Implementation of ICH Q3D for ANDAs Since June 2016: Generic Industry Perspective

PQRI/USP Workshop on ICH Q3D Requirements

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Outline

- ICH Q3D and USP<232> and Timelines
- ICH Q3D Risk Assessment Primer
- A primer for EI Analysis in Generics
- Recent queries on EIs in ANDAs
- Risk Assessment Considerations
- GMPs as enabler of derisking EIs
- Summary

Q3D Elemental Impurities Guidance for Industry

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2015
ICH

⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

⟨233⟩ ELEMENTAL IMPURITIES—PROCEDURES

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Timelines of ICH Q3D Implementation

- ICH Q3D Guideline released on December 2014
- FDA Adoption of ICH Q3D: September 2015
- Apply to all to-be-submitted ANDAs/NDAs
- Applies to approved ANDAs effective January 1, 2018

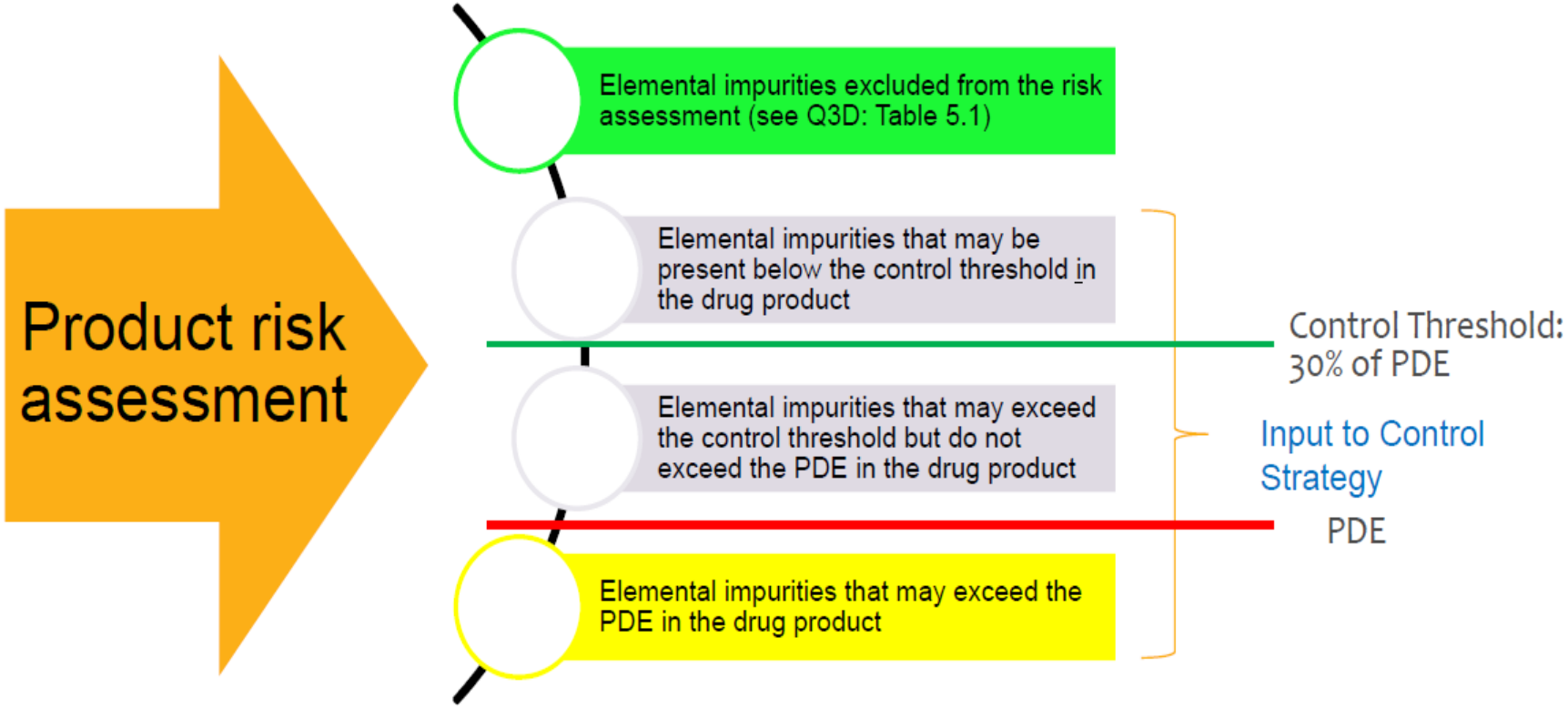
ICH Q3D-Risk based Assessment

- Identify known and potential sources of elemental impurities that may find their way into the drug product
- Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE
- Summarize and document the risk assessment
  - Identify if controls built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product

