Publications and Lhasa Database Update

John Glennon, GSK
For
Elemental Impurities Data Sharing Consortium
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Disclaimer

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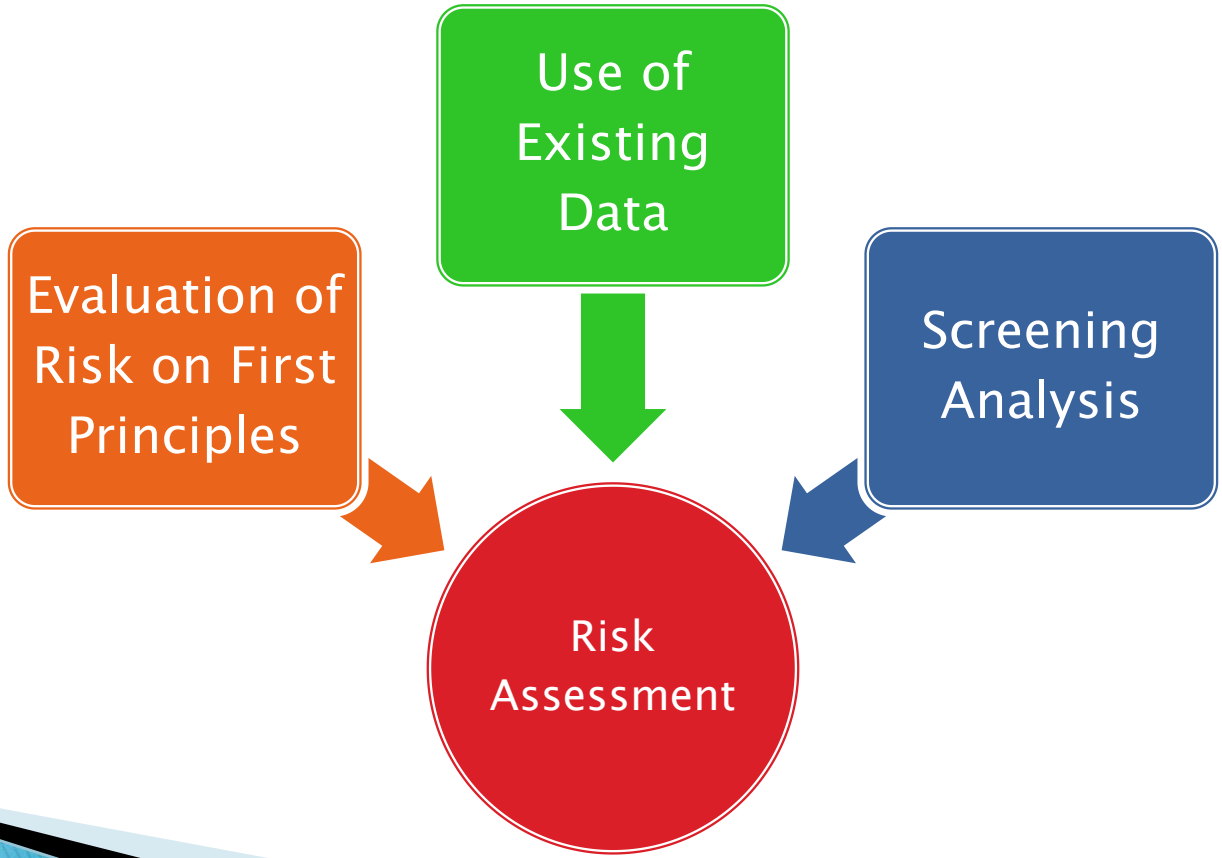
Q3D Risk Assessment – Evaluate

- Moving away from test everything.
- **Screening every component for 24 elements is not a risk assessment!**
- Evaluation can include a combination of:



Q3D Risk Assessment – Evaluate

Where is the biggest risk

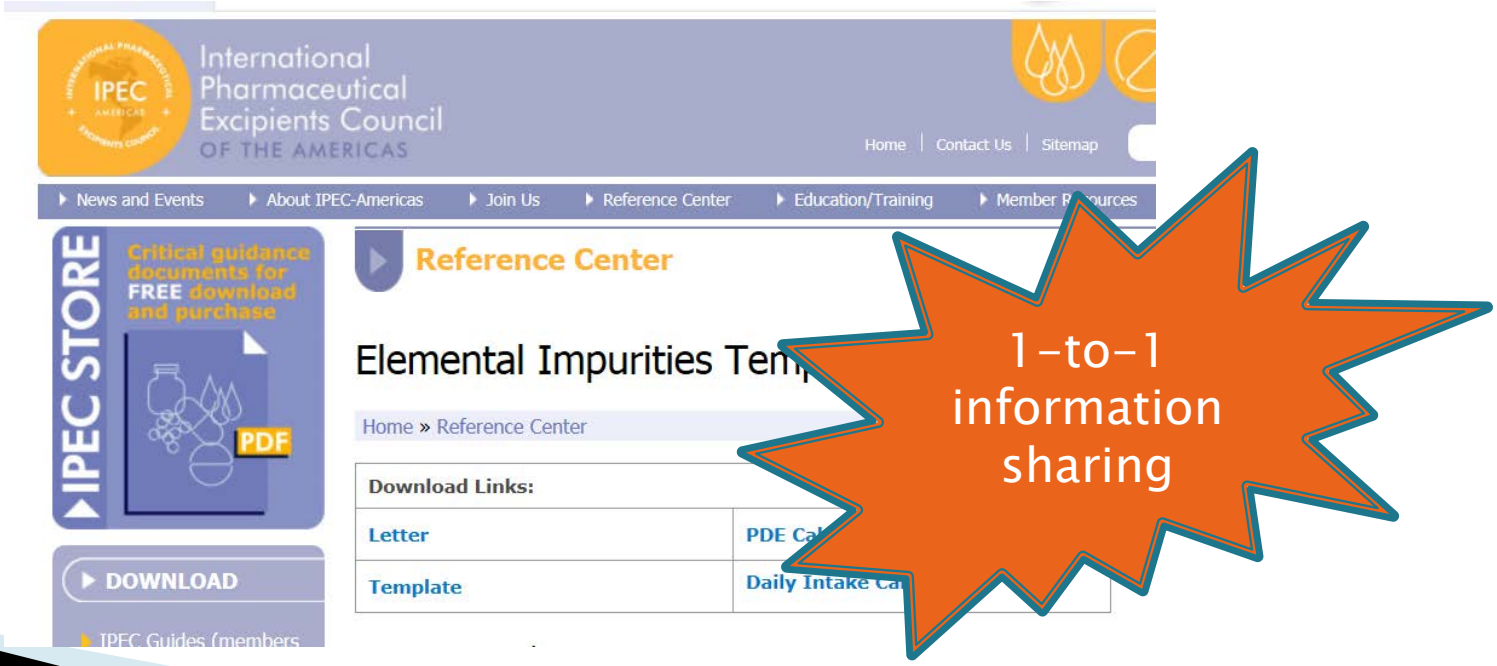
Excipients…

but why?

