CANADIAN SUBMISSION:

ICH Q3D Elemental Impurities Submission Feedback

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Elemental Impurities

Goals

- Share submission approach
- Describe submission preparation
- Share challenges
- Share regulatory feedback

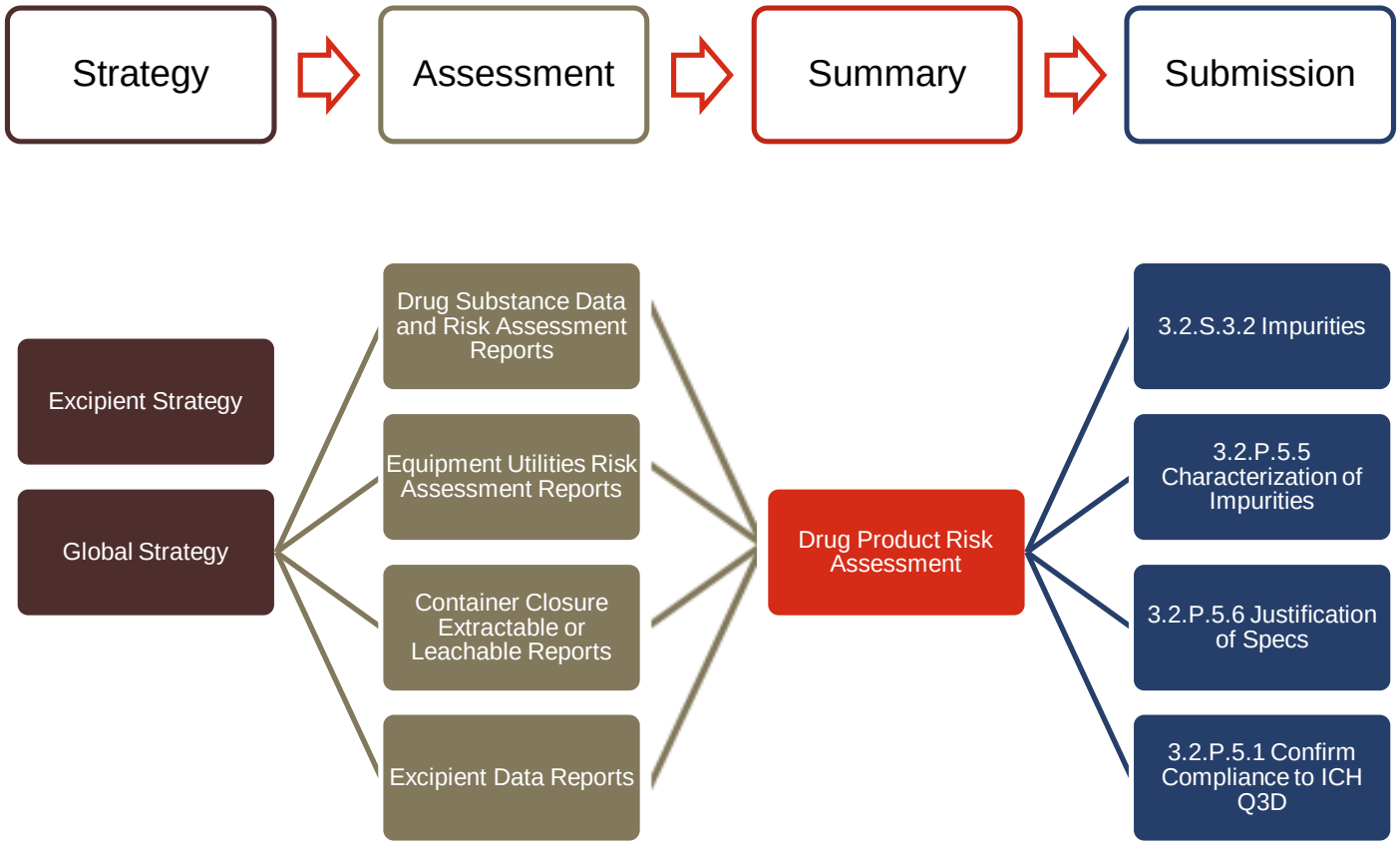
Why are we anxious, about regulatory submissions?

Anxiety

We all have a lot of questions:

- Did we adequately explain our risk-based approach?
- Did we include enough data?
- Did we interpret ICH Q3D correctly?
- Will elemental impurities questions impact the approval of the submission?

Lilly Approach



Lilly Approach

- Updated 3.2.S.3.2 Impurities
  - to supplement drug substance impurities with elemental impurities information.
- Updated 3.2.P.5.5 Characterization of Impurities
  - to include elemental impurities information for utilities, excipients, container closure to supplement with elemental impurities information. Included data.
- Updated 3.2.P.5.1 Specifications
  - to add a NOTE confirming compliance to ICH Q3D.
- Updated 3.2.P.5.6 Justification of Specifications
  - to state elemental impurities testing strategy and refer to Module 3 documents where we justified and explained.

