Module 7

Converting between PDEs and Concentration Limits

ICH Q3D Elemental Impurities

Disclaimer:
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The presentation does not represent official guidance or policy of authorities or industry.

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General Principles (1)

- PDEs provide safety based limits to patient exposure.
- Q3D Section 7 provides some options for converting PDEs to concentration limits.
- Concentrations derived from PDEs may be used during the risk assessment to evaluate the significance of predicted levels of elemental impurities.
- Concentrations derived from PDEs may be used to convey the suitability of controls on elemental impurities.

General Principles (2)

- **"The applicant may select any of these options as long as the resulting permitted concentrations assure that the drug product does not exceed the PDEs."**
- **Permitted concentrations may be used:**
  - As a risk assessment tool to compare observed or predicted concentrations to PDEs.
  - In discussions with suppliers regarding upstream controls
  - To convey information on controls in regulatory submissions

General Principles (3)

- **Sources to be considered when applying options**
  - Components of the drug product
    - Drug substances & excipients
  - Container/Closure systems (CCS)
  - Manufacturing Equipment
    - When it is determined that CCS or manufacturing equipment do not contribute to the elemental impurity level in the drug product, they are not included in the option calculations.
    - When CCS or manufacturing equipment contribute to the elemental impurity levels in the drug product, the estimated daily intake from these sources may be subtracted from the PDE before calculation of the allowed concentrations in excipients and drug substances.

Examples

- Q3D Appendix 4 Example: solid oral product
- Parenteral product
- Inhalation product
- These examples are intended to illustrate the principles described in Section 7 of Q3D.

Q3D Appendix 4 Example: Solid Oral Dosage Form

- **Maximum daily intake of drug product: 2.5 grams**
- **9 components: 1 drug substance, 8 excipients**
  - See table on next slide for product formulation
- **Drug substance: Pd and Ni catalysts**
- **Risk Assessment: Pb, As, Cd, Hg and V are potentially present in the drug product**

Q3D Appendix 4 Example: Solid Oral Dosage Form

Drug Product Formulation

Component	Daily Intake, g
Drug Substance	0.200
Microcrystalline cellulose (MCC)	1.100
Lactose	0.450
Ca Phosphate	0.350
Crospovidone	0.265
Mg Stearate	0.035
Hydroxypropylmethyl cellulose (HPMC)	0.060
Titanium Dioxide	0.025
Iron Oxide	0.015
Drug Product	**2.500**

Q3D Appendix 4 Example: Option 1

- **Compute maximum concentration limits common to all components using a maximum daily drug product dose of 10 grams.**
  - Q3D table A.2.2 provides these concentrations.
- **Use the Table A.2.2 concentrations and the actual mass of components to compute the maximum daily intake of elemental impurities in the drug product.**

Option 1 Concentrations and Daily Intakes

Component	Table A.2.2 Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	3	10	10	20
MCC	0.5	1.5	0.5	3	10	10	20
Lactose	0.5	1.5	0.5	3	10	10	20
Ca Phosphate	0.5	1.5	0.5	3	10	10	20
Crospovidone	0.5	1.5	0.5	3	10	10	20
Mg Stearate	0.5	1.5	0.5	3	10	10	20
HPMC	0.5	1.5	0.5	3	10	10	20
TiO_2	0.5	1.5	0.5	3	10	10	20
Iron Oxide	0.5	1.5	0.5	3	10	10	20
Max. Daily Intake (µg/day)	**1.25**	**3.75**	**1.25**	**7.5**	**25**	**25**	**50**
PDE (µg/day)	**5**	**15**	**5**	**30**	**100**	**100**	**200**

Q3D Appendix 4 Example: Option 2a

- Compute maximum concentration limits common to all components using the maximum daily dose of the drug product.
- The Appendix 4 example considers a drug product with 2.5 gram maximum daily dose.
- PDEs from Table A.2.1 are divided by 2.5 grams to compute the maximum permissible concentration of elemental impurities in the components.

Option 2a Concentrations and Daily Intakes

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	2	6	2	12	40	40	80
MCC	2	6	2	12	40	40	80
Lactose	2	6	2	12	40	40	80
Ca Phosphate	2	6	2	12	40	40	80
Crospovidone	2	6	2	12	40	40	80
Mg Stearate	2	6	2	12	40	40	80
HPMC	2	6	2	12	40	40	80
TiO_2	2	6	2	12	40	40	80
Iron Oxide	2	6	2	12	40	40	80
Max. Daily Intake (µg/day)	**5**	**15**	**5**	**30**	**100**	**100**	**200**
PDE (µg/day)	**5**	**15**	**5**	**30**	**100**	**100**	**200**

Q3D Appendix 4 Example: Option 2b

- **The applicant proposes permissible concentrations in each component of the drug product based on prior knowledge of expected concentrations of elemental impurities in the components.**
- **Expected concentrations derived from:**
  - Published literature
  - Elemental impurity limits in compendial grade materials when available
  - Vendor-supplied information
  - Data or information generated by the applicant

Option 2b Appendix 4 Example Concentrations[1]

Component	Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	<LoQ	0.5	<LoQ	<LoQ	20	<LoQ	50
MCC	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Lactose	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Ca Phosphate	1	1	1	1	*	10	5
Crospovidone	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
Mg Stearate	0.5	0.5	0.5	0.5	*	<LoQ	0.5
HPMC	0.1	0.1	0.1	0.1	*	<LoQ	<LoQ
TiO_2	20	1	1	1	*	1	<LoQ
Iron Oxide	10	10	10	10	*	2000	50

1. **Example data in this table may be derived from the sources described on the previous slide.**

***The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained.**

Option 2b Appendix 4 Example Estimated total daily intake

		Pb		As		Cd		Hg		Pd		V		Ni	
Component	Max. Daily Intake (g) (MDI)[1.]	C[2.]	MDI*C[3.]	C	MDI*C	C	MDI*C	C	MDI*C	C[2]	MDI*C	C	MDI*C	C	MDI*C
Drug Substance	0.2	0.0	0	0.5	0.1	0.0	0	0.0	0	20	4	0	0	50	10
MCC	1.1	0.1	0.11	0.1	0.11	0.1	0.11	0.1	0.11	0	0	0	0	0.0	0
Lactose	0.45	0.1	0.045	0.1	0.045	0.1	0.045	0.1	0.045	0	0	0	0	0.0	0
Ca Phosphate	0.35	1.0	0.35	1.0	0.35	1.0	0.35	1.0	0.35	0	0	10	3.5	5.0	1.75
Crospovidone	0.265	0.1	0.027	0.1	0.027	0.1	0.027	0.1	0.027	0	0	0	0	0.0	0
Mg Stearate	0.035	0.5	0.018	0.5	0.018	0.5	0.018	0.5	0.018	0	0	0	0	0.5	0.018
HPMC	0.06	0.1	0.006	0.1	0.006	0.1	0.006	0.1	0.006	0	0	0	0	0.0	0
Titanium Dioxide	0.025	20	0.5	1.0	0.025	1.0	0.025	1.0	0.025	0	0	1	0.025	0.0	0
Iron Oxide	0.015	10	0.15	10	0.15	10	0.15	10	0.15	0	0	2000	30	50	0.75
TOTAL INTAKE[4] (µg/day)		1.21		0.83		0.73		0.73		4		33.53		12.52	
PDE (µg/day)		5		15		5		30		100		100		200	

1. Intake of component (MDI) in grams
2. Concentration of elemental impurity (C) in micrograms per gram.
3. EI intake from component (MDI*C) in micrograms.
4. Total Intake of EI in the drug product is the sum of EI intake from components.

Potential Concentrations in Components

Component	Potential Concentration** (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	<LoQ	5	<LoQ	<LoQ	500	<LoQ	750
MCC	0.5	5	1	5	*	<LoQ	<LoQ
Lactose	0.5	5	1	5	*	<LoQ	<LoQ
Ca Phosphate	5	5	5	35	*	70	80
Crospovidone	0.5	5	1	5	*	<LoQ	<LoQ
Mg Stearate	5	10	5	125	*	<LoQ	100
HPMC	2.5	5	1	5	*	<LoQ	<LoQ
TiO_2	50	40	10	35	*	20	<LoQ
Iron Oxide	50	100	50	200	*	5000	1200
Daily Intake (µg/day)	**5.0**	**15.0**	**4.8**	**29.9**	**100**	**100**	**199.5**
PDE (µg/day)	**5**	**15**	**5**	**30**	**100**	**100**	**200**

** Maximum permitted concentrations are proposed by the applicant based on expected concentrations. Other sets of concentrations may also be proposed.

* The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained

Q3D Appendix 4 Example: Option 3

- **Option 3 determines the permissible concentrations of elemental impurities in the finished drug product.**
  - Based on the mass of the maximum daily dose

Option 3 Concentrations

		Maximum Permitted Concentration (µg/g)						
	Daily Intake (g)	Pb	As	Cd	Hg	Pd	V	Ni
Drug Product	2.5	2	6	2	12	40	40	80
Maximum Daily Intake (µg/day)		5	15	5	30	100	100	200
PDE (µg/day)		**5**	**15**	**5**	**30**	**100**	**100**	**200**

Outcome of Options

- **Examples above illustrate the use of the calculation options during the risk assessment.**
- **Option calculations may be used as a basis for setting specifications, when appropriate**
- **For an element that may exceed the control threshold:**
  - Tables in Option 2b may provide information on primary source of elemental impurity in the drug product

Parenteral Example: Solution for Injection

- **Maximum daily intake of drug product: 1.5 grams**
- **6 components: 1 drug substance, 5 excipients (including water for injection)**
  - See next slide for maximum daily masses of components
- **Drug substance: Pt catalyst**
- **Risk Assessment: Pb, As, V and Co are potentially present in the drug product**
  - Lead (Pb) may be an impurity in Sodium Carbonate,
  - Arsenic (As) may be an impurity in glass
  - Risk assessment determined that Cd and Hg are unlikely to be present in the drug product.