- “We” knew very little about their Elemental Impurity content

Use of Existing Data: Supplier-to-Customer

- Practical Implementation of ICH Q3D requires the sharing of knowledge between Suppliers and Drug Product Manufacturers
  - Need effective communication between all parties.
- To facilitate this, IPEC generated a questionnaire.
  - Other tools such as calculator are accessible.



Use of Existing Data:
External Data for Excipients

EXCIPIENTS

- Knowledge of the extent of the risk from excipients is increasing.
- Initial studies conducted by IPEC-Americas and the FDA proved illuminating.
- The studies involved over 200 samples, spanning a range of excipient types, including plant derived, synthetic and mined excipients.

Li, G., Schoneker, D., Ulman, K. L., Sturm, J. J., Thackery, L. M. and Kauffman, J. F. (2015), Elemental Impurities in Pharmaceutical Excipients. J. Pharm. Sci., 104: 4197–4206. doi:10.1002/jps.24650

Published information

Use of Existing Data: The Excipient Data Base

Elemental Impurities Data Sharing Consortium

- Borne out of discussions during a JPAG EI meeting October 2013.
- Agreed the value of pooling data

Elemental Impurities Data Sharing Consortium

Use of Existing Data: The Excipient Data Base

Building a Database – Design Specification

1. 3rd party to host and blind data
2. Integrity of the Data is important!
   - Want data on excipients *NOT* suppliers
     - There is no intent to use this to compare suppliers
   - Data is blinded by the third party.
   - Want to see where the real risk is before formulation development starts
3. Quality is critical
   - Minimum Standards for methods, including validation
   - Detailed proposals developed
     - Over 97% of data compiled is from validated quantitative methods

What's The Strategic Intent Of The Database?

- Provide data which can be used in the same way as information from the published literature to support the ICH Q3D risk assessment of excipient components

- Publish key findings which provide scientific underpinning to risk assessments and have the potential to reduce unnecessary testing.

How Is The Strategic Intent Of The Database Achieved?

The database and the data it contains must possess the following:

- A **sufficient number** of **relevant** excipients
  - Makes it commonplace to find data for an excipient of interest
- **Data** for **relevant elements**
  - Based on **route of administration** and the **method of manufacture** as recommended by ICH Q3D.
- **Multiple** excipient samples, from a **range** of suppliers.

Building the Database

How has the Database been built?

- Lhasa designed and developed the Elemental Impurities database based on Vitic™ Nexus platform
- Approved by the consortium in December 2015
  - Initial round of donations was received beginning of 2016
  - The database was first released at the end of March 2016

How much Data is in it?

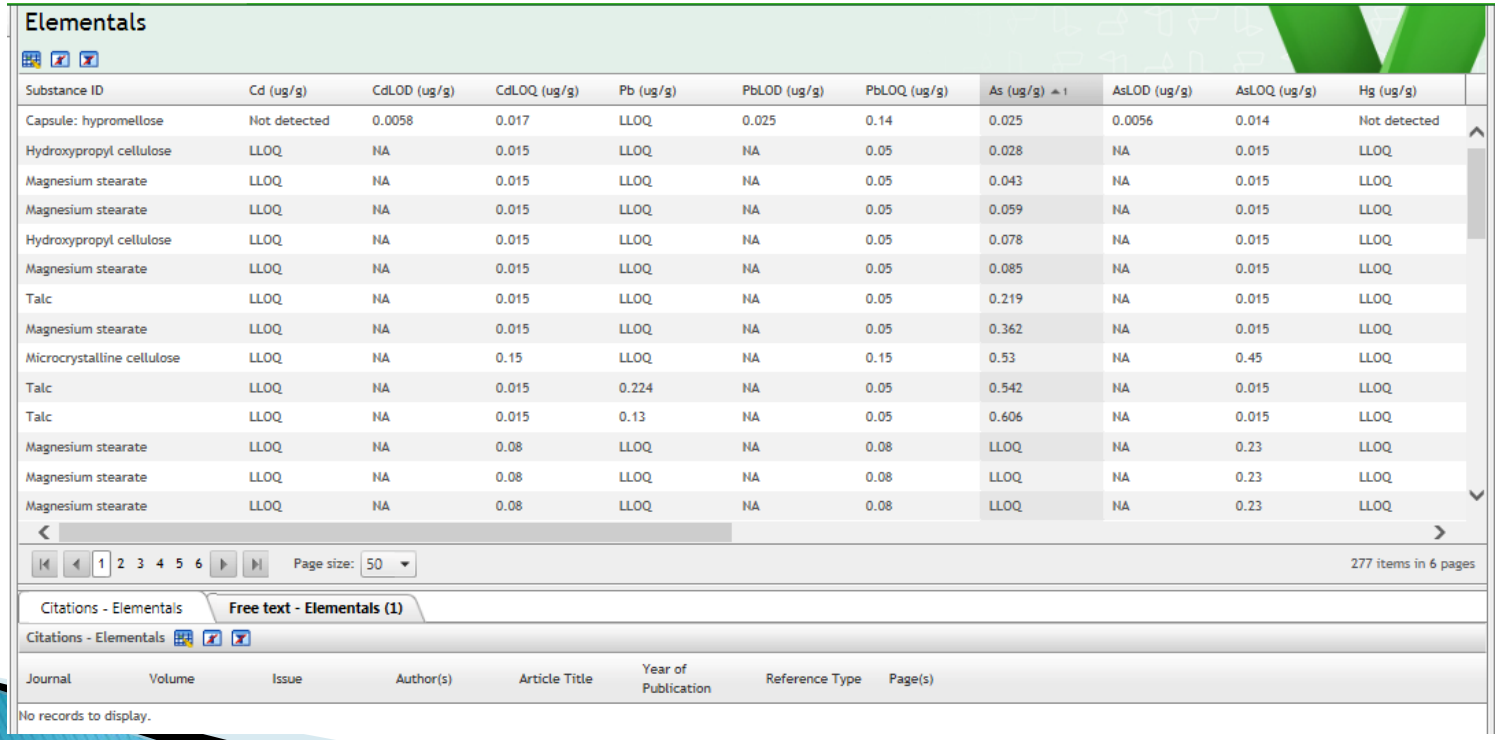
The Elementals database v2017.1 contains the following number of records:

- The results of 26723 elemental determinations from 1738 analytical studies for 201 excipients and represents the largest known collection of data of this type.

