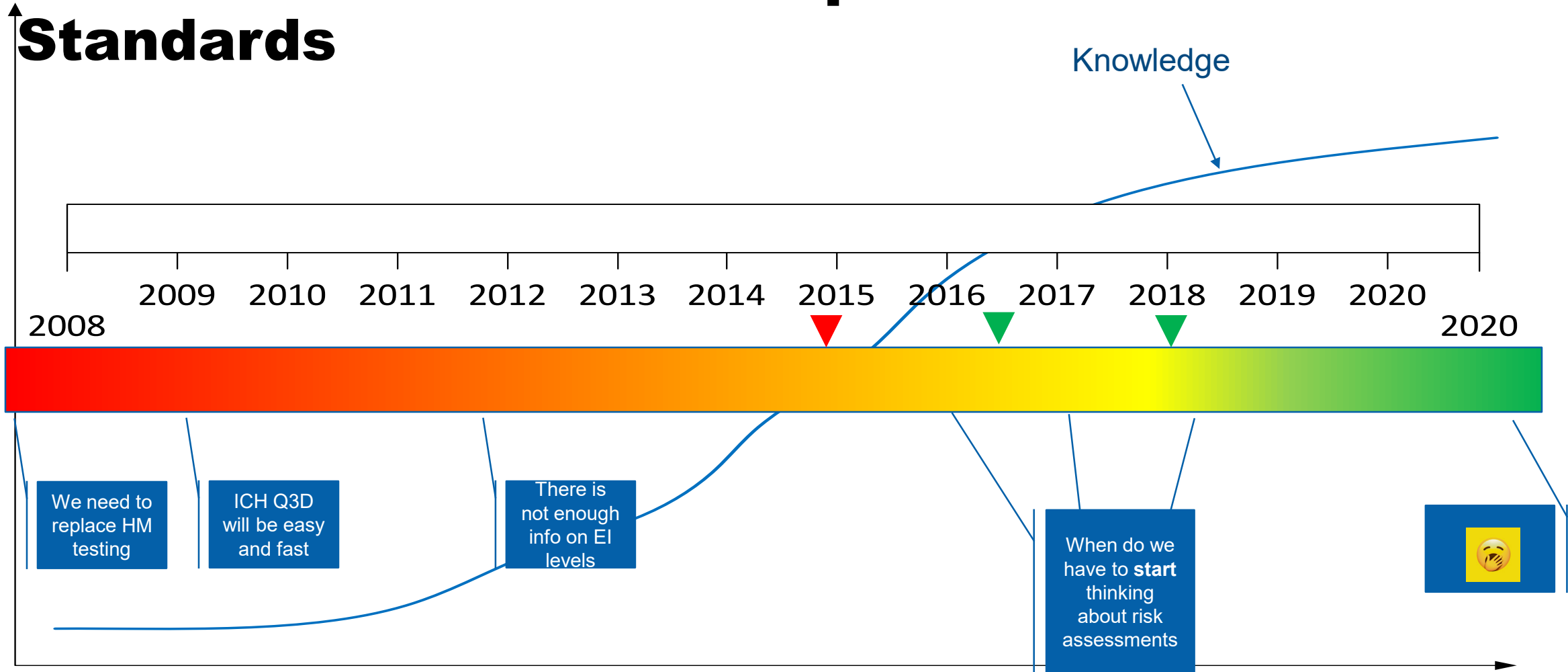
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Evolution of Elemental Impurities Global Standards



Learning curve/growing pains

- New product submissions post-July 2016
 - ‘Please include EI control limits for all elements listed in ICH Q3D to ensure EI control in the drug substance’
 - ‘Please provide the EI risk assessment and testing results for the specified elements in ICH Q3D for the excipients and drug substance’
 - The EI product risk assessment provided EI evaluation from the components, please provide testing results for the drug product and a proposal for DP EI specification
 - Component assessment demonstrated the only potential source of EI was the drug substance
 - Drug substance testing demonstrated control of relevant EI <10% of the PDE in the DP
 - The EI product risk assessment was based on DP testing results, please provide proposed specification limits for EI in the DP to be included in routine release testing
 - The DP testing of 6 clinical lots and 3 commercial lots showed no detectable levels of EI (LOQ represented <10% of the PDE)
- Marketed products (post-Jan 2018)
 - Challenges with high daily dose drugs with selected mined excipients and active ingredients (e.g. mineral supplements)