A Five-Step Risk Assessment Process

- Identify known and potential sources of elemental impurities
- Data gathering
- PDE calculations: ICH Q3D and USP<232>
- Batch analysis data for APIs, Excipients, Drug Products
- Control strategy

Risk Assessment Output



Is justification based on a theoretical risk assessment and screening data for 24 EIs sufficient?

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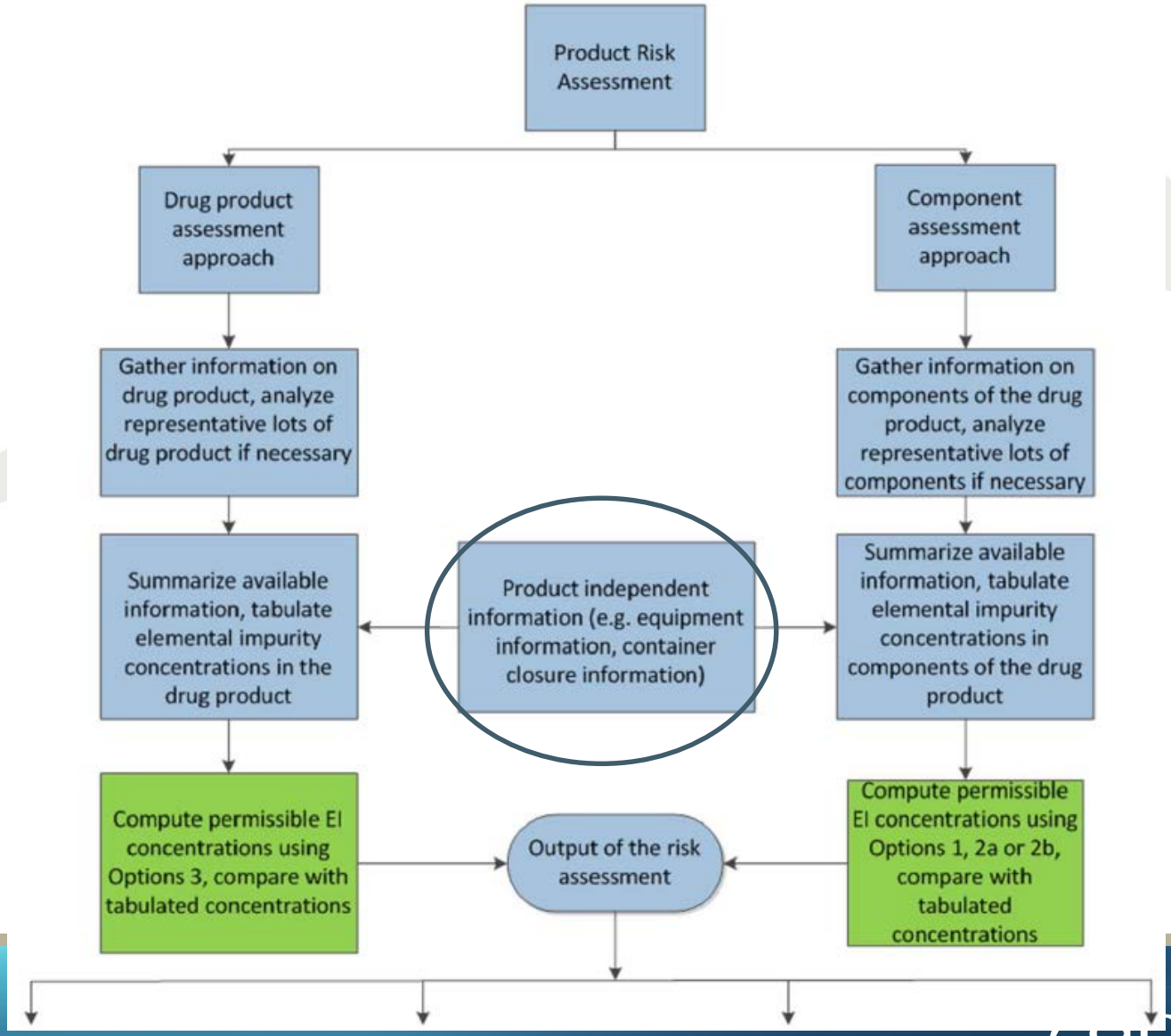
Two Approaches to Risk Assessment



Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

A Primer for EI Assessment of Generics

- Paper Screening (Evaluation) based on the details from API and excipients and process with with probability of carry forward
- Screening/analysis of 24 Elements by XRF: Dosage form screened through XRF to evaluate the risk in terms of the carry forward of elemental load from the each of the components.

Primer Contd..

- Method development and full validation for 7 elements (I and IIA) (also 3 additional III for parenterals) on ICP MS
- Generation of data on EB's and based on risk assessment if no risk (<30% of threshold values) : Data submission to FDA with all the method details
- If risk assessment and/or data shows >30% control threshold: Additional control – further testing is essential.

Recent Queries on EIs

- We expect you to comply with ICH Q3D as of January 1, 2018. Please acknowledge this in your next response.
- We acknowledge that you have provided the elemental impurities assessment in section 3.2.P.5.5. However, your assessment did not consider elemental impurities risk from water for injection, other excipients, manufacturing equipment and container closure system.

Recent Queries Contd..

We acknowledge the EI assessment provided in Module XX.. However, use of ICH Q3B Option 2B requires additional knowledge regarding your proposed permitted concentration of each EI in the components of the drug product and summation overall components in the DP. The calculations provided in Table 5 do not include your permitted concentration of each elemental impurity and summation over all components in the DP; therefore, the elemental impurities assessment does not satisfy the requirements of ICH Q3B Option 2B. Please acknowledge this in your response.

Recent Queries Contd..

- We acknowledge you have included risk assessment for elemental impurities in the PDR, however, given that the inorganic salt XX is a naturally occurring mineral that could contain other metal impurities, we request that you work with the DMF holder and investigate the potential presence of EIs in the API based on appropriate risk assessment per ICH Q3D.
- The proposed control limits of elemental impurities in the API specification and their justification, as well as analytical methods and their validation should be submitted for our review.

Recent Queries Contd..

- For the calculation of elemental impurities control in the drug product, Option 1 per ICHQ3D/USP <232> is not applicable as the MDD of the proposed drug product is greater than 10g. Instead please establish the <u>specification for the elemental impurities based on Option 2.</u>