Parenteral Example: Solution for Injection

Drug Product Formulation

Component	Daily Intake, g
Drug Substance	0.01
Mannitol	0.18
Polysorbate 80	0.01
Sodium Carbonate	0.1
Ethanol	0.2
Water for injection	1
Drug Product	**1.50**

Sodium carbonate is a potential source of Pb in the drug product. The Container is type I compendial glass, a potential source of As.

Solution for Injection: Consideration of As in Glass

- Estimated maximum contribution of arsenic in glass to drug product: 1 microgram.
- Established parenteral PDE for As: 15 micrograms/day
- Permitted daily exposure from drug substance and excipients: 15 - 1 = 14 micrograms/day

Example for illustrative purposes only.

Parenteral Example: Option 1 Concentrations and Daily Intakes

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pt	V	Co
Drug Substance	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Mannitol	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Polysorbate 80	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Sodium Carbonate	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Ethanol	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Water for injection	0.5	1.5	0.2	0.3	1.0	1.0	0.5
Max. Daily Intake (µg/day)	**0.8**	**2.3**	**0.3**	**0.5**	**1.5**	**1.5**	**0.8**
PDE (µg/day)	**5**	**14[1]**	**2**	**3**	**10**	**10**	**5**

1. The permitted daily exposure has been adjusted to subtract the contribution from container/closure system.

Parenteral Example: Option 2a Concentrations and Daily Intakes

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pt	V	Co
Drug Substance	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Mannitol	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Polysorbate 80	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Sodium Carbonate	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Ethanol	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Water for injection	3.3	9.3	1.3	2.0	6.7	6.7	3.3
Max. Daily Intake (µg/day)	**5.0**	**14**	**2.0**	**3.0**	**10.0**	**10.0**	**5.0**
PDE (µg/day)	**5**	**14[1]**	**2**	**3**	**10**	**10**	**5**

1. The permitted daily exposure has been adjusted to subtract the contribution from container/closure system.

Parenteral Example: Option 2b Expected Concentrations

Component	Observed Concentration (µg/g)						
	Pb	As	Cd	Hg	Pt	V	Co
Drug Substance	<LOQ	<LOQ	<LOQ	<LOQ	1	1	0.5
Mannitol	<LOQ	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Polysorbate 80	<LOQ	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Sodium Carbonate	2	1	0.2	<LOQ	*	0.1	0.1
Ethanol	<LOQ	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Water for injection	0.003	0.001	<LOQ	<LOQ	*	<LOQ	0.001

*** The risk assessment determined that Pd was not a potential elemental impurity; a quantitative result was not obtained**

Parenteral Example: Option 2b Exposures from Expected Concentrations

		Pb		As		Cd		Hg		Pt		V		Co	
Component	MDI[1]	C[2]	MDI*C[3]	C	MDI*C	C	MDI*C	C	MDI*C	C	MDI*C	C	MDI*C	C	MDI*C
Drug Substance	0.01	0	0	0	0	0	0	0	0	1	0.01	1	0.01	0.5	0.005
Mannitol	0.18	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Polysorbate 80	0.01	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sodium Carbonate	0.10	2	0.2	1	0.1	0.2	0.02	0	0	0	0	0.1	0.01	0.1	0.01
Ethanol	0.20	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Water for Injection	1.00	0.003	`	0.001	0.001	0	0	0	0	0	0	0	0	1	1
TOTAL INTAKE[4] (μg/day)	1.50	0.20		0.10		0.02		0.00		0.01		0.02		1.02	
PDE(μg/day)		5		14[5]		2		3		10		10		5	

1. Maximum Daily Intake of component (MDI) in grams
2. Concentration of elemental impurity (C) in micrograms per gram.
3. EI intake from component (MDI*C) in micrograms.
4. Total Intake of EI in the drug product is the sum of EI intake from components.
5. Use adjusted PDE for arsenic that accounts for contribution from container.

Parenteral Example: Option 2b Proposed Concentrations

Component	Potential Concentration (µg/g)**						
	Pb	As	Cd	Hg	Pt	V	Co
Drug Substance	0.01	<LOQ	<LOQ	<LOQ	5	5	5
Mannitol	0.01	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Polysorbate 80	0.01	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Sodium Carbonate	10	5	1	<LOQ	*	1	1
Ethanol	0.01	<LOQ	<LOQ	<LOQ	*	<LOQ	<LOQ
Water for injection	0.03	0.01	<LOQ	<LOQ	*	<LOQ	0.01
Max. Daily Intake (µg/day)	**1.03**	**0.51**	**0.1**	**0**	**0.05**	**0.15**	**0.16**
PDE (µg/day)	**5**	**14**	**2**	**3**	**10**	**10**	**5**

** Maximum permitted concentrations are proposed by the applicant based on expected concentrations. Other sets of concentrations may also be proposed.

* The risk assessment determined that Pt was not a potential elemental impurity; a quantitative result was not obtained

Parenteral Example: Option 3 Concentrations

		Maximum Permitted Concentration (µg/g)						
	Daily Intake (g)	Pb	As	Cd	Hg	Pt	V	Co
Drug Product	1.5	3.33	9.3	1.33	2.0	6.67	6.67	3.33
Maximum Daily Intake (µg/day)		5	14	2	3	10	10	5
PDE (µg/day)		**5**	**14**	**2**	**3**	**10**	**10**	**5**

Inhalation Example

- **Maximum daily intake drug product: 0.1733 grams**
- **4 components: 1 drug substance, 3 excipients (including water for injection)**
  - See following slide for maximum daily mass of components
- **Risk Assessment**
  - Co, V and Cu are potentially contributed from container/closure system
  - Drug product synthesis uses Cd.

Inhalation Example

Drug Product Formulation

Component	Daily Intake, g
Drug Substance	0.0003
Polysorbate	0.1100
NaCl	0.0030
Water for injection	0.0600
Drug Product	**0.1733**

Consideration of elemental impurities contributed from container/closure

- **Maximum expected contributions from container/closure system**
  - Co: 0.5 micrograms
  - V: 0.25 micrograms
  - Cu: 1 microgram
  - Adjusted PDEs
    - Co = 3 – 0.5 = 2.5
    - V = 1 – 0.25 = 0.75
    - Cu = 30 – 1 = 29

Example for Illustrative purposes only.

Inhalation Example: Option 1 Concentrations and Daily Intakes

Component	Maximum Permitted Concentration (µg/g)			
	Pd	Co	V	Cu
Drug Substance	0.10	0.25	0.075	2.9
Polysorbate	0.10	0.25	0.075	2.9
NaCl	0.10	0.25	0.075	2.0
Water for injection	0.10	0.25	0.075	2.9
Max. Daily Intake (µg/day)	**0.02**	**0.04**	**0.01**	**0.5**
PDE (µg/day)[1]	**1**	**2.5**	**0.75**	**29**

1. The permitted daily exposure has been adjusted to subtract the contribution from container/closure system.

Inhalation Example: Option 2a Concentrations and Daily Intakes

Component	Maximum Permitted Concentration (µg/g)			
	Pd	Co	V	Cu
Drug Substance	5.8	14.42	4.32	167.3
Polysorbate	5.8	14.42	4.32	167.3
NaCl	5.8	14.42	4.32	167.3
Water for injection	5.8	14.42	4.32	167.3
Max. Daily Intake (µg/day)	**1**	**2.5**	**0.75**	**29**
PDE (µg/day)[1]	**1**	**2.5**	**0.75**	**29**

1. Use the adjusted permitted daily exposure that accounts for contribution from container/closure system

Inhalation Example: Option 2b Expected Concentrations

Component	Observed Concentration (µg/g)			
	Pd	Co	V	Cu
Drug Substance	0.10	<LOQ	1.0	1.0
Polysorbate	<LOQ	0.10	<LOQ	<LOQ
NaCl	<LOQ	<LOQ	<LOQ	<LOQ
Water for injection	<LOQ	0.001	0.001	0.001

Inhalation Example: Option 2b Exposures from Expected Concentrations

		Pd		Co		V		Cu	
Component	Max. Daily Intake (MDI)[1]	C[2]	MDI*C[3]	C	MDI*C	C	MDI*C	C	MDI*C
Drug Substance	0.0003	0	0	0	0	1	0.0003	1	0.0003
Polysorbate	0.11	0.1	0.011	0.1	0.011	0	0	0	0
NaCl	0.003	0	0	0	0	0	0	0	0
Water for Injection	0.06	0.001	6E-05	0.001	6E-05	0.001	6E-05	0.001	6E-05
TOTAL INTAKE (μg/day)[4]	0.1733	0.01		0.01		0.00		0.00	
PDE (μg/day)[5]		1	2.5	0.75	29	1	2.5	0.75	29

1. Maximum Daily Intake of component (MDI) in grams
2. Concentration of elemental impurity (C) in micrograms per gram.
3. EI intake from component (MDI*C) in micrograms.
4. Total Intake of EI in the drug product is the sum of EI intake from components.
5. Use adjusted PDE for arsenic that accounts for contribution from container.

Inhalation Example: Option 2b Proposed Concentrations

Component	Potential Concentrations (µg/g)			
	Pd	Co	V	Cu
Drug Substance	0	0	10	10
Polysorbate	1.0	1.0	0	0
NaCl	0	0	0	0
Water for injection	0.01	0.01	0.01	0.01
Max. Daily Intake (µg/day)	**0.11**	**0.11**	**0.004**	**0.004**
PDE (µg/day)[1]	**1**	**2.5**	**0.75**	**29**

1. Use adjusted PDE for arsenic that accounts for contribution from container.

Inhalation Example: Option 3 Concentrations

		Maximum Permitted Concentration (µg/g)			
	Daily Intake (g)	Pd	Co	V	Cu
Drug Product	0.1733	5.8	14.42	4.32	167.3
PDE (µg/day)		**1**	**2.5**	**0.75**	**29**

Questions?