Building the Database

Developed a procedure/process for organizations to share their in-house data

- Template defined to allow error free parsing of data.
- Data anonymised and checked by Lhasa.



Elementals

Substance ID	Cd (ug/g)	CdLOD (ug/g)	CdLOQ (ug/g)	Pb (ug/g)	PbLOD (ug/g)	PbLOQ (ug/g)	As (ug/g)	AsLOD (ug/g)	AsLOQ (ug/g)	Hg (ug/g)
Capsule: hypromellose	Not detected	0.0058	0.017	LLOQ	0.025	0.14	0.025	0.0056	0.014	Not detected
Hydroxypropyl cellulose	LLOQ	NA	0.015	LLOQ	NA	0.05	0.028	NA	0.015	LLOQ
Magnesium stearate	LLOQ	NA	0.015	LLOQ	NA	0.05	0.043	NA	0.015	LLOQ
Magnesium stearate	LLOQ	NA	0.015	LLOQ	NA	0.05	0.059	NA	0.015	LLOQ
Hydroxypropyl cellulose	LLOQ	NA	0.015	LLOQ	NA	0.05	0.078	NA	0.015	LLOQ
Magnesium stearate	LLOQ	NA	0.015	LLOQ	NA	0.05	0.085	NA	0.015	LLOQ
Talc	LLOQ	NA	0.015	LLOQ	NA	0.05	0.219	NA	0.015	LLOQ
Magnesium stearate	LLOQ	NA	0.015	LLOQ	NA	0.05	0.362	NA	0.015	LLOQ
Microcrystalline cellulose	LLOQ	NA	0.15	LLOQ	NA	0.15	0.53	NA	0.45	LLOQ
Talc	LLOQ	NA	0.015	0.224	NA	0.05	0.542	NA	0.015	LLOQ
Talc	LLOQ	NA	0.015	0.13	NA	0.05	0.606	NA	0.015	LLOQ
Magnesium stearate	LLOQ	NA	0.08	LLOQ	NA	0.08	LLOQ	NA	0.23	LLOQ
Magnesium stearate	LLOQ	NA	0.08	LLOQ	NA	0.08	LLOQ	NA	0.23	LLOQ
Magnesium stearate	LLOQ	NA	0.08	LLOQ	NA	0.08	LLOQ	NA	0.23	LLOQ

1 2 3 4 5 6 Page size: 50 277 items in 6 pages

Citations - Elementals | Free text - Elementals (1)

Citations - Elementals

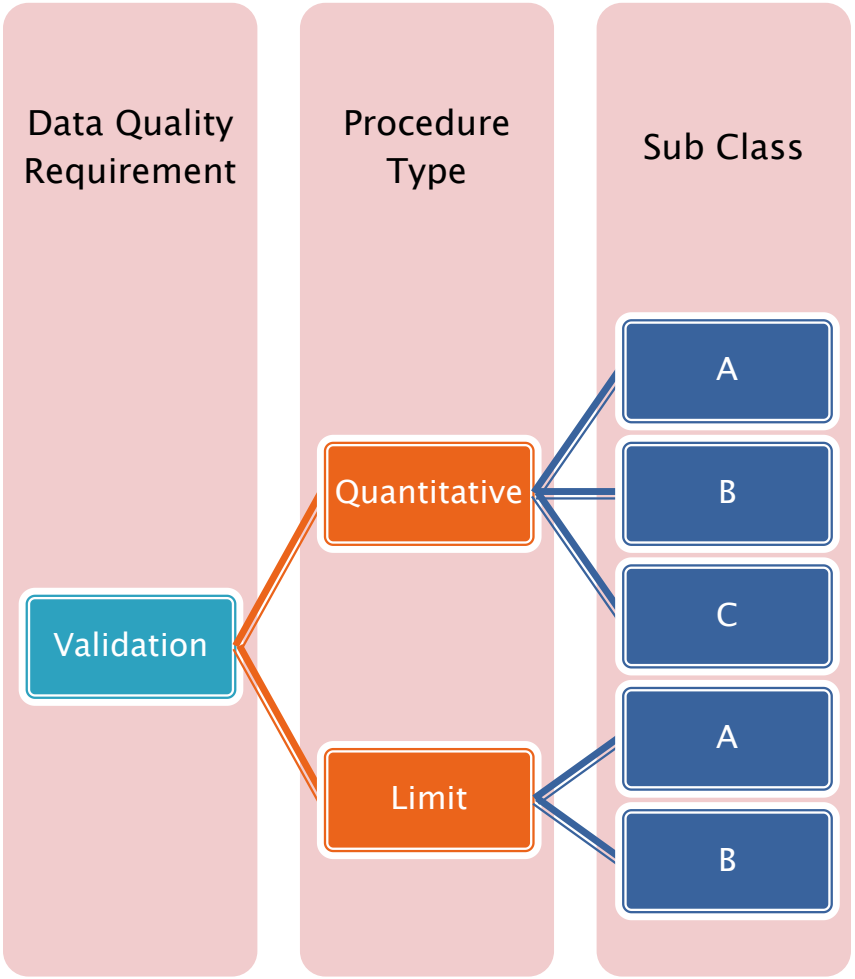
Journal	Volume	Issue	Author(s)	Article Title	Year of Publication	Reference Type	Page(s)

No records to display.

