Development of Elemental Impurity risk assessments for existing prescription products

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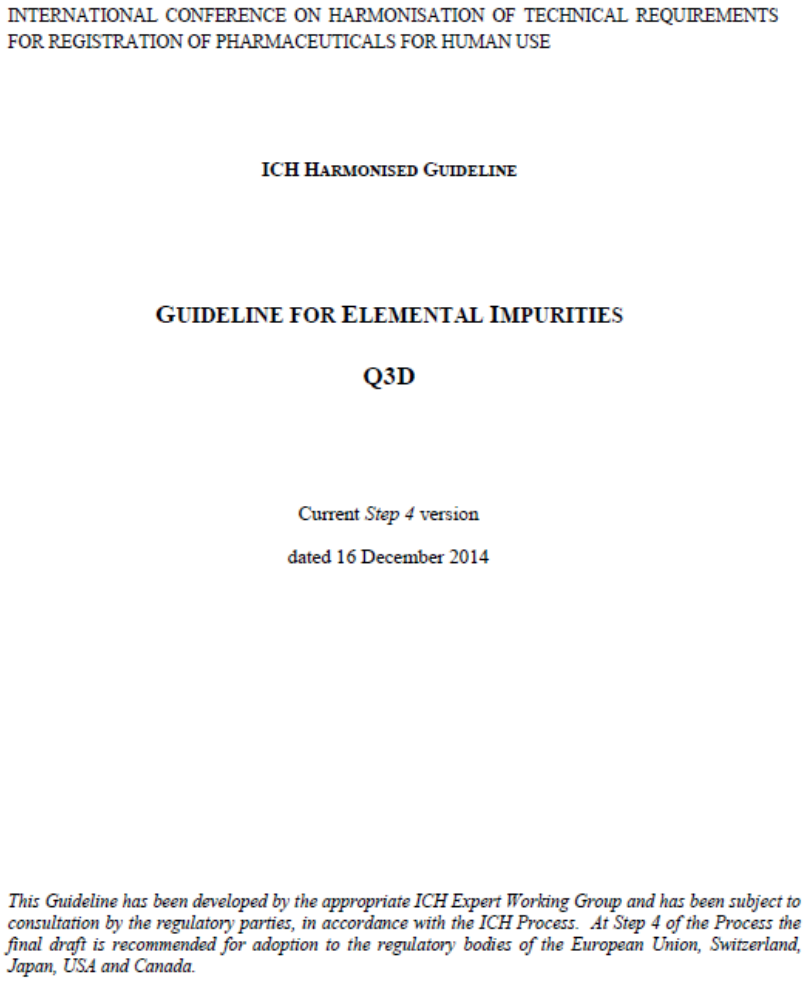
Expectations

- EI product risk assessments complete by 31 Dec 2017
- Science and risk based approach will be accepted
- Limits will not be expected if the EI risk assessments demonstrate control at or below 30% of respective PDE
- Data in some form is needed to support product risk assessments



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR ELEMENTAL IMPURITIES

Q3D

Current *Step 4* version

dated 16 December 2014

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Switzerland, Japan, USA and Canada.