FDA Training Workshop on Elemental Impurities (ICH Q3D)

22-23 August 2016
White Oak, MD

Elemental Impurity Product Risk Assessments

Mark Schweitzer, Ph.D.
ICH Q3D IWG Topic Lead

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Overview

- Potential sources of elemental impurities
- Risk assessment approaches
- Output of elemental risk assessment
- Product risk assessment process
  - Drug product based
  - Drug product component based
- Evaluation

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Elemental impurity risk assessment process

ICH Q3D defines a science and risk based assessment process to identify, evaluate, and define controls to limit elemental impurities in drug products

- 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.

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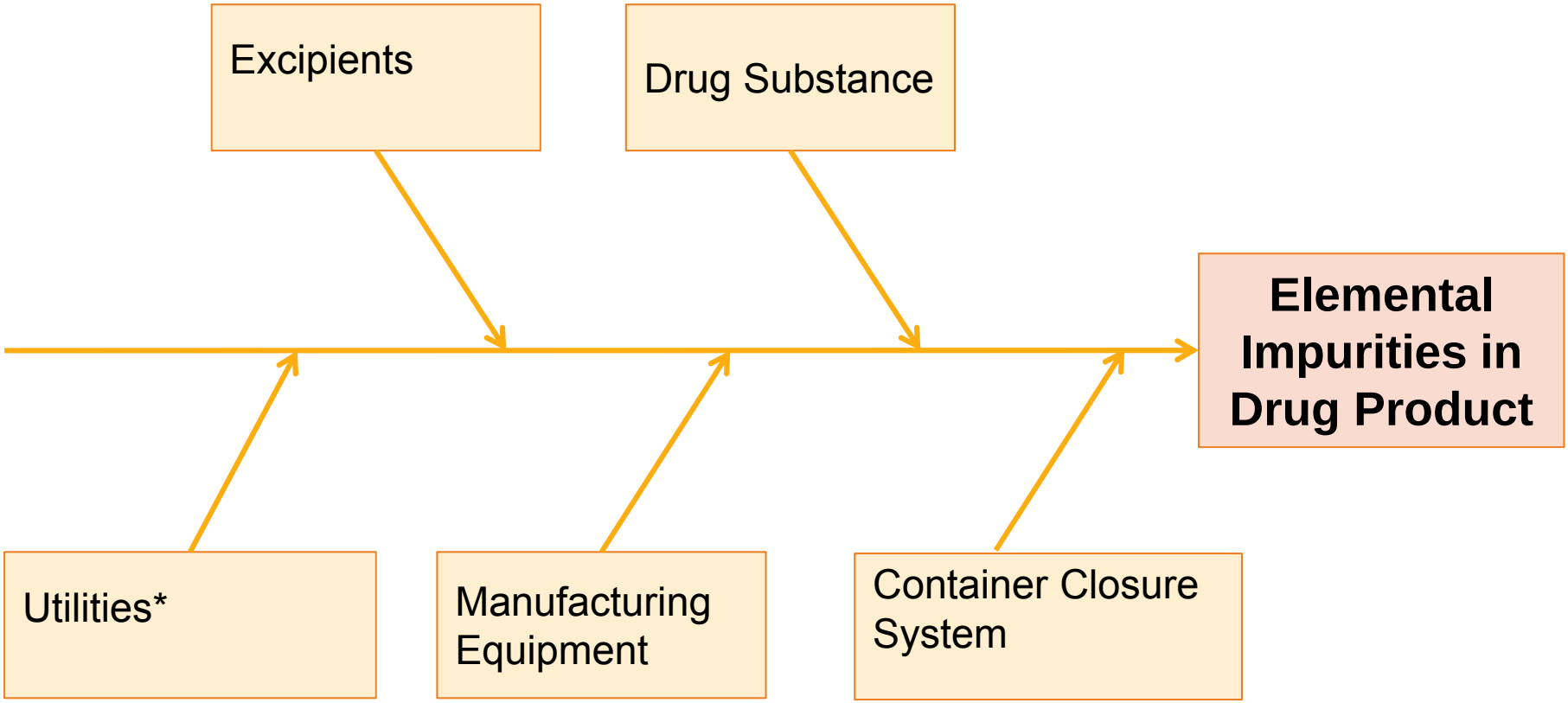
Potential sources of elemental impurities



* 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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Risk assessment approaches

Examples of general approaches that may be considered during elemental impurities risk assessment are:

- Assessment of potential elemental impurities in the drug product
  - Determine or assess the levels of elemental impurities in the final drug product
  - Depending on the formulation type, an evaluation from the container closure system may also be required
- Assessment of potential elemental impurities from each component of the drug product (API, excipients, container closure system)
  - Assess each component for potential sources of elemental impurities
  - Identify known or likely elemental impurities
  - Determine the contribution of each component or source of elemental impurity to the levels in the final drug product
- Irrespective of the approach chosen – consider the elemental impurity classification and recommendations in Table 5-1 (see following slide)
- These approaches or others may change as information becomes available or additional experience is gained.

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Q3D 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
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

Reference this table in the summary of the risk assessment.

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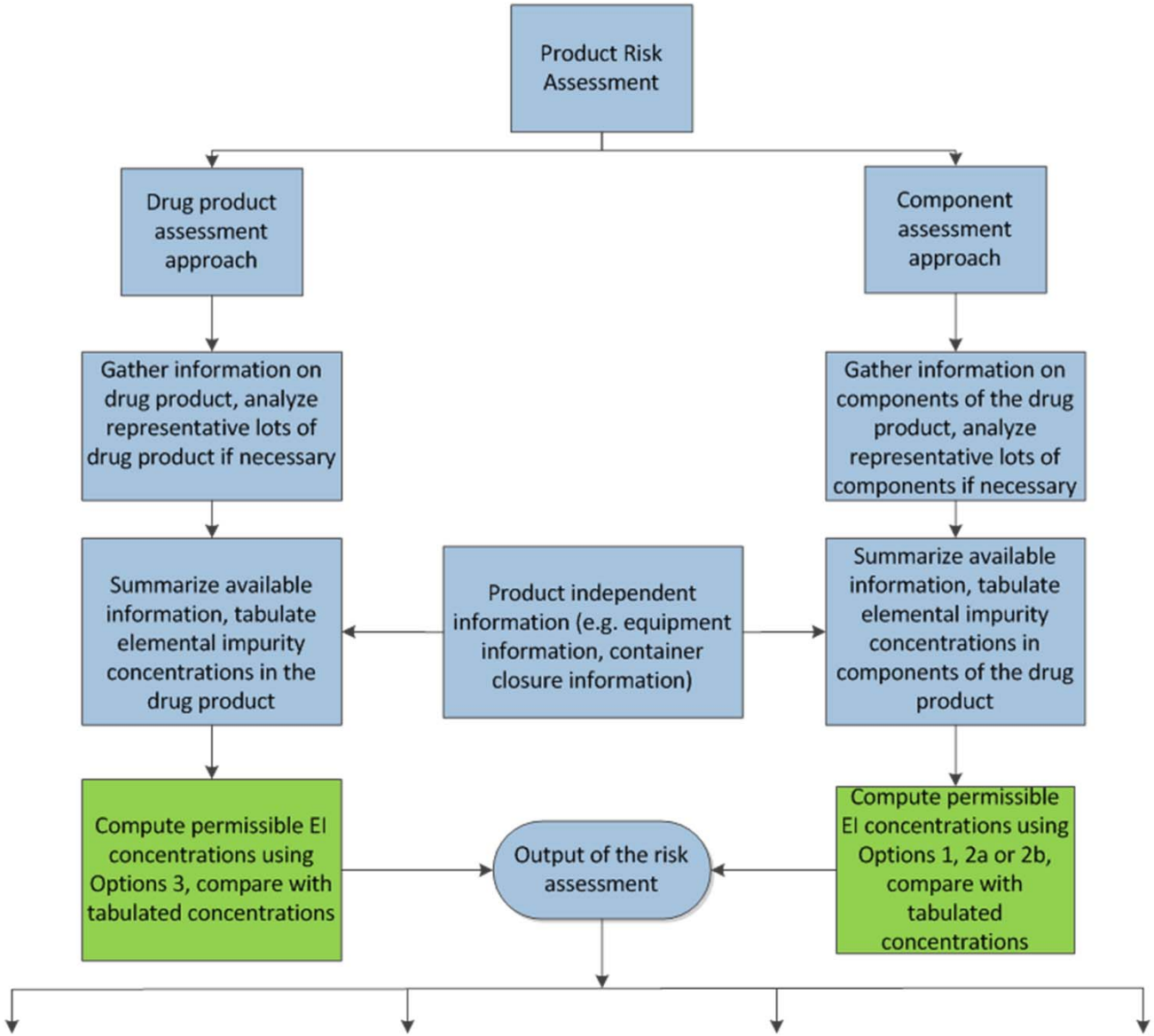
Generalized risk assessment process flow