Submission Preparation

3.2.S.3.2 Impurities – Drug Substances

Table	Description	
Table 1	Elements to be evaluated	List
Table 2	Drug substances assessment of controls	Assessment
Table 3	Drug substances data table	Data

Table 2	Drug Substances Assessment of Controls
Risks	Catalyst?
	Equipment
	Container Closure
Controls	Process Removal
	Specification

Submission Preparation

3.2.P.5.5 Characterization of Impurities

Table	Description	Details
Table 1	Elements to be evaluated	List
Table 2	Equipment and utilities assessment	MOC, STD*
N/A	Drug substances elemental impurities assessment summary	Statement
Table 3	Excipients assessment	Assessment
Table 4	Excipients data table	Data
Table 5	Container closure system – Materials of construction	MOC
Table 6	Container closure systems – Risk assessment	Assessment
Table 7	Maximum daily intake calculation	Calculations
Table 8	Daily contribution to the total mass of elemental impurities in drug product	Calculations
Table 9	Final assessment conclusions and action plan	Action

*MOC – Materials of Construction, STD - Standards

Submission Preparation

3.2.P.5.5 Characterization of Impurities – Excipients

Table 3	Excipient Assessment
Section 1	Origin
Section 2	Catalyst
Section 3	Control

Submission Preparation

3.2.P.5.5 Characterization of Impurities – Components

Table 6	Container Closure Systems – Risk Assessment (Yes/No and Conclusions)
Section 1	Dosage Form
Section 2	Protective Barrier
Section 3	Materials of Construction List
Section 4	Extractable or Leachable Studies

Submission Preparation

Table 8: Daily contribution to the total mass of elemental impurities in product

Our Approach: Refer to Table A.4.8 Example in ICH Q3D

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Component	Daily intake, g	Measured Concentration (µg/g)							Total Daily Mass of Elemental Impurity, µg						
		Pb	As	Cd	Hg	Pd	V	Ni	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.2	ND	0.5	ND	ND	20	ND	50	0	0.1	0	0	4	0	10
MCC	1.1	0.1	0.1	0.1	0.1	*	ND	ND	0.11	0.11	0.11	0.11	0	0	0
Lactose	0.45	0.1	0.1	0.1	0.1	*	ND	ND	0.045	0.045	0.045	0.045	0	0	0
Ca Phosphate	0.35	1	1	1	1	*	10	5	0.35	0.35	0.35	0.35	0	3.5	1.75
Crospovidone	0.265	0.1	0.1	0.1	0.1	*	ND	ND	0.0265	0.0265	0.0265	0.0265	0	0	0
Mg stearate	0.035	0.5	0.5	0.5	0.5	*	ND	0.5	0.0175	0.0175	0.0175	0.0175	0	0	0.0175
HPMC	0.06	0.1	0.1	0.1	0.1	*	ND	ND	0.006	0.006	0.006	0.006	0	0	0
Titanium Dioxide	0.025	20	1	1	1	*	1	ND	0.5	0.025	0.025	0.025	0	0.025	0
Iron Oxide	0.015	10	10	10	10	*	400	50	0.15	0.15	0.15	0.15	0	6	0.75
							total daily mass, µg/day		1.2	0.8	0.7	0.7	4.0	9.5	12.5

Add drug product results and 30% control threshold to bottom of table.

Submission Preparation

Table 9: Final assessment conclusions and action plan

Our Approach: Refer to Table A.4.9 Example in ICH Q3D

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	1	2	3	4	5	6	7	8
Element	Intentionally added (if used in the process)	Elemental impurities with a relatively high abundance and/or are impurities in excipients or reagents	Manufacturing equipment	Leached from container closure systems	Total elemental impurity contribution µg/day	Acceptable variability of elemental impurity contribution	Control threshold	Action
As	No	Observed contaminant in all excipients and drug substance	No	No	0.8	yes	4.5	no further controls required
Cd	No	Observed contaminant in all excipients	No	No	0.7	yes	1.5	no further controls required
Hg	No	Observed contaminant in all excipients	No	No	0.7	yes	12	no further controls required
Pb	No	Observed contaminant in all excipients	No	No	1.2	yes	1.5	no further controls required
Pd	API catalyst	No	No	No	4.0	yes	30	no further controls required
Ni	API catalyst	Observed in 3 excipients	No	No	12.5	yes	180	no further controls required
V	No	Observed in 3 excipients	No	No	9.5	yes	36	no further controls required

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Submission Preparation

3.2.P.5.1 Specifications

- Statement of ICH Q3D Compliance

Submission Preparation

3.2.5.6 Justification of Specifications

- Adequacy of existing controls
- Summary of Data
  - Below ICH Q3D Permitted Daily Exposure control threshold

Challenges

Challenges	Solutions
No Roadmap	Learned from the first one.
During submission preparation, it was determined that some sections of the risk assessment needed clarification. (e.g. excipient origin and reference)	Ensure all key stakeholders are engaged early in the risk assessment process.

Feedback

- One parenteral drug product submission
  - No elemental impurities questions.
  - Submission was approved.

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Questions