Feedback from non-ICH regions post-ICH Q3D implementation

- Mis-application of the ICH Q3D product risk assessments to materials other than the DP
- Limited number of requests to establish “ICH” EI limits for DS and excipients
- Experience level in developing and completing EI product risk assessments was variable (industry and regulators)
 - A number of companies began considering the approaches too close to the effective date of the local regulation implementation
 - Lack of clear guidance from some HAs regarding what constituted a “good” EI product risk assessment and variable feedback on what constituted and unacceptable EI product risk assessment

Assumptions vs reality

Assumptions

- There is no data available for EI levels in materials
- Vendors and suppliers have no data and will not share data
- Everything needs to be tested regardless of the conclusions of the risk assessment
- We only have to do a paper assessment and if there are no risks testing is not required

Reality

- While true in the early stages, the knowledge base has increased
- Many vendors when asked would willingly share screening data available. Partial reality – not all were covered
- Successful assessments were accepted using a risk based approach
- Absence of data (published or laboratory) was rapidly confirmed to be unacceptable to most if not all regulatory authorities

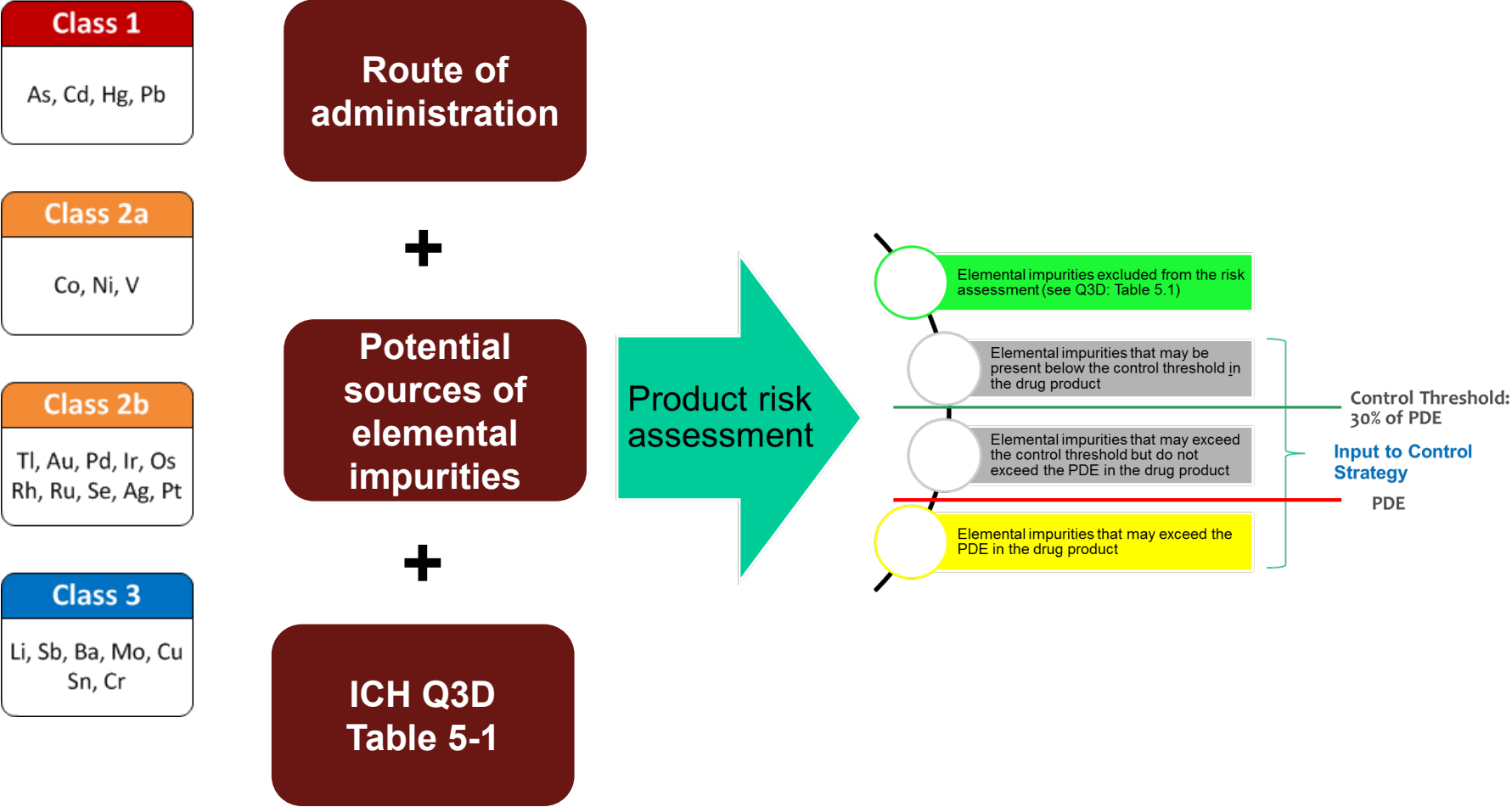


Implemented elemental impurity assessment strategy

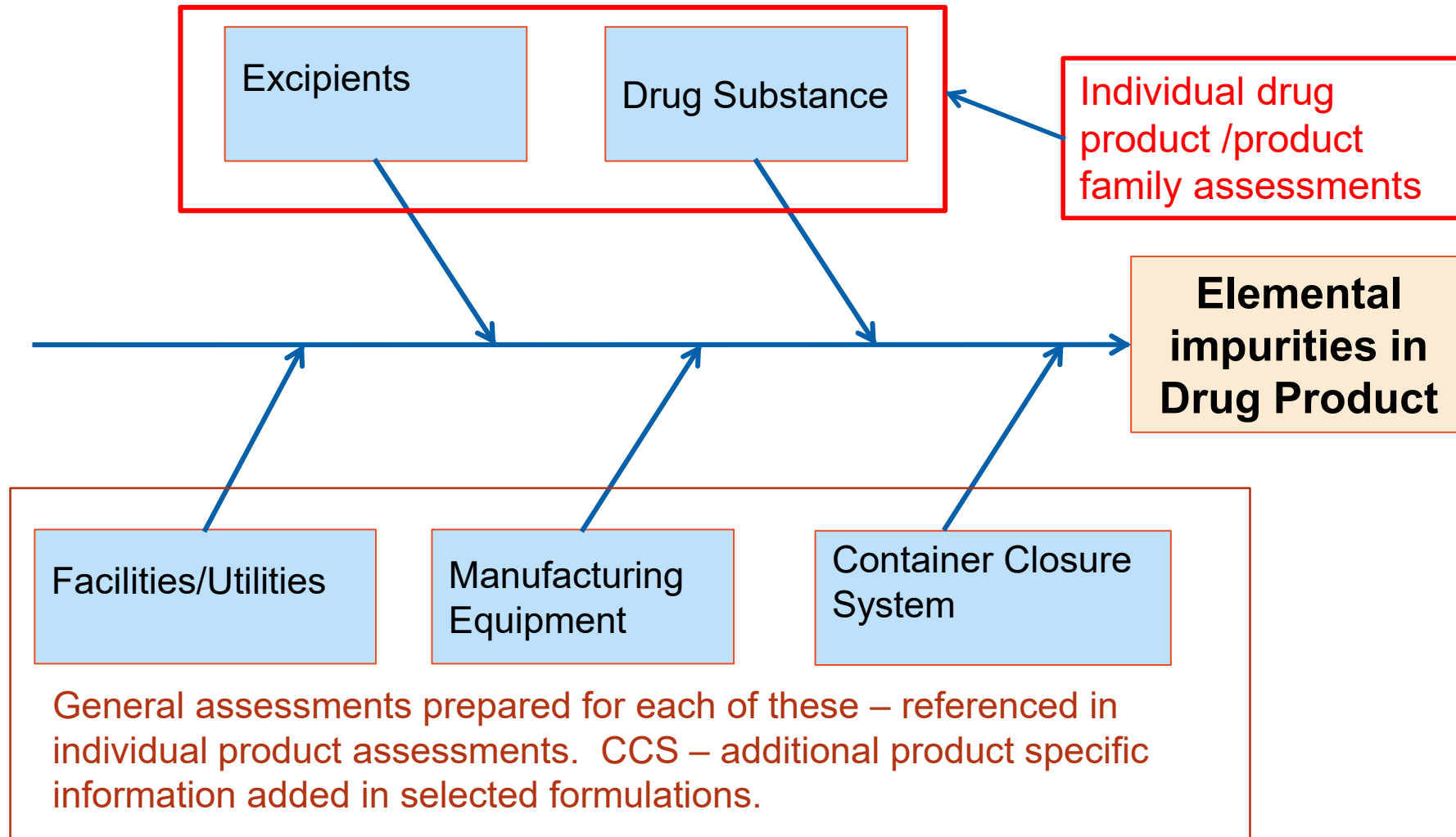
To know where to start, one must first know.....