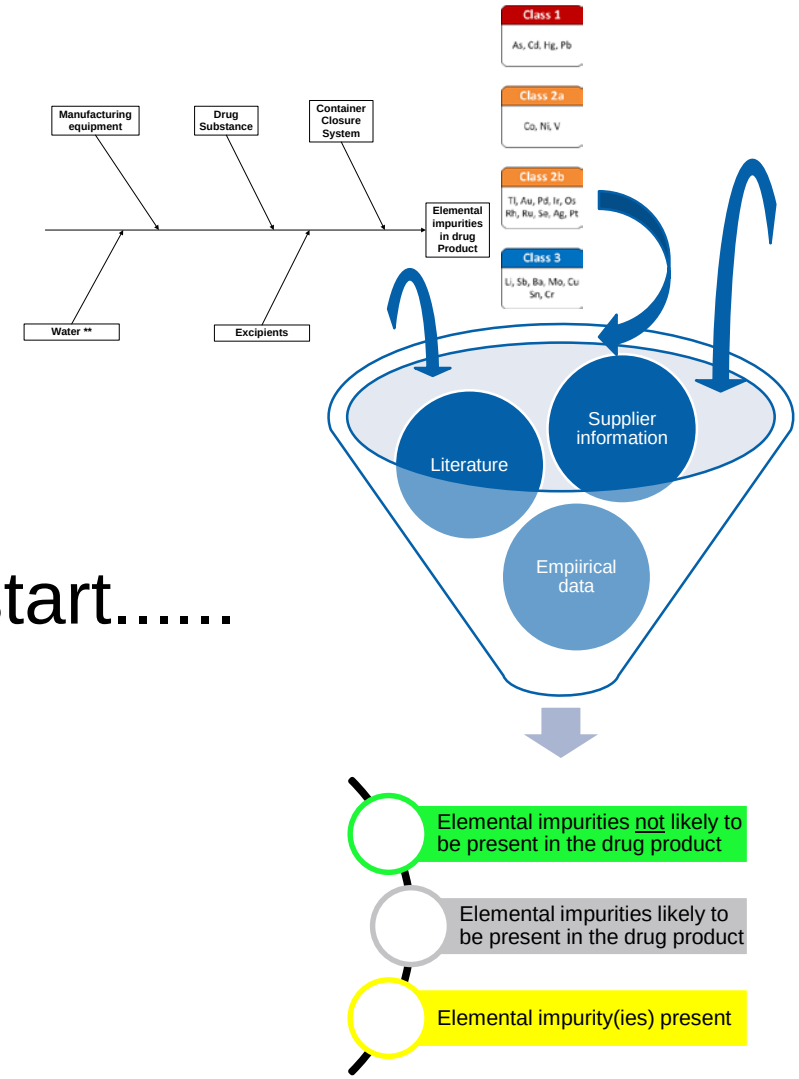
Implementation challenges

- Internal
  - Product vs component approach
  - Data availability
  - Limited knowledge of expected format of EI product risk assessments
  - Multiple sites
  - Multiple suppliers

- HA Expectations
  - Level of detail
  - Amount of data that will be acceptable
  - Regional interpretation differences
  - Will three lots of data be sufficient
  - Consistency in inspector understanding and interpretations

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

Where to start.....



Elements to be considered in the product risk assessment (ICH Q3D Table 5.1)