Building the Database
Data Quality Requirements

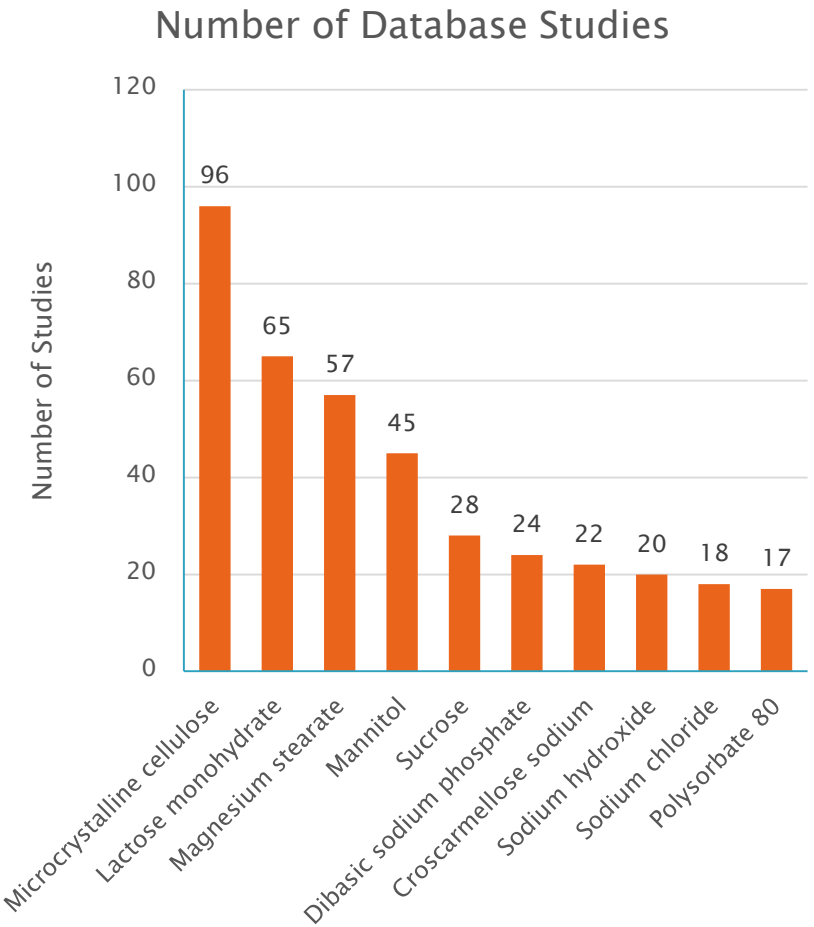
- Extensive discussions relating to data requirements
- Validation Classification Rubric generated
- For each sample the Database Records
  - Extent of Validation
  - Digestion Conditions

There is no difference between data donated to the database and data published in a peer review journal in terms of vindication of data



Building the Database
Is there a diversity of materials?

- The content of the database will be <u>actively managed</u>
- There is a clear commitment from members to generate data if gaps are identified



Building the Database
Are Relevant Excipients Included?

A review was conducted, focused on new drug approvals in 2016:

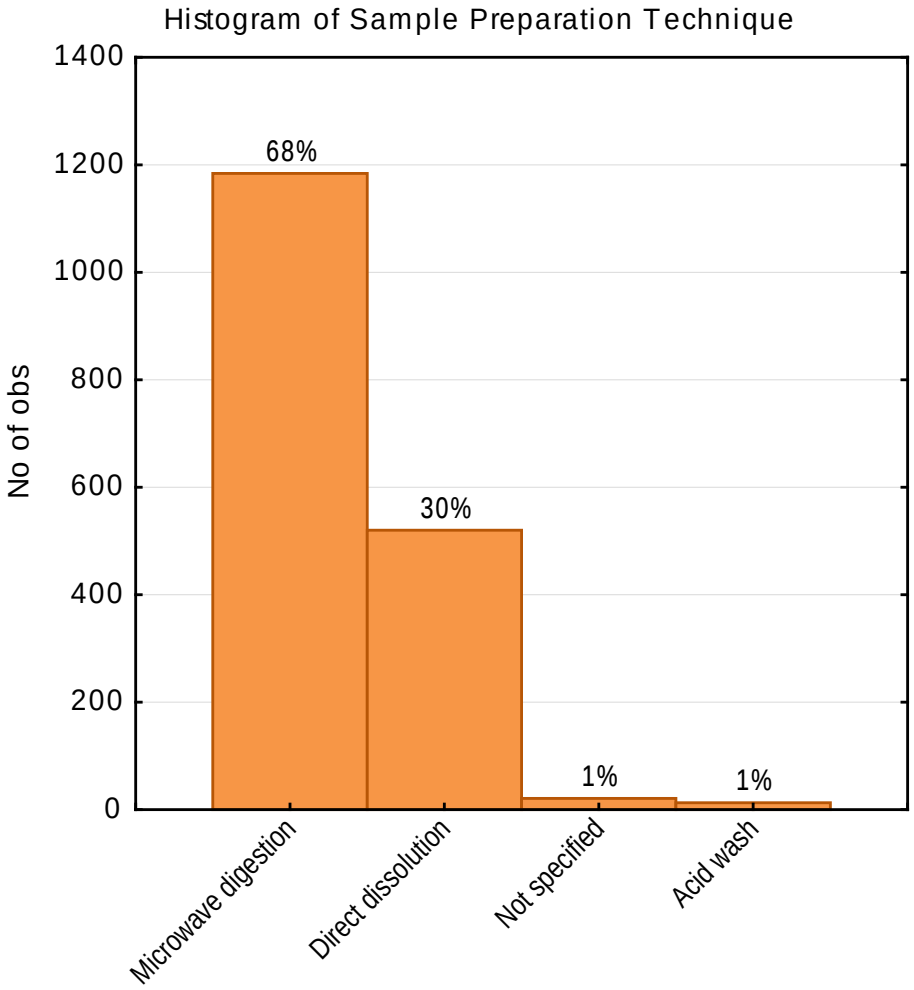
- Examined the list of excipients included in the formulation of novel drugs compiled from label information
  - Available through the Drugs@FDA service.
- 22 novel drugs from 19 organisations representative of the pharmaceutical industry were evaluated:
  - 7 oral
  - 13 parenteral
  - 2 topical administration

20 excipients were present in more than one formulation.

18 (90%) of the 20 excipients had at least three analytical studies in the database