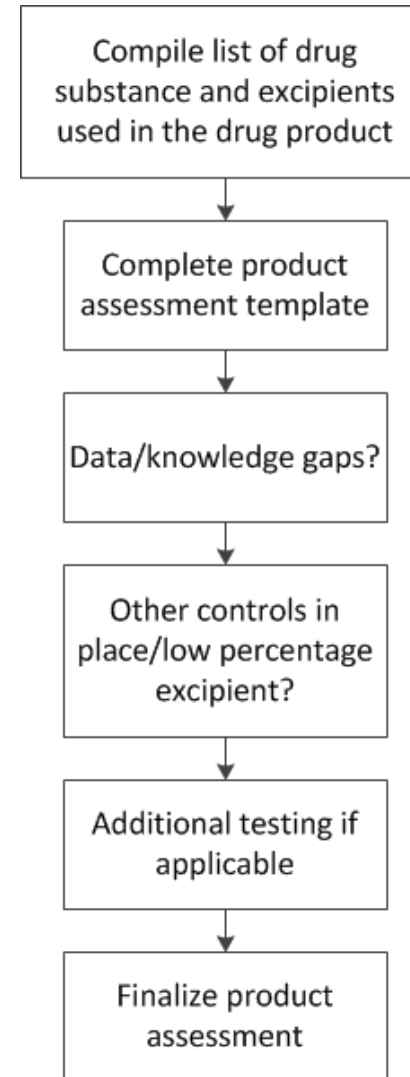
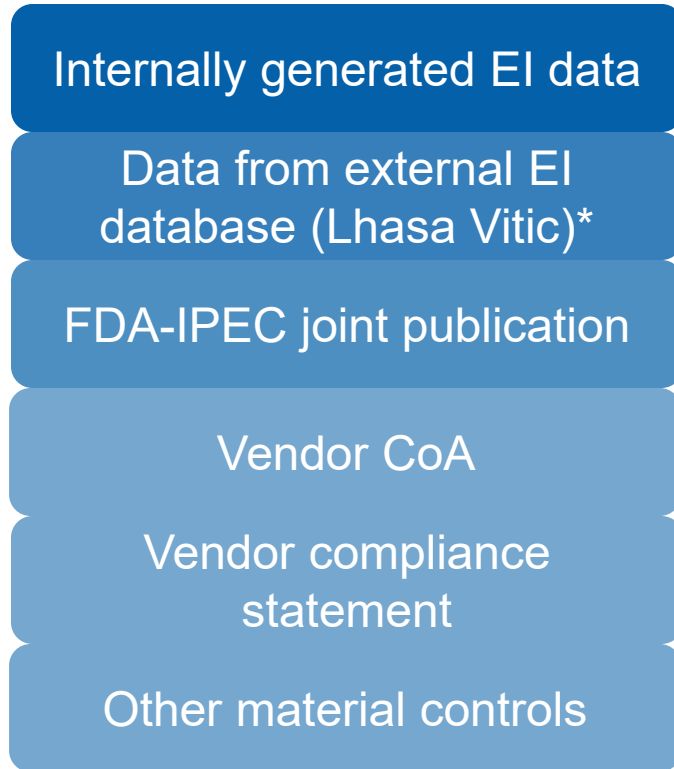
Assessment objective