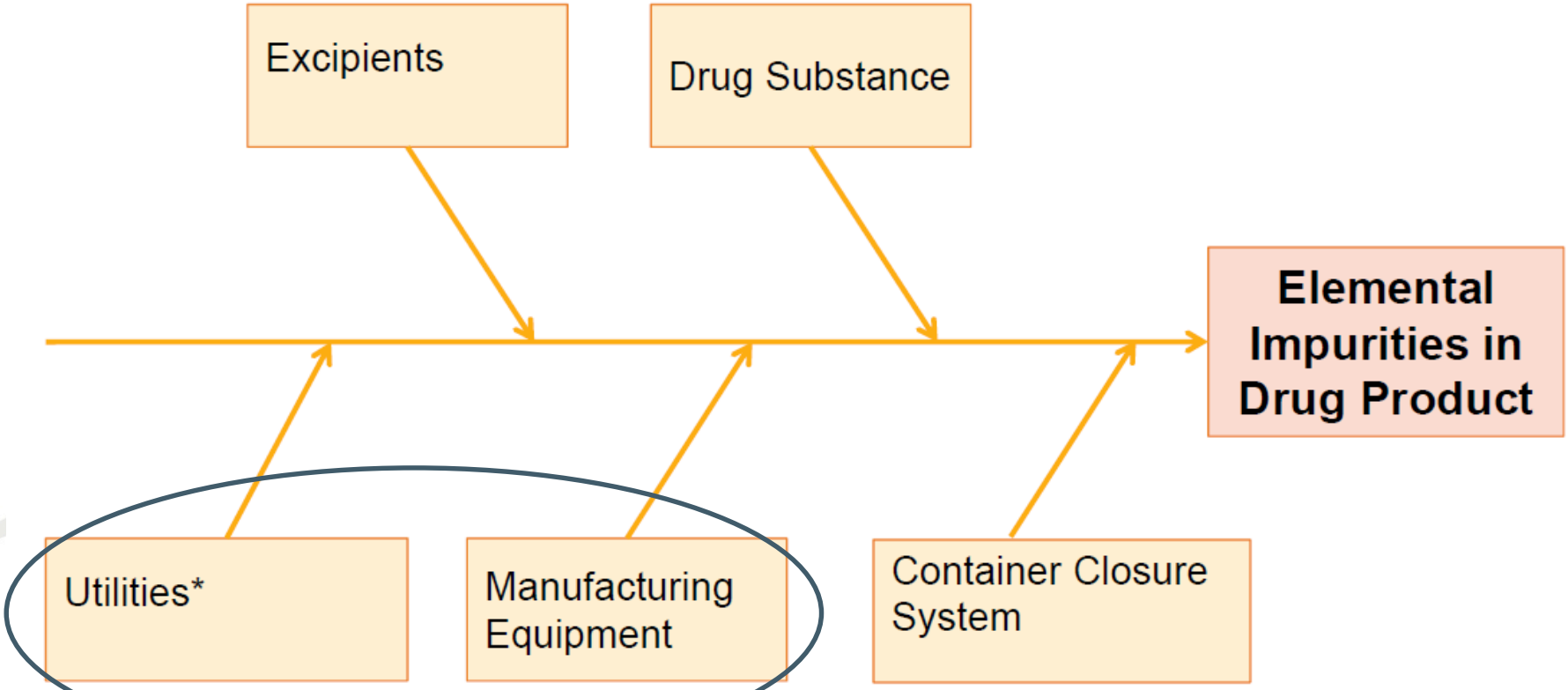
Recent Queries Continued

- Since, the DS is natural origin material, and the variability in elemental impurities is expected, please include testing of elemental impurities belonging to class 1 and 2A in the proposed DS and DP using the correct option as per ICHQ3D/USP <232>.
- Also, provide method validation for the proposed testing methods in the revised submission for Agency's review.

Elemental Analysis Results of An Oral Drug Product

Class	Element	Acceptance Criteria	Results (ppm)						
			Drug Product Oral Solution, USP Strength 1			Acceptance Criteria	Drug Product Oral Solution, USP Strength 2		
			EB 1	EB 2	EB 3		EB 1	EB 2	EB 3
1	Cd	NMT 0.025 ppm	0.0000 (<LOD)	0.0000 (<LOD)	0.0000 (<LOD)	NMT 0.05 ppm	0.0000 (<LOD)	0.0000 (<LOD)	0.0000 (<LOD)
	Pb	NMT 0.025 ppm	0.0073	0.0071	0.0106	NMT 0.05 ppm	0.0272	0.0157	0.0212
	As	NMT 0.08 ppm	0.0024 (<LOQ)	0.0013 (<LOQ)	0.0008 (<LOD)	NMT 0.16 ppm	0.0013 (<LOD)	0.0003 (<LOD)	0.0005 (<LOD)
	Hg	NMT 0.17 ppm	0.0004 (<LOD)	0.0004 (<LOD)	0.0003 (<LOD)	NMT 0.33 ppm	0.0005 (<LOD)	0.0003 (<LOD)	0.0003 (<LOD)
2A	Co	NMT 0.25 ppm	0.0000 (<LOD)	0.0000 (<LOD)	0.0000 (<LOD)	NMT 0.5 ppm	0.0000 (<LOD)	0.0000 (<LOD)	0.0000 (<LOD)
	V	NMT 0.5 ppm	0.0140 (<LOQ)	0.0103 (<LOQ)	0.0092 (<LOQ)	NMT 1.1 ppm	0.0188 (<LOQ)	0.0176 (<LOQ)	0.0147 (<LOQ)
	Ni	NMT 1.15 ppm	0.0038 (<LOD)	0.0018 (<LOD)	0.0018 (<LOD)	NMT 2.25 ppm	0.0034 (<LOD)	0.0013 (<LOD)	0.0025 (<LOD)