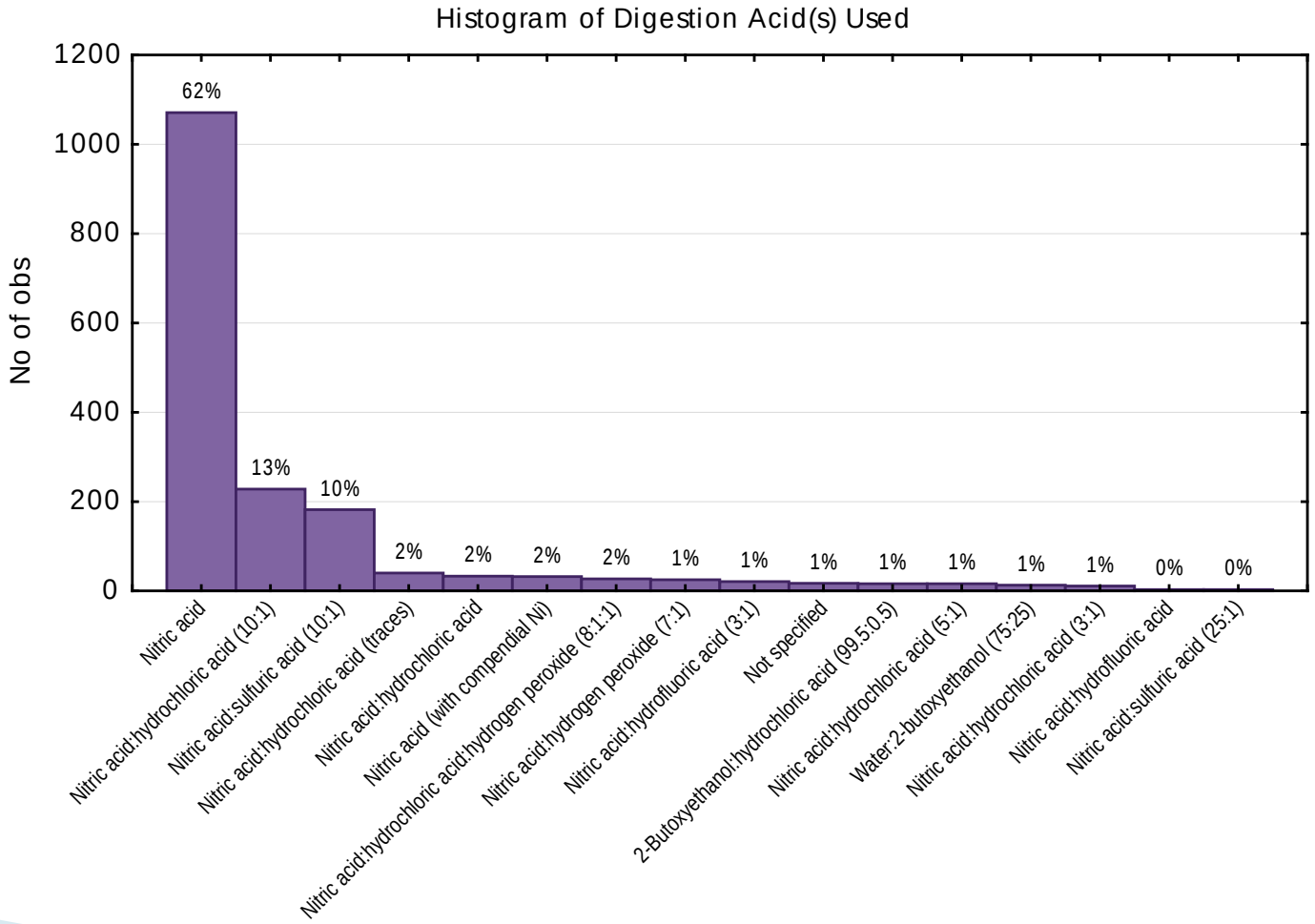
Data Review: Analytical Methodology
Based on 1738 studies

- All generated using ICP-MS
  - 68% Microwave Digestion
  - 30% Direct dissolution
  - 1% Acid Wash
  - 1% Not specified



Lhasa Elemental Impurities Database 2017.1

Data Review: Analytical Methodology
Acid used for Digestion



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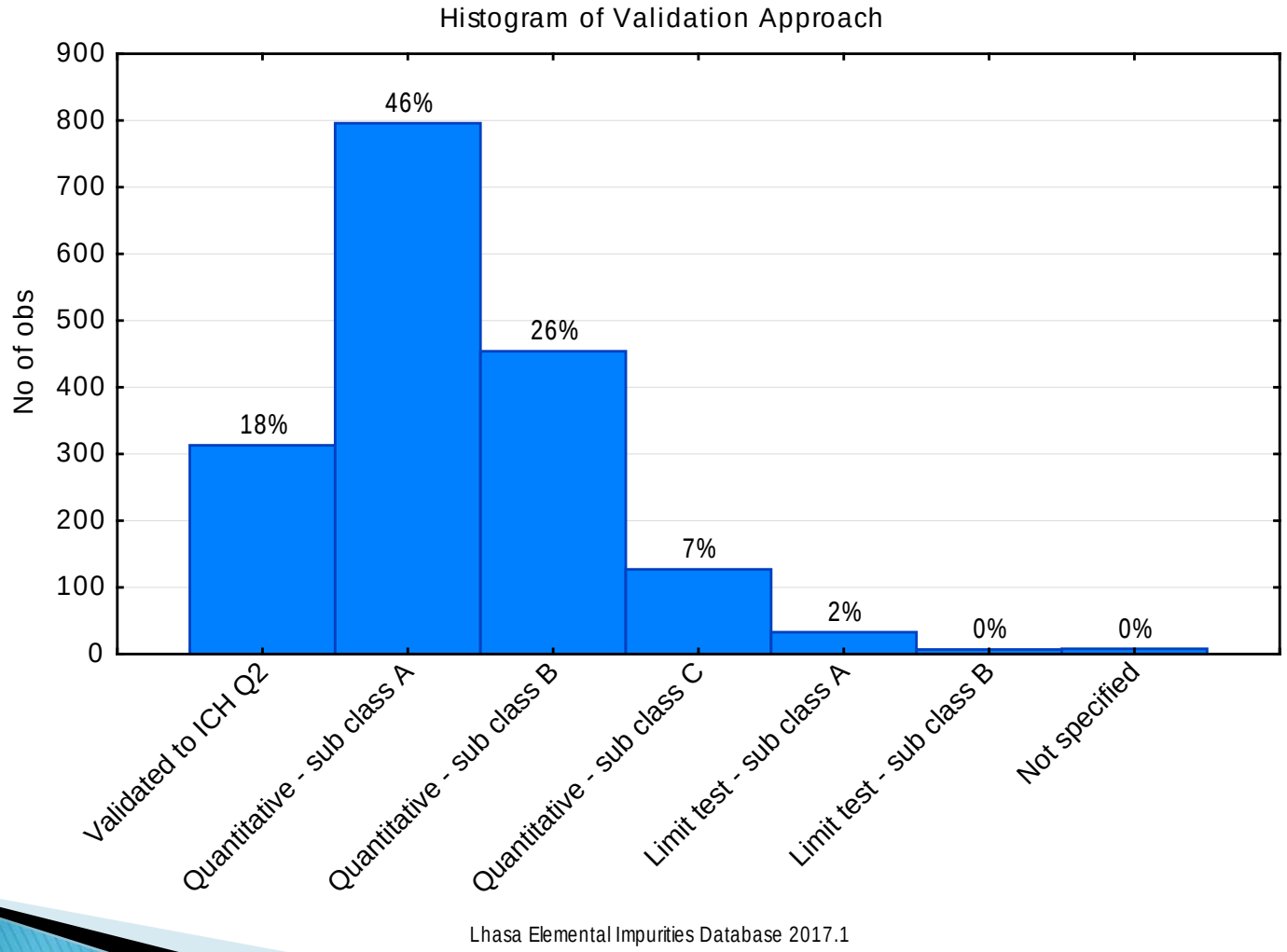
Data Review – Analytical Methodology
Validation Approaches Used