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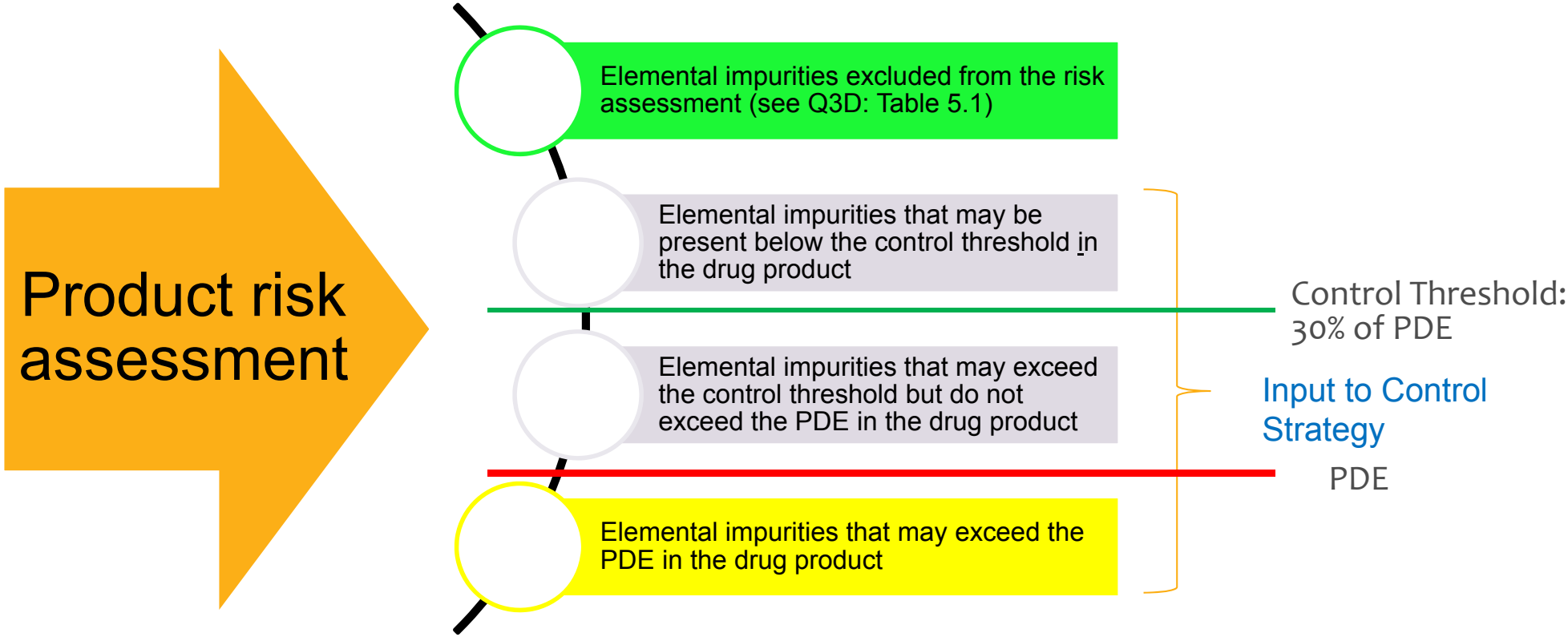
Risk Assessment Output



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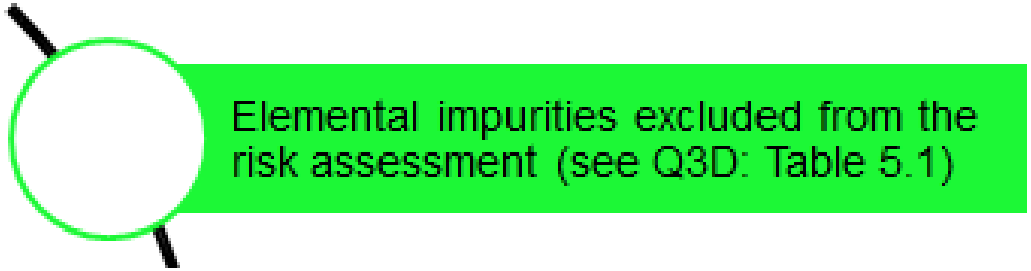
Examples of potential outputs of the risk assessment



- Class 2B elements that are not intentionally added
- Elements in Table 5.1 that may be excluded based on the route of administration

Example:

- For a solid oral drug product, the following class 3 elemental impurities were not intentionally added and therefore were not considered in the risk assessment: Li, Sb, Ba, Mo, Cu, Sn, and Cr.

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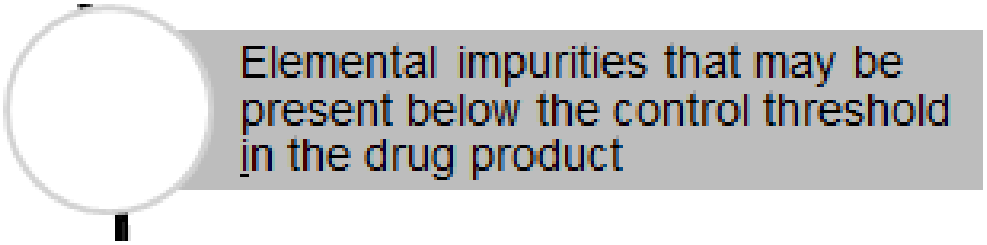
Examples of potential outputs of the risk assessment



Elemental impurities in this category would be those that have the potential to be found, but if present would be found at low levels They are often associated as low level impurities in components that can be handled through incoming material controls or with GMP Quality System elements (e.g. vendor/supplier qualification processes and procedures)

Example:

- Pb is a potential impurity in TiO_2. If the formulation contained 10 mg TiO_2 in a 1 g tablet (1% TiO_2) and the observed Pb level in TiO_2 was 1-10 µg/g; the total amount of Pb contribution to the drug product would be (0.01-0.1 µg/day), less than the control threshold of Pb (1.5 µg/g) in the drug product.

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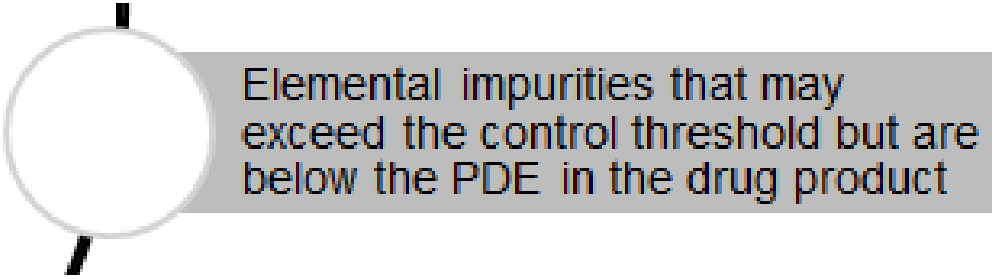
Examples of potential outputs of the risk assessment



Elemental impurities in this category would be those that have the potential to be found in the drug product or in drug product components.

Example:

- Pb is a potential impurity in K_2CO_3. If the formulation contained 500 mg K_2CO_3 in a 1 g tablet and the observed Pb level in K_2CO_3 was 1-8 µg/g, the total amount of Pb contribution to the drug product would be 0.5-4 ppm. The range of observed levels is above the control threshold but below the PDE (5 µg/g).

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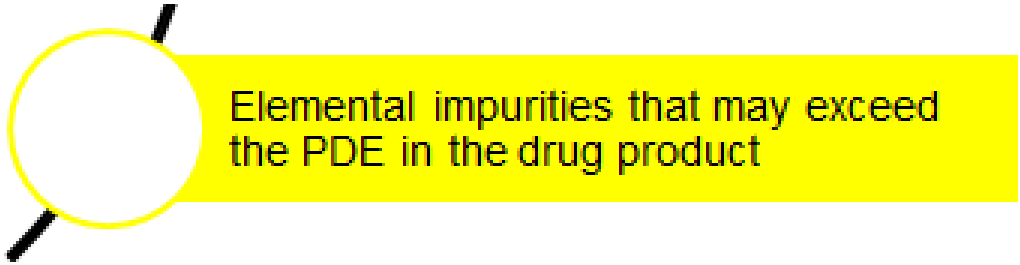
Examples of potential outputs of the risk assessment



Elemental impurities in this category would be those that exceed the PDE in the drug product.

Example:

- Cd is a potential impurity in $CaHPO_4$. If the formulation contained 500 mg $CaHPO_4$ in a 750 mg tablet and the observed Cd level in $CaHPO_4$ was 8-9 µg/g, the total amount of Cd contribution to the drug product (5.3 - 6 µg) would exceed the PDE for Cd 5 (µg/day).

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Information to consider in the risk assessment

- Assumptions, risks considered and identified, controls inherent in the process and product evaluated
- Data where available and estimated levels when literature or published data or calculations are used to justify exclusion of elemental impurities from further consideration
- The rationale for elemental impurity clearance steps/reduction steps included or inherent in the process design
- Consideration of using compendial quality components
- Consideration of GMP controls and
- Discussion of any additional controls to be considered when developing the drug product control strategy

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Special considerations for biotechnologically derived products

- It is recognized that the risks associated with the presence of elemental impurities at levels of safety concerns for biotechnology-derived products are low
  - This is generally due to the absence of use of inorganic catalysts or reagents and to the typical purification schemes used in the manufacture of biotechnology-derived products

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Documentation

Documentation to be maintained in Company Pharmaceutical Quality System	Documentation to be included in regulatory dossiers (new or updates)
Complete risk assessment document describing process, data used, data references and information needed to support dossier summary	Summary of product risk assessment process used
GMP related processes to limit the inclusion of elemental impurities	Summary of identified elemental impurities and observed or projected levels
Change management processes (defining triggers for product assessment or control strategy updates)	Data from representative commercial or pilot scale batches (component or drug product as appropriate)
Periodic review processes	Conclusion of the product risk assessment
Original data used in the product risk assessments, quality agreements, supplier qualification, etc.	

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Considerations in determining drug product assessment approach

The decision of the risk assessment approach (component or drug product) is dependent on many factors, including but not limited to the following;

- Knowledge of the elemental impurity levels of components of the drug product
- Situations where the drug substance (or drug product or both) is managed by a third party manufacturer with potentially different internal quality systems and controls
- Demonstrated high variability of the elemental impurity levels in one or more components of the drug product
- High formulation percentages of excipients known to have concomitant elemental impurities
- Knowledge of the levels of elemental impurities in the drug product components or excipients that have been established as having limited potential to introduce elemental impurities
- Primary contribution of elemental impurities to the drug product can be traced to a limited number of components
- Identification of one or more components that contribute the greatest to the elemental impurity 'burden' providing improved control options (material controls, periodic verification testing, etc.)