Risk Assessment Considerations



* Water is the primary utility of potential concern

The product assessment should consider the potential of each of these categories to contribute elemental impurities to the drug product

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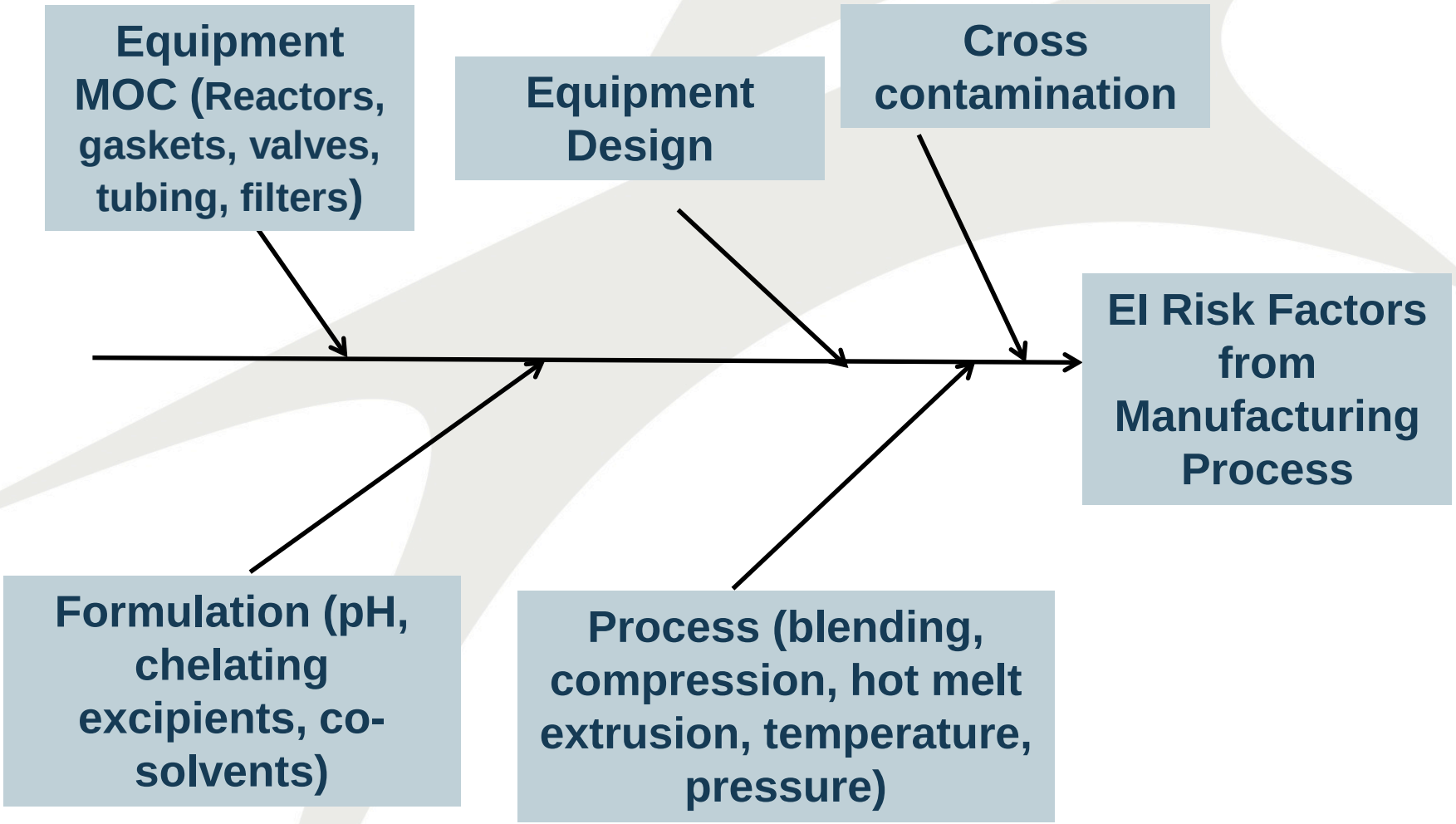