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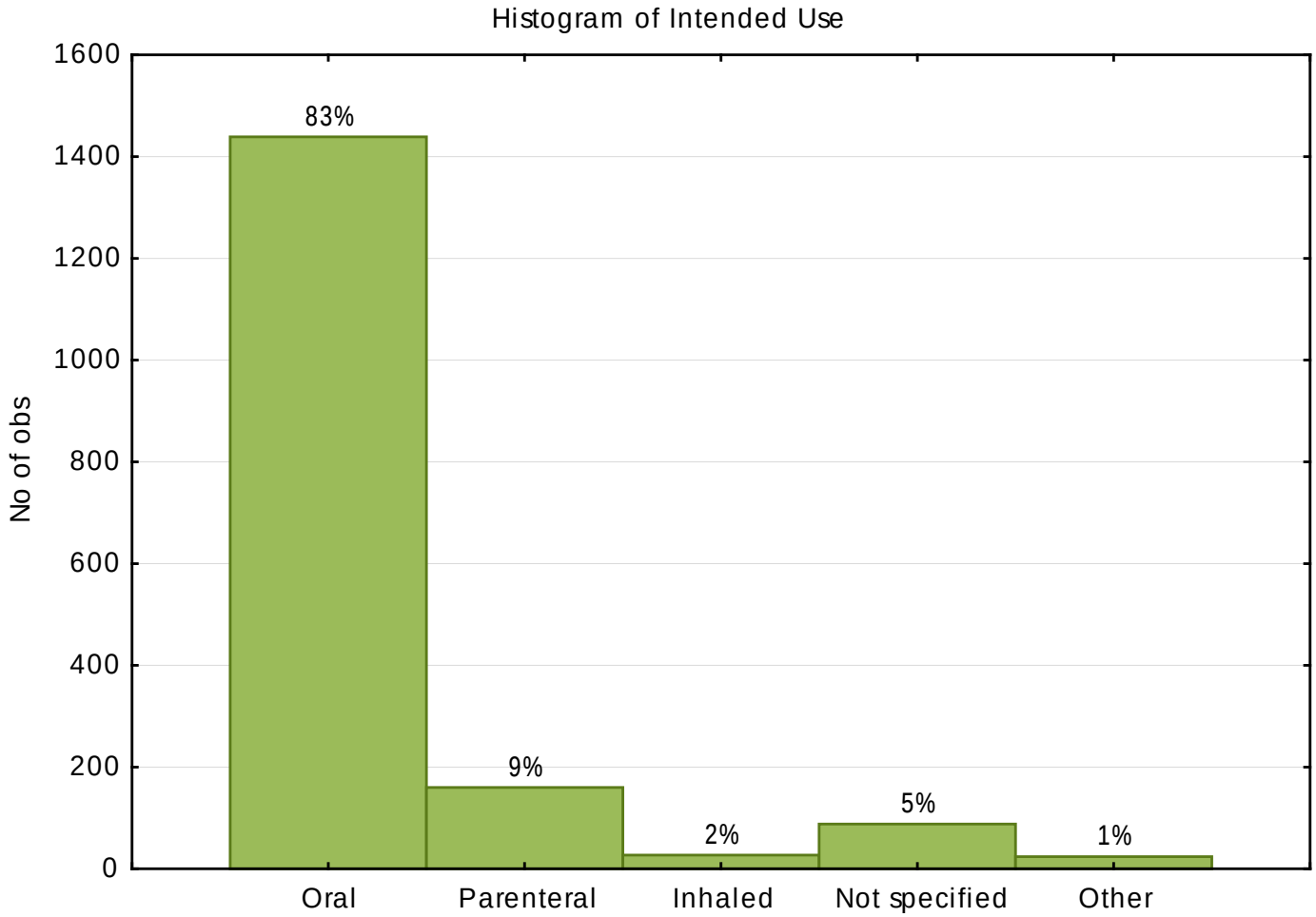
Data Review – Routes of Administration