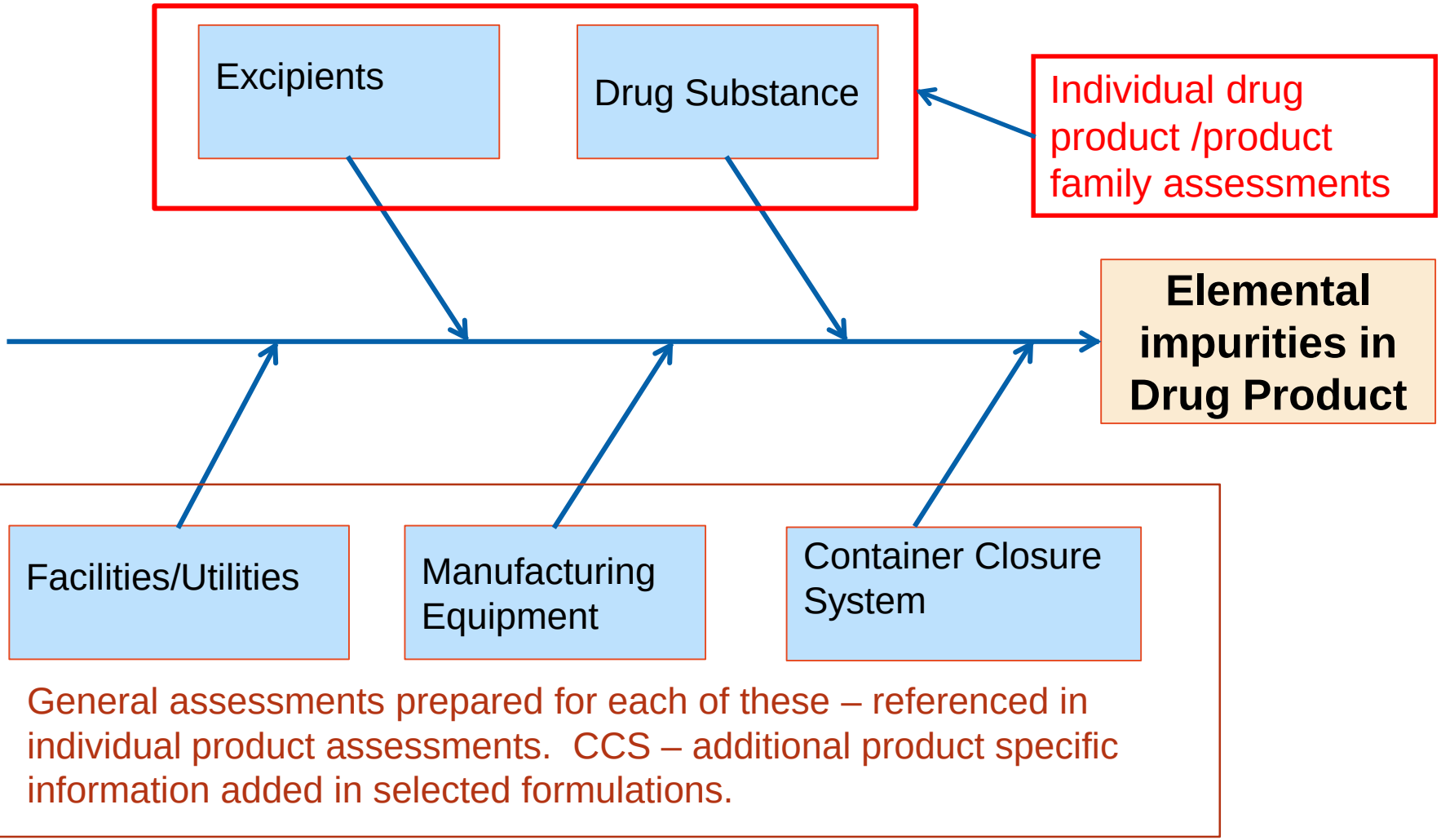
Overview of the program at Novartis

- More than 10,000 excipients and drug substances
  - Multiple suppliers
  - Multiple manufacturing sites
  - One overall quality system
- Small molecule
- Biologicals
- Wide range of drug products
  - Oral
  - Parenteral
  - Inhalation
  - Topical
  - Ophthalmic
  - Combination products
- 67 manufacturing locations