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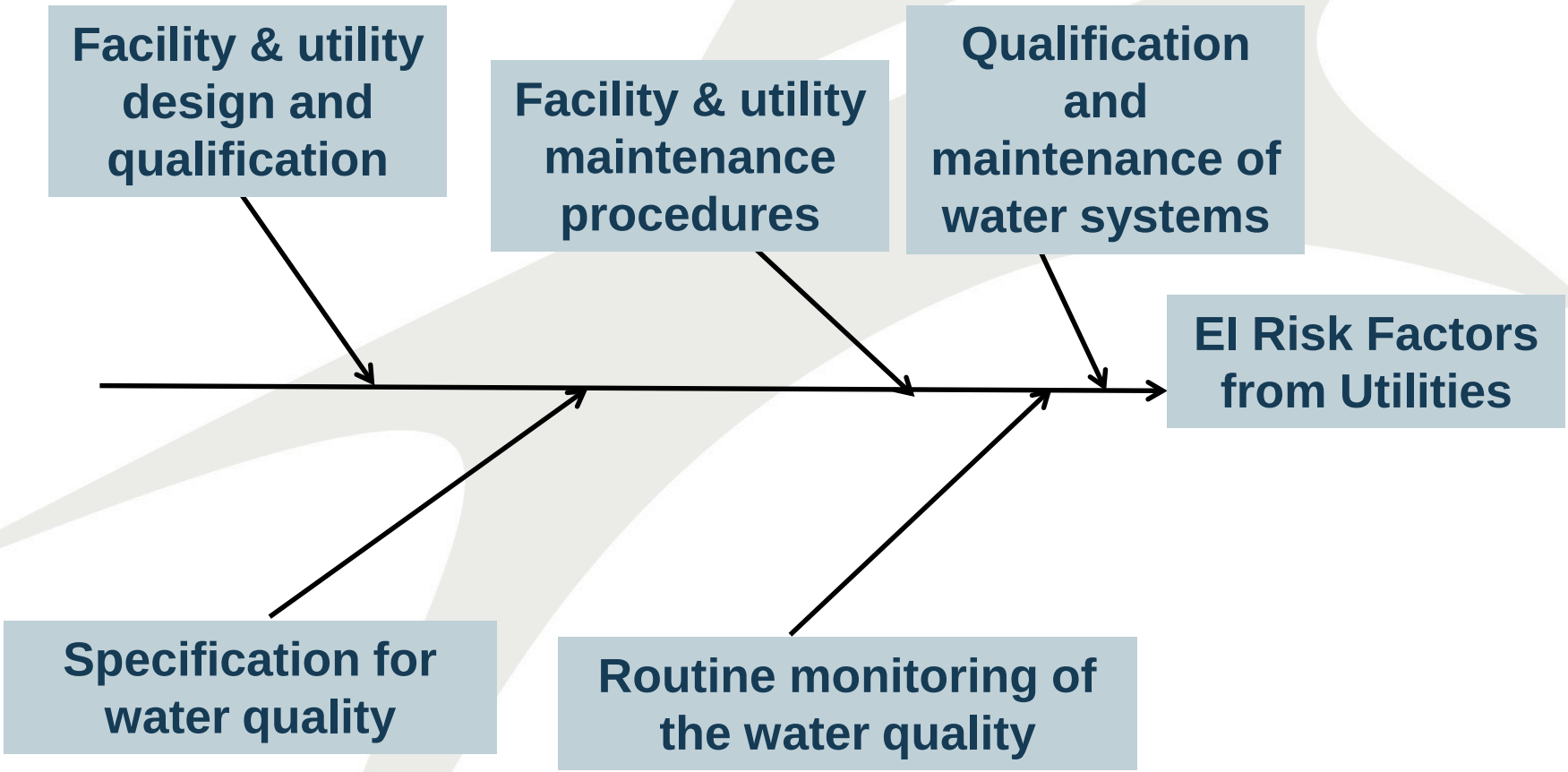

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GMPs Impact Analysis of EIs

21 CFR 211.65

- Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

ICH Q7 5.1

- Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications

GMPs Derisk EIs

- **GMP policies, processes and procedures**
  - Equipment design and qualification
  - Equipment maintenance procedures
  - Equipment cleaning/visual inspection procedures
  - Qualification, usage, maintenance, cleaning of equipment, change control
  - Quality agreement with vendors including auditing
- Ensure that the contribution of elemental impurities to the drug products is low

Thank you for your attention!

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