Preparation of EI product risk assessments

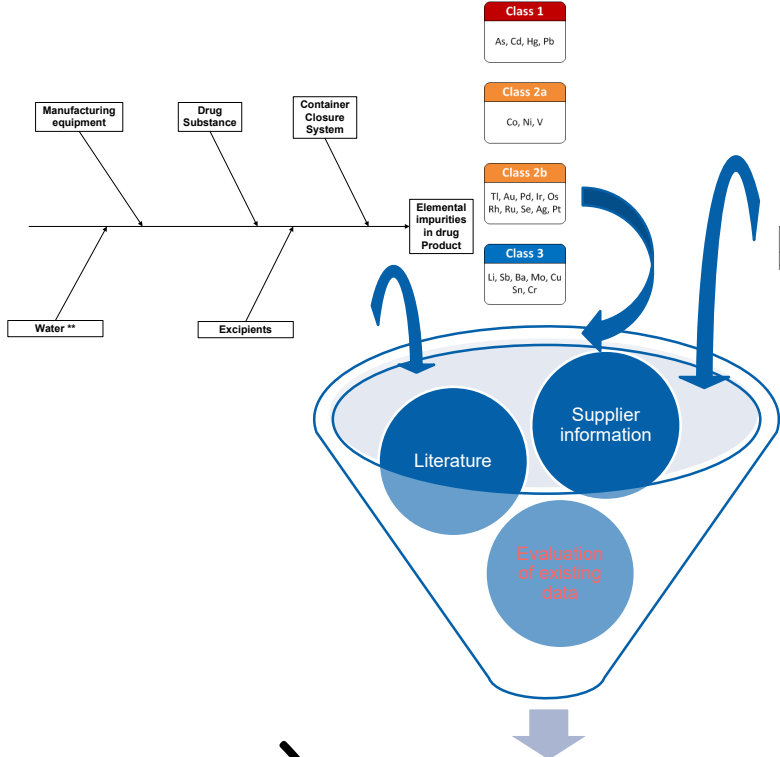


Sources of data for EI product risk assessments



* Boetzel R, Ceszlak A, Day C, Drumm P, Gil Bejar J, Glennon J, Harris L, Heghes CI, Horga R, Jacobs PL, Keurentjes WJTM, King F, Lee CW, Lewen N, Marchant CA, Maris FA, Nye W, Powell S, Rockstroh H, Rutter L, Schweitzer M, Shannon E, Smallshaw L, Teasdale A, Thompson S, Wilkinson D. An Elemental Impurities Excipient Database: A Viable Tool for ICH Q3D Drug Product Risk Assessment. *J Pharm Sci.* 2018 Apr 18. pii: S0022-3549(18)30212-0. doi: 10.1016/j.xphs.2018.04.009. [Epub ahead of print] PubMed PMID: 29679706. : <https://doi.org/10.1016/j.xphs.2018.04.009>

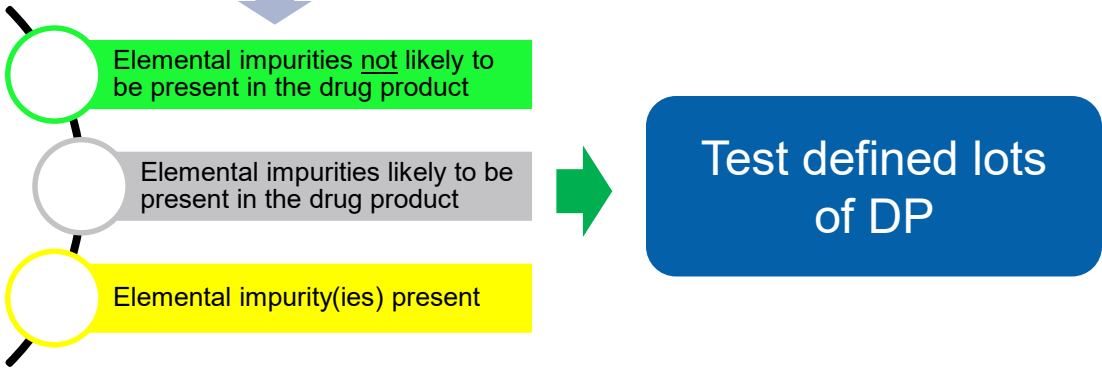
Assessment approach based on final drug product



5.4 Recommendations for Elements to be Considered in the Risk Assessment
The following table provides recommendations for inclusion of elemental impurities in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 5.1: Elements to be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation

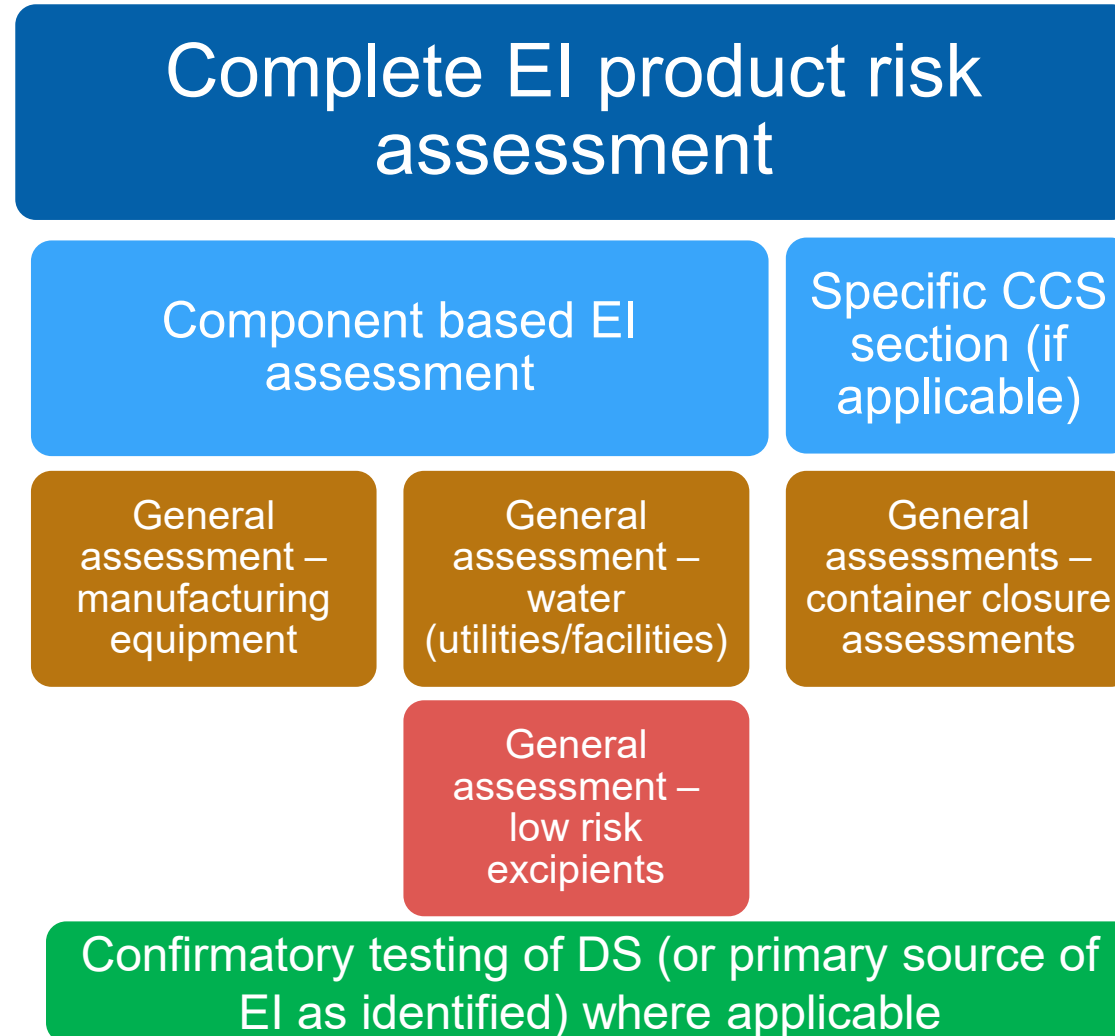


Verification of consolidation of component data and information

1	Drug product testing – product 1	3 lots representative drug product lots
2	Component testing drug product 1	3 Representative lots of DS 3 Representative lots of each excipient from the current vendors supplying materials for drug product 1
3	Product assessment – drug product 1	Component assessment: <ul style="list-style-type: none">• Utilized internal and external excipient EI database• Literature information• Vendor statements



Product assessment package



How has this strategy worked to date (applied to new Rx and Gx submissions)

- Risk assessment submitted with supplemental confirmatory testing using commercial or representative material
- Several submissions with only completed risk assessment (including component testing data, published data or data from Lhasa Vitic database)
- All assessments based on potential EI defined by ICH Q3D for route of administration and if intentionally added element during the process.

EI assessments in all submissions accepted with no challenge or questions



Thank you