In many situations, the risk assessment may be a combination of both the component approach and the drug product approach. Knowledge of components that have potential elemental impurities can provide information to improve the drug product assessment approach

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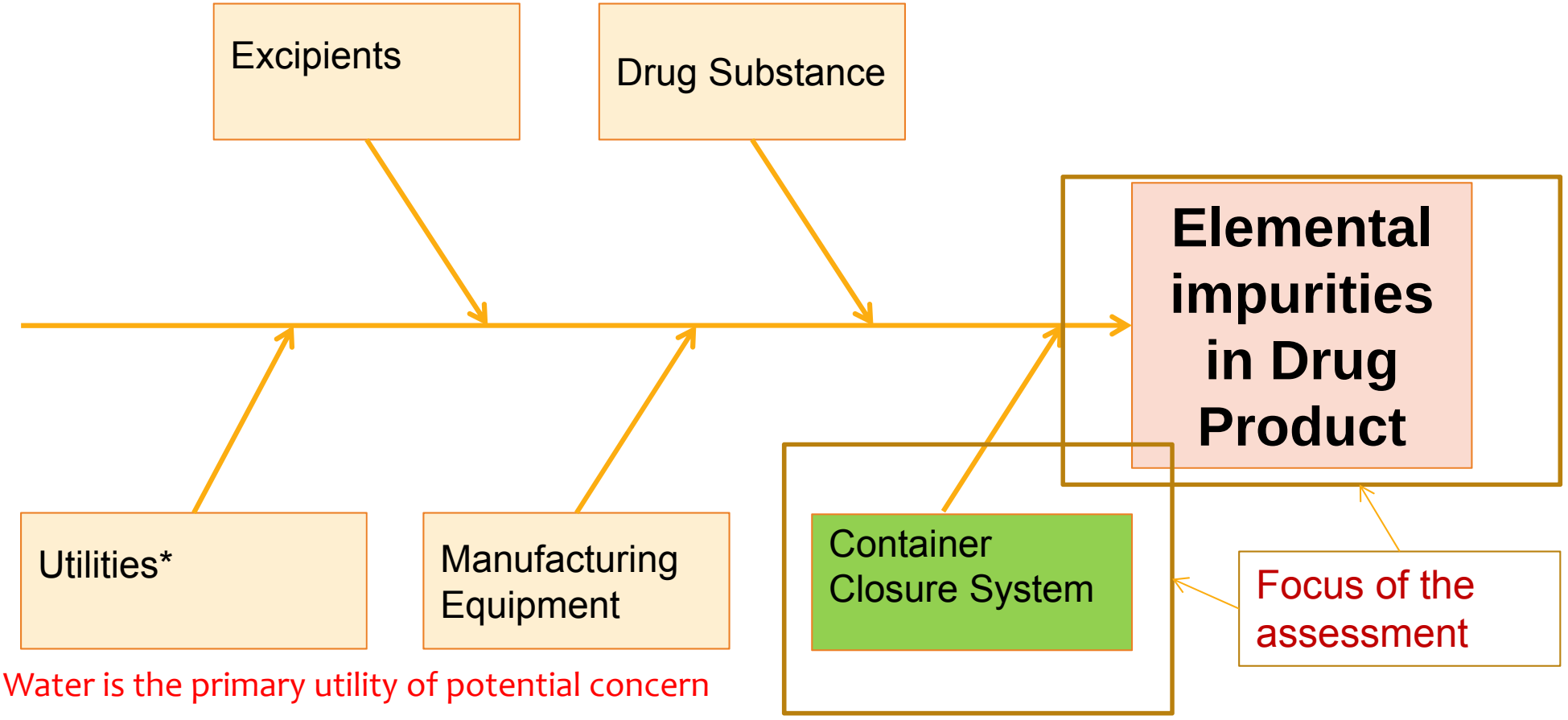
Product Assessment –Drug Product Approach

Potential sources of elemental impurities – drug product approach



* Water is the primary utility of potential concern

- This risk assessment focuses on the measured levels of potential elemental impurities in the drug product
- The assessment may require the evaluation of the impact of the container closure system on the drug product and the potential to contribute elemental impurities to the drug product

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Drug product assessment approach

- Implicit in the drug product risk assessment approach is the availability of data concerning elemental impurity levels in the drug product
- Justification of the elemental impurities included in the assessment
  - Preliminary multiple element screening methods can establish the elemental impurities of interest (if any)
  - Table 5.1 in the guideline provides guidance on what elements should be considered in the assessment
- In the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product.
  - For some components that have inherent variability (e.g., mined excipients), additional data may be needed

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Drug product assessment approach – container closure systems

- Depending on the drug product type, additional evaluation for potential elemental impurity introduction into the drug product may be needed
  - Solid oral dosage forms
    - The interaction of solid oral dosage forms with packaging components has essentially a negligible risk of transferring elemental impurities from the container closure system (packaging) to the drug product.
    - No further evaluation is required
  - Liquid, suspension and semi-solid dosage forms
    - Depending on the packaging material and the formulation components, there may be a potential for leaching of elemental impurities from the packaging components
    - Data may be generated in leachable studies (evaluating the potential for inclusion of elemental impurities using an appropriate methodology)
    - Table 1 provides additional information on the level of risk associated with various drug products and container closure systems.
- Questions for consideration
  - Does the packaging inherently contain large quantities of metals which might leach?
  - Is the drug product likely to leach metals from its packaging over the shelf-life?

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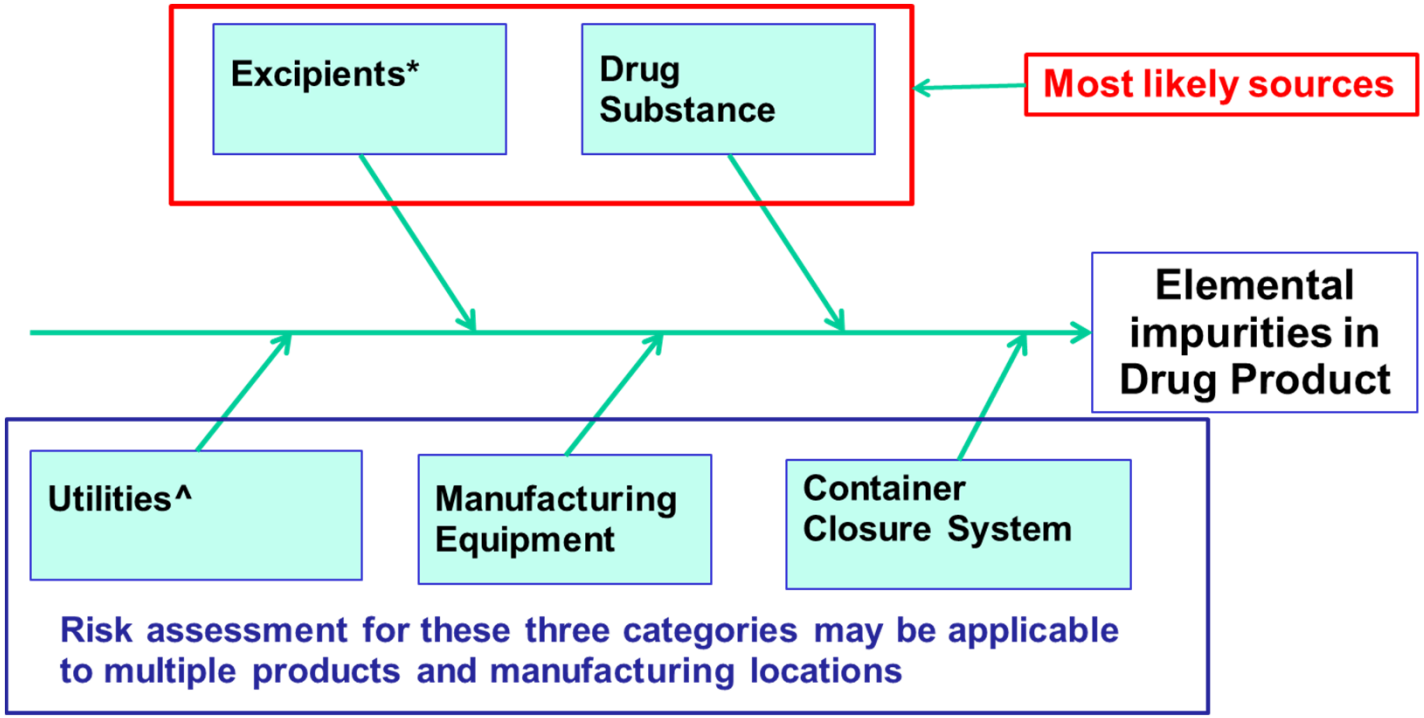
Product Assessment – Component Approach

Potential sources of elemental impurities – component approach



* Water may need to be considered as an excipient (component) depending on the formulation

^ Water is the primary utility of potential concern

Following the component approach, all the potential sources of elemental impurities should be considered and evaluated for contribution to the drug product

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Lower risk sources of elemental impurities – assessment for contibutions from utilities

- In general GMP policies, processes and procedures ensure that the contribution of elemental impurities to drug products is low.
  - Facility & utility design and qualification
  - Facility & utility maintenance procedures
- Water produced under GMP controls ensures that the contribution of elemental impurities from water to the drug product is low
  - Qualification and maintenance of water systems
  - Specification for water quality
  - Routine monitoring of the water quality
- Use of compendial grade water (*e.g. PW, WFI)* further reduces the potential contribution of elemental impurities
  - The source water used to prepare WFI or PW is first required to meet drinking water standards which already include strict control on the levels of elemental impurities of concern.
  - The purification processes employed to produce WFI or PW provide a mechanism to further reduce the elemental impurity content

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Lower risk sources of elemental impurities – assessment for Manufacturing Equipment Contributions

- In general GMP policies, processes and procedures ensure that the contribution of elemental impurities to the drug products is low.
  - Equipment design and qualification
  - Equipment maintenance procedures
  - Equipment cleaning/visual inspection procedures
- Knowledge of the elemental impurity profile of drug substance can assist in the evaluation of potential contributions from manufacturing equipment
  - Drug substance processes often are more chemically aggressive than drug product processes.
  - Monitoring of drug substance for potential impurities from manufacturing equipment (e.g. stainless steel – Cr, Mn, Mo, V, Ni) can provide insight into potential impact to the drug product

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Lower risk sources of elemental impurities – assessment for CCS contributions

- The potential of release of elemental impurities from CCS components into the drug product depends on the dosage form
- **Empirical results confirmed low potential of introduction of elemental impurities to the drug product from the CCS**
  - *Jenke, D. et.al.,* "A Compilation of Metals and Trace Elements Extracted from Materials Relevant to Pharmaceutical Applications Such as Packaging Systems and Devices", PDA J. Pharm. Sci. Technol., 67(4):354-75, 2013
- Potential risk may be further explored by use of prior knowledge or conducting an appropriate leachables study.