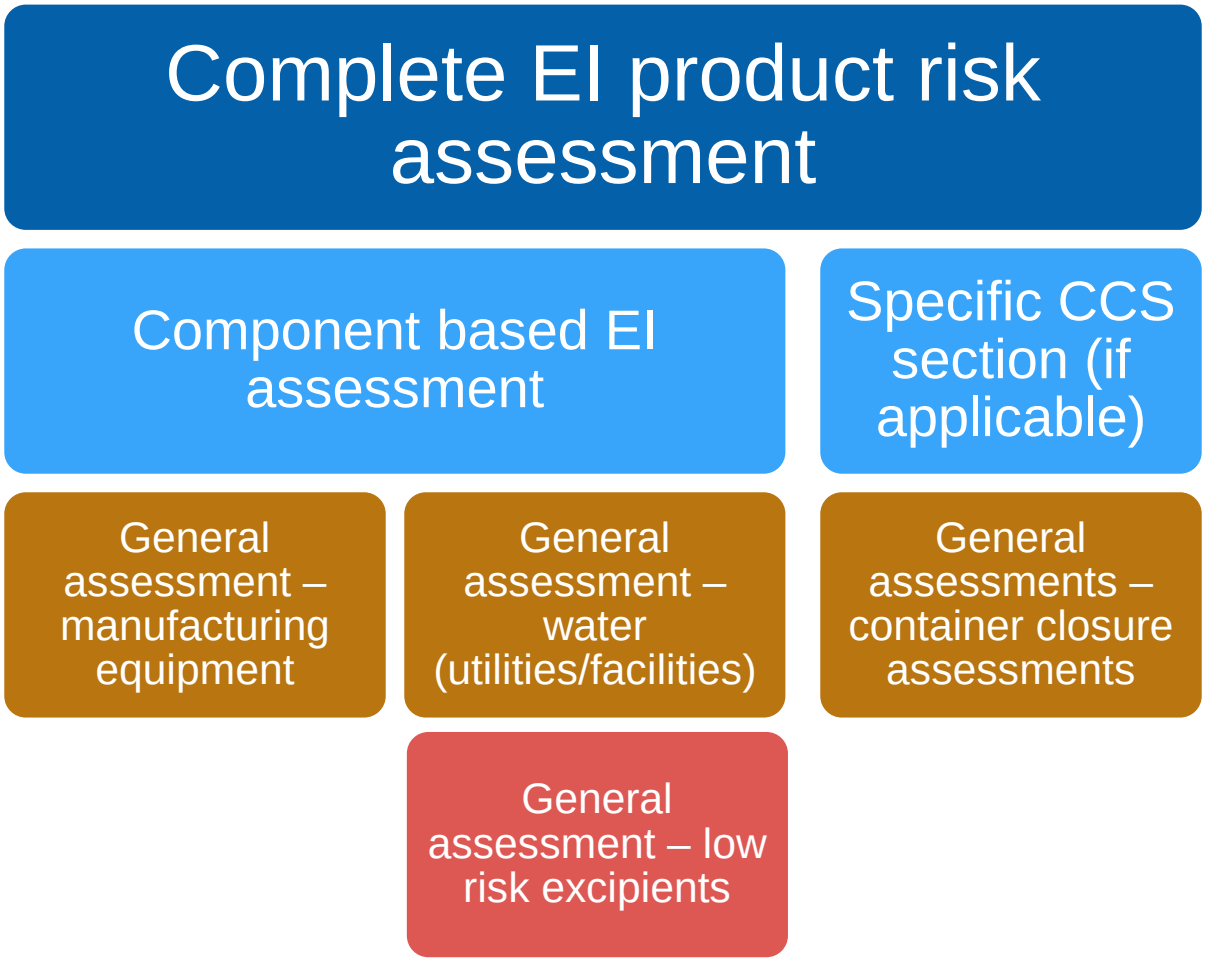
Novartis EI compliance background

- From 2012, initiated development of ICP-MS data for selected excipients, drug substances and drug product
- Drug substance screening
  - 100+ drug substances over
- Preparation of product assessments began in 2015
  - Standard template based on Q3D potential sources of elemental impurities
- Revised product assessment approach (2017) to reflect increasing knowledge and ability to mine expanding database of EI profiles

