Module 7

Converting between PDEs and Concentration Limits

ICH Q3D Elemental Impurities

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Legal Notice

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 183

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**