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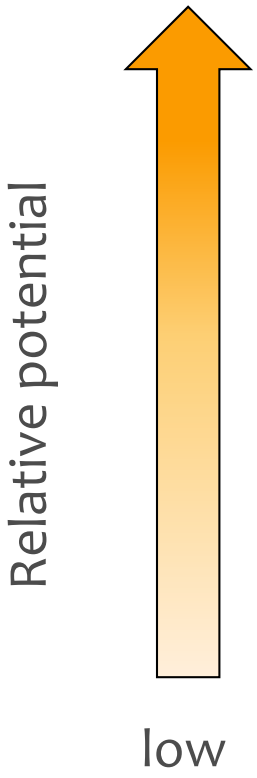
Relative potential of interaction of CCS with drug product categories



Potential for inclusion of elemental impurities introduced to the drug product from the container closure system	Specific drug product classes	Example considerations/potential packaging components of concern
	Injections and Injectable Suspensions	Glass containers – potential to leach As
	Inhalation Aerosols and Solutions;	
	Parenteral solutions	
	Ophthalmic Solutions and Suspensions;	Glass containers - potential to leach As Metal containers – potential to leach elemental impurities (dependent upon composition of CCS and composition/pH of formulation
	Transdermal patches	
	Ointments and Creams	
	Nasal Aerosols and Sprays	
	Topical Solutions and Suspensions;	Plastic containers - potential to leach elemental impurities from polymeric materials is low
	Topical and Lingual Aerosols;	
	Oral Solutions and Suspensions	
	Oral Tablets	Solid – solid interaction provides little or no opportunity to transfer elemental impurities from CCS to drug product
	Oral (Hard and Soft) Capsules	
	Oral Powders	
	Sterile Powders	
	Inhalation Powders	
	Powders for Injection	
	Topical Powders	

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Product risk assessment – Excipient contribution

- A limited number of excipients of mineral origin may include elemental impurities that are embedded in or tightly bound to the solid matrix preventing their release except with extreme extraction procedures
  - *e.g.* smectic (mineral) clays[1,2]
- Some mined excipients (e.g. Talc, Titanium dioxide) are known to have low but variable levels of some elemental impurities of concern (e.g. As and Pb)
  - Due to the nature of the isolation of the excipients, it is often not possible to reduce the level of elemental impurity
  - Some demonstrate variation in the observed level based on mine location as well as variation within the same mine

[1] Morman SA, Plumlee GS, Smith DB (2009) Application of in vitro extraction studies to evaluate element bioaccessibility in soils from a transect across the United States and Canada, Applied Geochemistry 24, 1454–1463

[2] Oomen AG, Hack A, Minekus M, Zeijdner E, Cornelis C, Schoeters G, Verstraete W,Van de Wiele T, Wragg J, Rompelberg CJM, Sips A, Van Wijnen JH, (2002) Comparison of five in vitro digestion models to study the bioaccessibility of soil contaminants. Environmental Science & Technology, 36, 3326-3334

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Sources of information on elemental impurities in excipients

The amount of information in refereed publications and sources is increasing

RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Elemental Impurities in Pharmaceutical Excipients

GANG LI,[1] DAVE SCHONEKER,[2,5] KATHERINE L. ULMAN,[3,3] JASON J. STURM,[4] LISA M. THACKERY,[4] JOHN F. KAUFFMAN[1]

[1]U.S. Food and Drug Administration, Division of Pharmaceutical Analysis, St. Louis, Miss
[2]Colorcon Inc., Harleysville, Pennsylvania 19438
[3]Dow Corning Healthcare Business, Midland, Michigan 48686-0994
[4]Dow Corning Analytical Sciences, Midland, Michigan 48686-0994
[5]IPEC-Americas, Arlington, Virginia 22201

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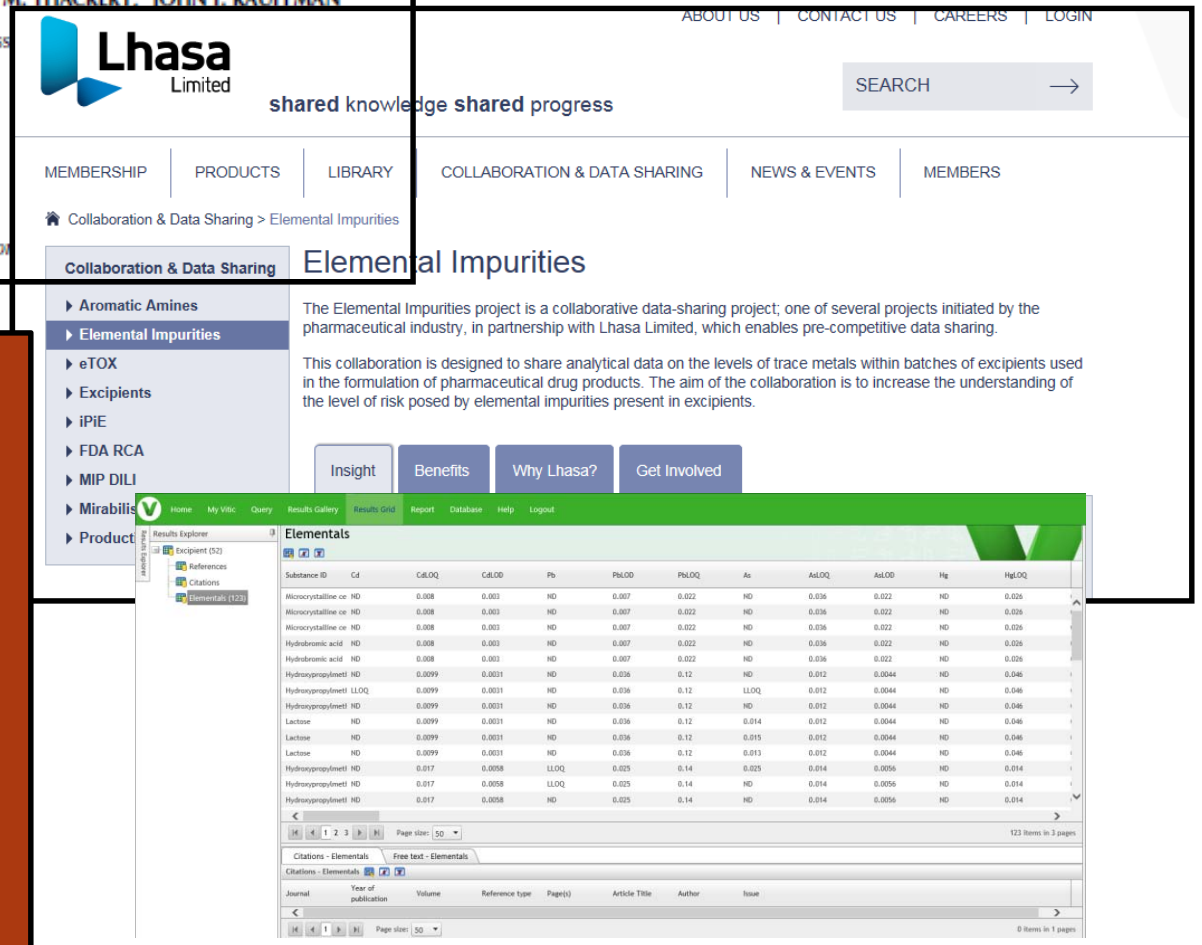

Excipient database rel. 1

- Consortium of 8 pharma companies donating data
- 125 data points generated using validated methods
- 50 excipients
- Rel. 2 with additional data uploaded anticipated in Q4 2016

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Product risk assessment – drug substance contribution

- A significant potential source of elemental impurities arises from the use of metal catalysts in the synthesis of drug substances, especially if used in the latter stages of synthesis
  - Knowledge of potential elemental impurities in synthetic steps prior to the final drug substance may provide information that can assist in the preparation of the risk assessment

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Evaluation

- Compile data for components of the drug product
  - Published information
  - Data generated by the applicant or suppliers
  - Where data are not available, consider if surrogate information can be used to establish a reasonable estimate of the elemental impurity potential for inclusion
- Calculate the observed elemental impurities for each component, in which elemental impurities are identified, as a function of the percent composition of the formulation and the total daily dose of the drug.
- The level of each elemental impurity should be determined by summing the contribution from each component to determine the final amount in the drug product

$$Amount_{of}\ Elemental\ Impurity\ in\ drug\ product\ = \sum_{i=1}^{n} Ci \times Mi$$

where, i = an index for each of N components in the drug product, C_i = permitted concentration of the elemental impurity in component i (µg/g), and M_i = mass of component i in the maximum daily intake of the drug product (g)

- Compare the total daily amount of each elemental impurity with the established Permitted Daily Exposure value (PDE).

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Comparison of Observed Levels with PDE

- Elemental impurities excluded from the risk assessment (see Table 5.1)
- The elemental impurity level is <30% of the PDE. If this is the case, then no additional controls are deemed necessary.
- The elemental impurity level in the drug product is greater than the control threshold but does not exceed the PDE; additional measures may be implemented to insure that the level does not exceed the PDE
- The elemental impurity level exceeds the PDE,
  - Additional measures should be considered so that the levels do not exceed the PDE.
  - When additional measures are either not feasible or unsuccessful, levels of elemental impurities higher than the established PDE may be justified in certain circumstances.
    - The safety impact of the elemental impurity level should be evaluated as described in Q3D and Training Module 2.

It should be noted that if an AL is the level forming the basis of the comparison, the final acceptance of the proposed limit is dependent on approval by the appropriate regulatory authority.

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QUESTIONS?