Preparation of EI product risk assessments



Product assessment package

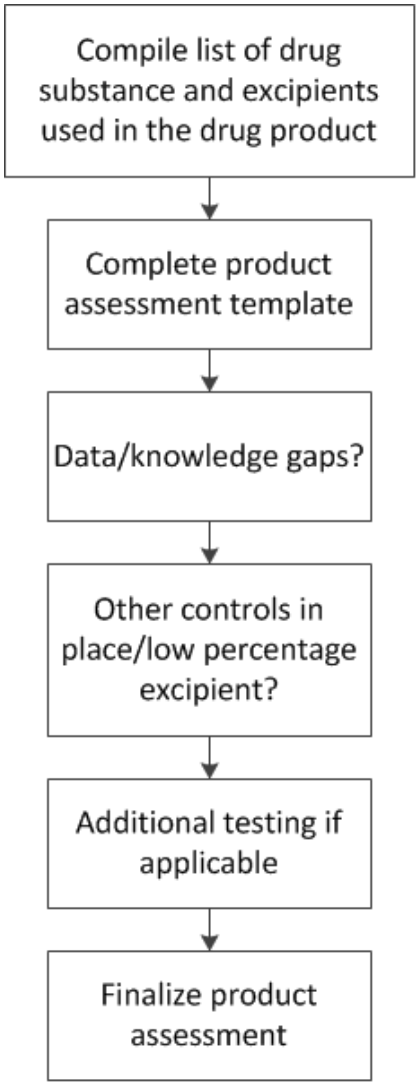


Manufacturing equipment general assessment

- Generation of screening data
  - Evaluated screening data from >100 different drug substances (>600 lots)
    - Class 1, 2A and select class 3 elements (As, Cd, Hg, Pb, Co, Ni, V, Cr, Mo)
    - Wide range of reaction chemistries, pH profiles, solvent profiles, temperature extremes
    - Most products with >5 lots tested
    - Screening from development through commercialization
- GMP controls established across manufacturing sites
  - Engineering standard
  - Equipment design and installation qualification
  - Equipment cleaning and maintenance (includes visual inspection for wear/surface losses)
  - One quality system across Novartis sites
- Data shows that observed levels (if detected, >LOD - >LOQ)
  - No significant EI contribution to drug product (even at 10g daily dose)

Sources of data for EI product risk assessments

- Internally generated EI data
- Data from external EI database
- FDA-IPEC joint publication
- Vendor CoA
- Vendor compliance statement
- Other material controls



Product assessment template

Component	Name	Percent in formulation	Data in NVS database	Data in external database	Data in FDA publication	Supplier data/comp. statement	Data sufficient for assessment	Additional actions/testing planned
Drug substance								
Justification of actions								
Excipient 1								
Justification of actions								
Excipient 2								
Justification of actions								
Excipient 3								
Justification of actions								
Excipient 4								

- Composite data from one or more sources is used in the assessment

EI product risk assessment summary

Component Name	Max. Daily Intake (grams/day)	Class 1 Elemental Impurities, (µg/g)				Class 2A Elemental Impurities (µg/g)		
		As	Cd	Hg	Pb	Co	Ni	V
Drug substance	0.035	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Excipient 1	0.125	<LOQ	<LOQ	<LOQ	0.02	0.006	0.01	0.005
Excipient 2	0.020	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.49	<LOQ
Excipient 3	0.005	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Excipient 4	0.012	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.055	0.17
Excipient 5	0.003	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.019	<LOQ
Excipient 6	0.006	11.121	<LOQ	<LOQ	1.17	12.031	18.225	58.49
EI levels in drug product	0.211	0.32	<LOQ	<LOQ	0.046	0.35	0.59	1.72
NVS observed LOQ		0.015	0.015	0.012	0.015	0.002	0.005	0.004
PDE		15	5	30	5	50	100	200

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:** • **Utilized NVS and external excipient EI database** • **Literature information** • **Vendor statements**

1 = 2 = 3

Consolidated excipient data utilization – comparative evaluation

Luck, random chance, expected outcome?

- Survey of data
  - Majority of data from multiple excipients, multiple lots, multiple global vendors have EI profiles characterized by levels <LOQ
  - Most drug products evaluated < 1g daily dose
  - Standardized validated analytical procedure in use in 8 laboratories and 2 contract laboratories
- GMP controls
  - Vendor qualification program
    - Periodic testing to ensure quality
- Assessment on-going

Challenges and conclusions

- A pragmatic risk assessment approach has been implemented to prepare over 2300 individual EI product risk assessments
  - Incorporate science and risk based assessments
  - Component approach and recommendation from ICH Q3D to simplify the assessments where possible
- Increasing amount of data is enabling more pragmatic approaches to development of product risk assessments
- Significant challenge that is still out there – what constitutes an acceptable EI product risk assessment

Questions?

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Thank you

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