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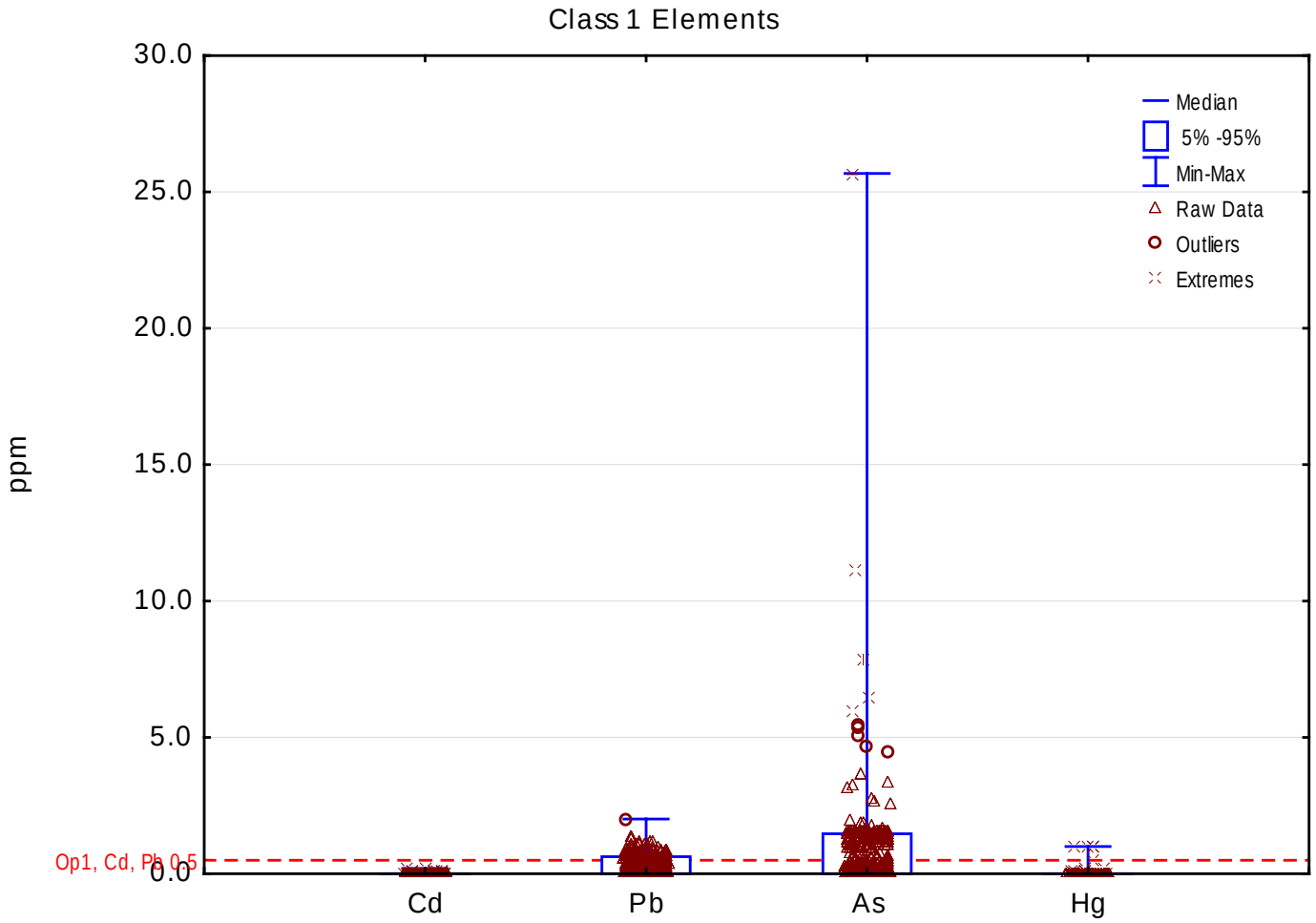
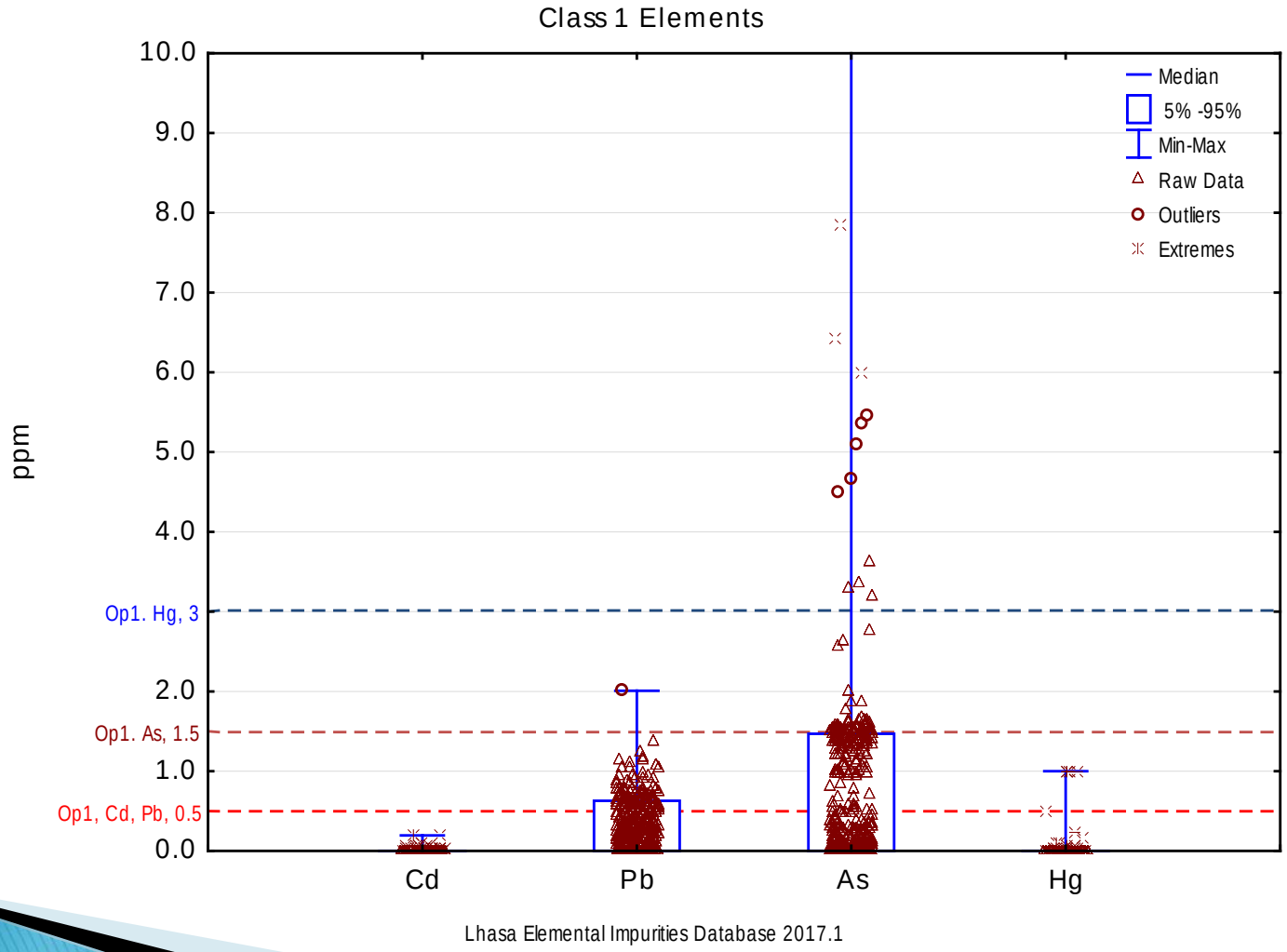
Data Review – Class 1 Elements