Q3D Risk Assessment and Control FDA Perspective

Training Workshop: ICH Q3D
August 22 – 23, 2016

Frank O. Holcombe, Jr. Ph.D.
CDER/OPQ
Office of Lifecycle Products

Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

Q3D Overview

Q3D Context – Permitted Daily Exposure of selected elemental impurities

Q3D Content – Assurance of Permitted Daily Exposure of EI from drug products

Q3D Focus – Use of rrisk assessment as a tool in assuring acceptable exposure

Risk assessment is based on scientific knowledge and principles and is used to link safety considerations for patients with an understanding of the product and its manufacturing process.

Risk Assessment Process

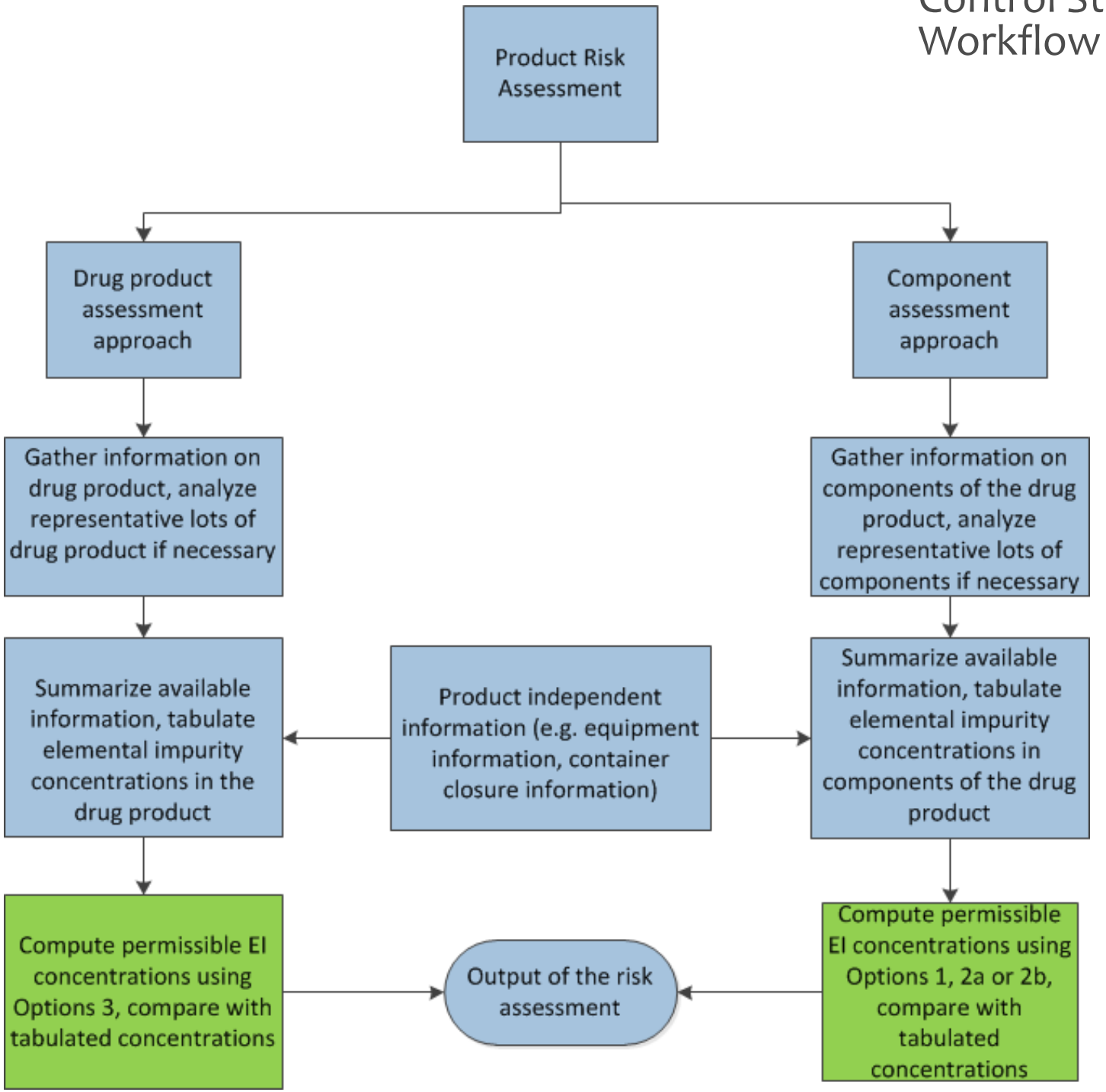
Identify known and potential sources of elemental impuiries in drug product

Evaluate presence of elemental impurity through observed or predicted level in drug product, comparing to PDE

Summarize and document risk assessment identifying adequacy of controls built into the process and need for any additional controls to assure PDE is not exceeded

Final outcome may be the result of iterative processes

Control Strategy Workflow



Potential Sources of Elemental Impurities in Drug Product

Intentionally added in excipients, components, or during formation of drug substance (e.g., catalysts)

Not intentionally added but potentially present in drug substance, water, excipients

Potentially introduced into drug product through manufacturing equipment

Potentially introduced through leaching from container/closure

Identification of Potential Elemental Impurities in Drug Product:

Intentionally added EI should be included

Potentially present through drug substance or excipients included based on routes of administration

Potentially derived from manufacturing equipment, depending on equipment

Potentially introduced from container closure system materials of construction

- Drug product interaction with container/closure materials
- Effects of processing cpmtaomer/closure system or packaged product

Q3D Table 5-1: Elements considered in the 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

Reference this table in the summary of the risk assessment.

Evaluation Outcomes

Risk assessment does not identify any potential elemental impurities

- Document the assessment and supporting information

Risk assessment Identifies potential elemental impurities

- Document the assessment and supporting information

Information includes prior knowledge, published literature, data from similar processes, supplier information or data, component testing, drug product testing

Evaluation Outcomes

Additional Considerations

- Efficiency of removal of EI by processing
- Natural abundance of elements
- Prior knowledge of impurity concentrations from specific sources
- Drug product composition

Summary of Risk Assessment Process

Reflects data/information review of product, process, materials identifying probable elemental impurities

Identify significant observed or predicted EI levels relative to the PDE

Provides a meaningful discussion addressing the decisions made regarding assurance that product is acceptable

Significance of Observed or Predicted EI Levels

Serves as a measure of need for additional controls

Level of 30% of PDE is designated “control threshold”

Levels demonstrated at consistently less than 30% of the PDE may not need additional controls

For levels between the control threshold and the PDE, additional controls should be established to assure that the PDE is not exceeded

Significance of Observed or Predicted EI Levels

Sources of variability should be considered in applicability of the control threshold, including

- Variability in analytical method
- Variability due to material sources
- Variability of elemental impurities in drug product

Level and variability may be established through data from 3 representative commercial scale batches or 6 representative pilot scale batches of component, components, or drug product. Application of the control threshold may require additional data

Format

There are many acceptable approaches to the summary and documenting of the risk assessment, including tables or written summaries

The summary should identify elemental impurities, their sources, and controls and associated acceptance criteria

Biotechnologically-derived Products

Risk of presence of elemental impurities at levels of safety concern are low, due to absence of use of inorganic catalysts or reagents, and the use of typical purification schemes

Consideration should be given to potential introduction of elemental impurities by excipients, environmental sources, and manufacturing process conditions

Approaches Toward Control of Elemental Impurities

Modification of manufacturing process (e.g., purification steps)

Implementation of in-process or upstream controls

Specification limits for excipients or materials

Specifications for drug substance

Specifications for drug product

Selection of container/closure system

Questions?

ICH Q3D Workshop - FDA/OPF's Perspective

Edwin Jao, Ph. D.
Acting Branch Chief
FDA/CDER/OPQ/OPF/DIVIII/BranchVII

This presentation reflects the opinions of the author and should not be construed to represent FDA's views or policies

Overview

- **Laws, regulations, guidances, and compendial**
- **Source of elemental impurities introduced during manufacturing**
- **Risk based control strategy**

Law, Regulation, Guidances, and Compendial

21 US Code 351 (a)(2)(B) (based on which FD&C 501(a)(2)(B) was enacted)

- A drug or device shall be deemed to be adulterated—if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics

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

Law, Regulation, Guidances, and Compendial (Cont.)

FDA Guidance on Process Validation

- For stage 2 process validation "selecting utilities and equipment construction materials, operation principles, and performance characteristics based on whether they are appropriate for their specific uses"
- Qualification (of equipment) refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale

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

Law, Regulation, Guidances, and Compendial (Cont.)

ICH Q3D

- In considering the production of a drug product, there are broad categories of potential sources of elemental impurities
  - Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product
  - Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment

USP <665> and **<1665>** Plastic Components and Systems Used in the Manufacturing of Pharmaceutical Drug Products (at development stage)

USP <662> metal packaging system and their materials of construction (at development stage)

- The principles and recommendations should be applicable to equipment as well

Law, Regulation, Guidances, and Compendial (Cont.)

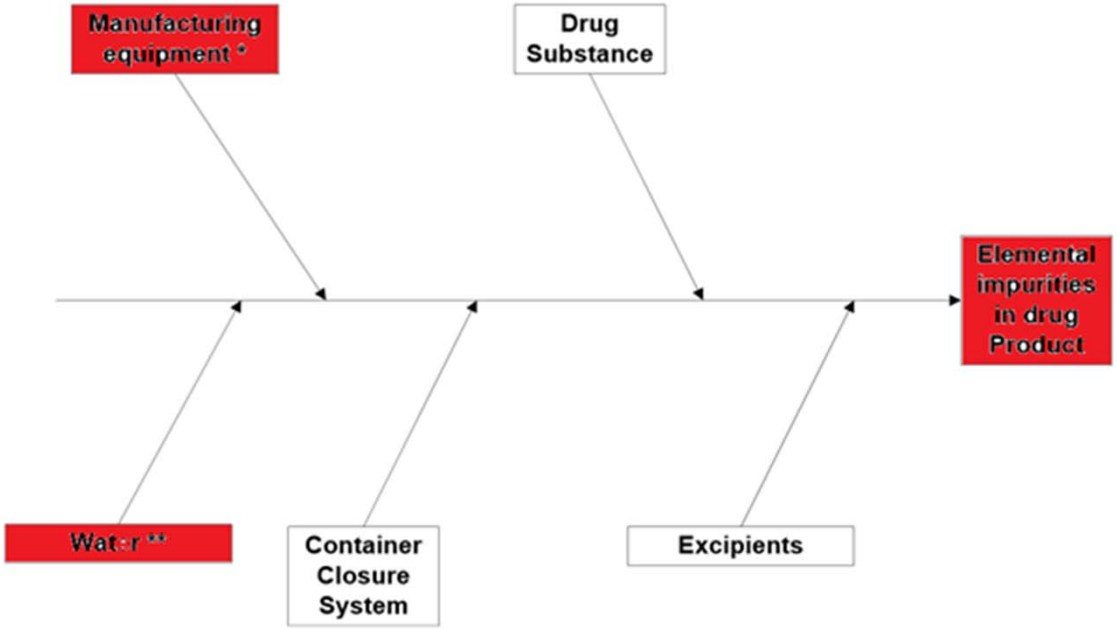
USP <661.1> plastic packaging systems and their materials of construction

- specification and extraction method for extractable metals for representative polymers (e.g. PVC, Polypropylene, Polyethylene Terephthalate)

USP <1663> assessment of extractables associated with pharmaceutical packaging/delivery systems

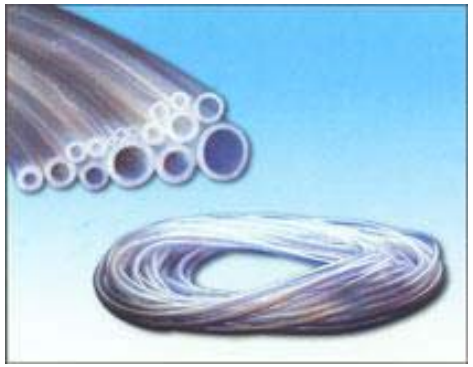
- For inorganic extractables, utilization of a simulating solvent having similar metal-chelating properties as the drug product vehicle may also be appropriate and justifiable.
- The principles and recommendations should be applicable to equipment as well

Source of elemental impurities introduced from process

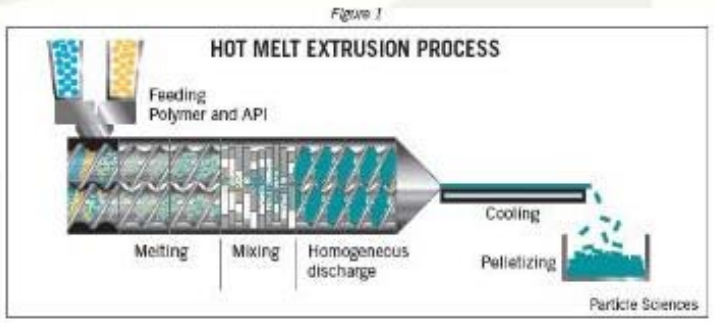


- Equipment wear and tear (e.g., chipping, grinding, friction)
- Extractable metals (stainless steel and polymeric equipment)
- elemental impurities from processing solvents (water, petro derived solvents)

Commonly Used Manufacturing Equipment for Liquid Dosage Form



Commonly Used Manufacturing Equipment for Solid Dosage Form



Source of Elemental Impurities Introduced from Process

- ASTM 316/316/L stainless steel

Chemical Composition :

UNS/Euro	ASTM/Euro	Carbon	Manganese	Phosphorous	Sulfur	Silicon	Chromium	Nickel	Nitrogen	Molybdenum
S31600	316	0.08 max	2 max	0.045 max	0.03 max	0.75 max	16-18	10-14	0.1 max	2-3
S31603	316L	0.03 max	2 max	0.045 max	0.03 max	0.75 max	16-18	10-14	0.1 max	2-3
X2CrNiMo17-12-2	1.4404	0.03 max	2 max	0.045 max	0.015 max	0.75 max	16.5-18.5	10-13	0.1 max	2-2.5
X5CrNiMo17-12-2	1.4401	0.07 max	2 max	0.045 max	0.015 max	0.75 max	16.5-18.5	10-13	0.1 max	2-2.5

- Polymeric material

  elemental impurities from petroleum raw material, catalysts, reagents used during polymerization and fabrication
- Processing solvents
  - Water

    EPA controlled metals: Cd, Pb, As, Hg, Cr, Se, Tl, Ba, Cu, Ni et al
  - Petro based solvents: various
- Cross contamination during manufacturing: various

Risk Factors

- **Construction material of the equipment**
- **Design of equipment**
- **Formulation (pH, chelating excipients, co-solvents)**
- **Process (blending, compression, hot melt extrusion, temperature, pressure)**

Risk Based Control Strategies

cGMP

- Qualification, usage, maintenance, cleaning of equipment, change control
- Quality agreement with vendors including auditing
- The responsibility is on the drug product manufacturers

  Vender provided compatibility information is always helpful; however, the applicability of the information is process and product dependent and therefore generally established by drug product manufacturer

Risk Based Control Strategies

cGMP

- Qualification, usage, maintenance, cleaning of equipment, change control
- Quality agreement with vendors including auditing
- The responsibility is on the drug product manufacturers

Product and process specific understanding

- Equipment understanding: construction material, operation principles and compatibility
- Product understanding: formulation, physical and chemical characteristics
- Process understanding: impact on the equipment and quality of the drug product
- Drug usage understanding: indication, maximum daily dose, route of administration, duration

Risk based control strategies (cont.)

Process introduced elemental impurities controls

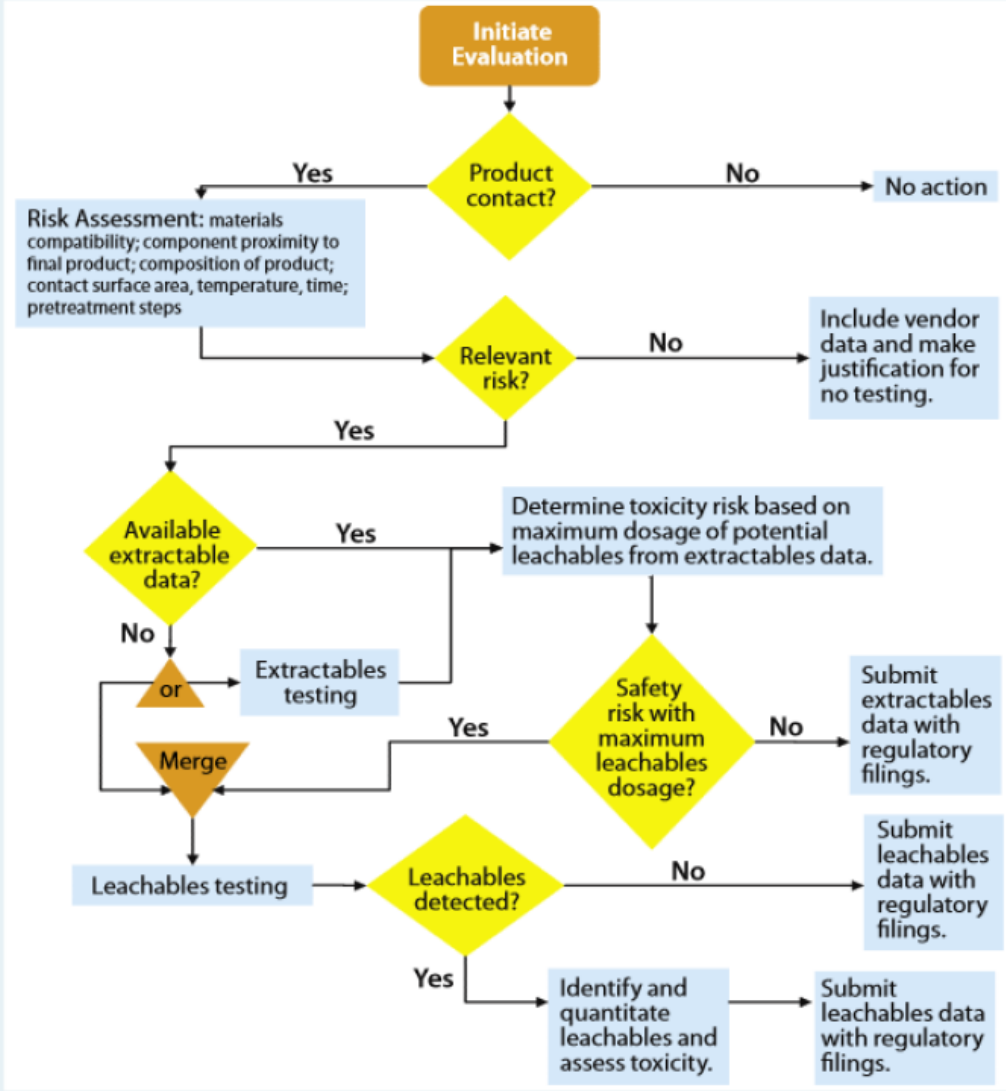
- Construction materials: compliance to ASTM and equivalent standards and CFR requirements for indirect food additives
- Qualify all equipment under worse case manufacturing condition
  - Load (contacting surface/volume)
  - Usage (single, multiple)
  - pH
  - Chelating reagent
  - Temperature, pressure, and duration
- Extractable/leachable elemental impurities investigation (liquid and semi-liquid dosage form)
  - Placebo formulation or simulating solvent having similar metal-chelating properties
- Metal detector (low risk solid dosage form)

Risk Based Control Strategies (cont.)

- The detection methods for and qualification of extractable/leachable elemental impurities can be the same as those used for drug product and container/closure system.

Bio-Process Systems Alliance (BPSA) Recommendations for Extractables & Leachables Testing (2008)

Figure 1: Extractables and leachables evaluation flow chart



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