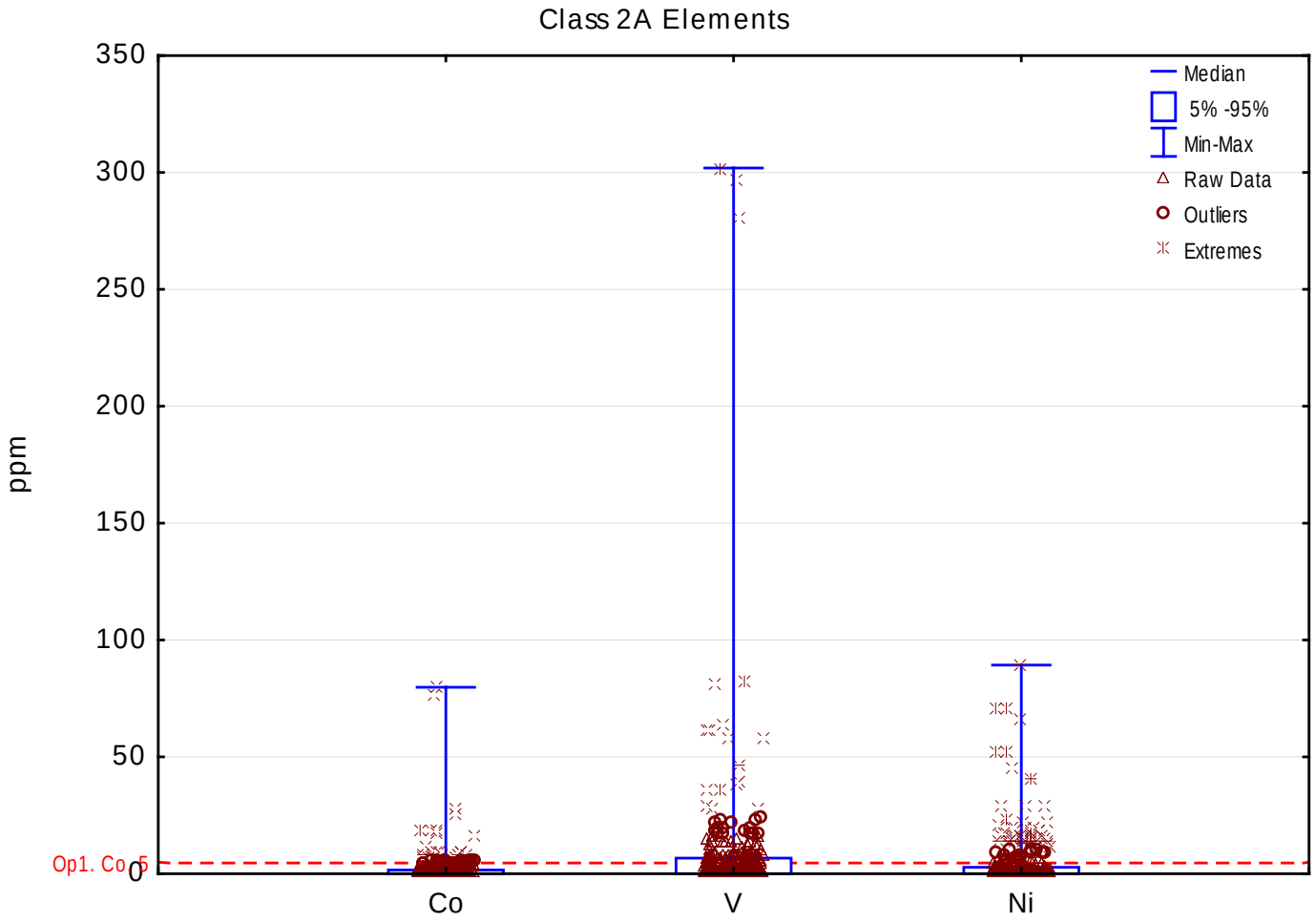


Data Review – Class 1 Elements

Zoomed in



Data Review – Class 2A Elements



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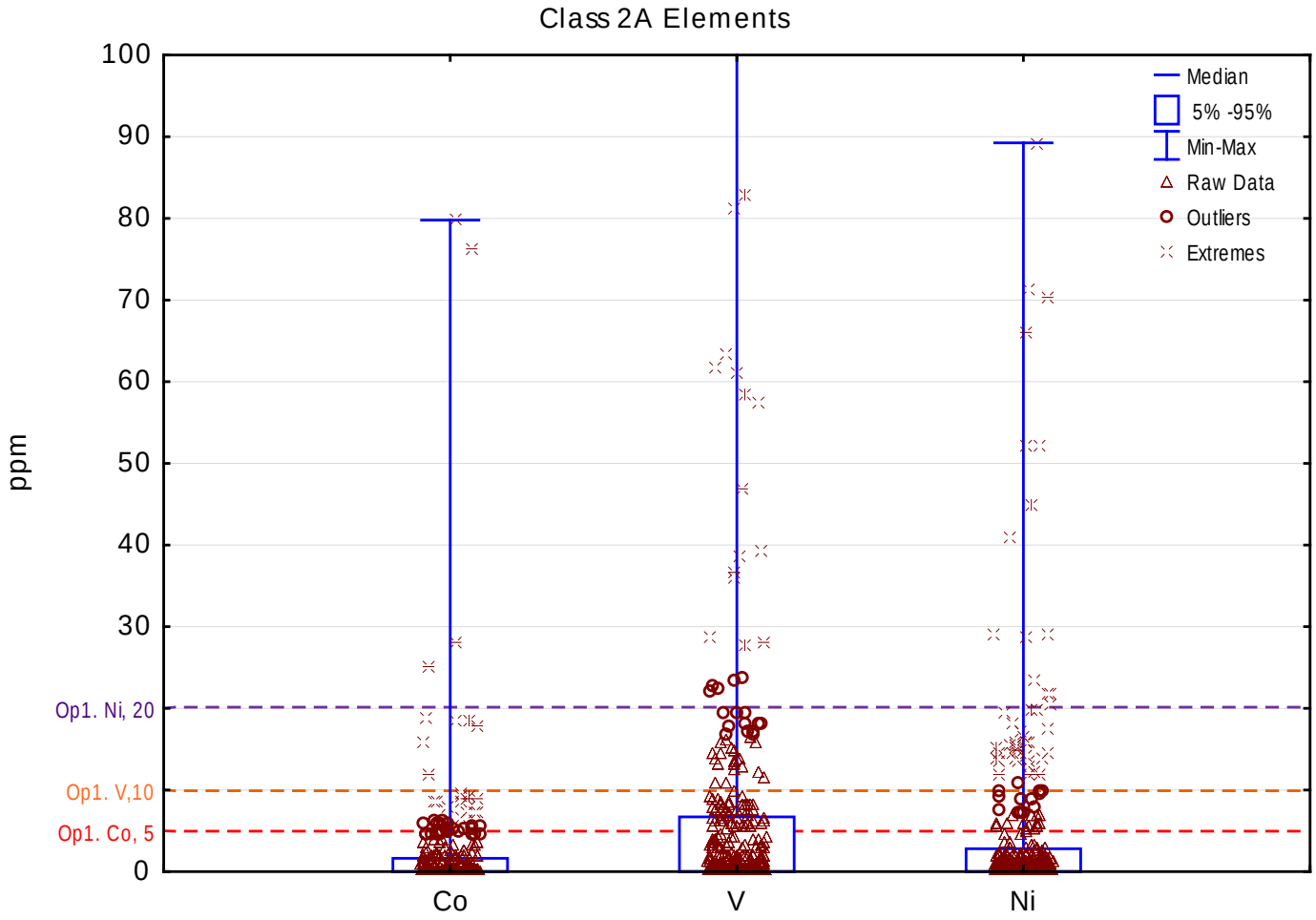
Data Review – Class 2A Elements

Zoomed in



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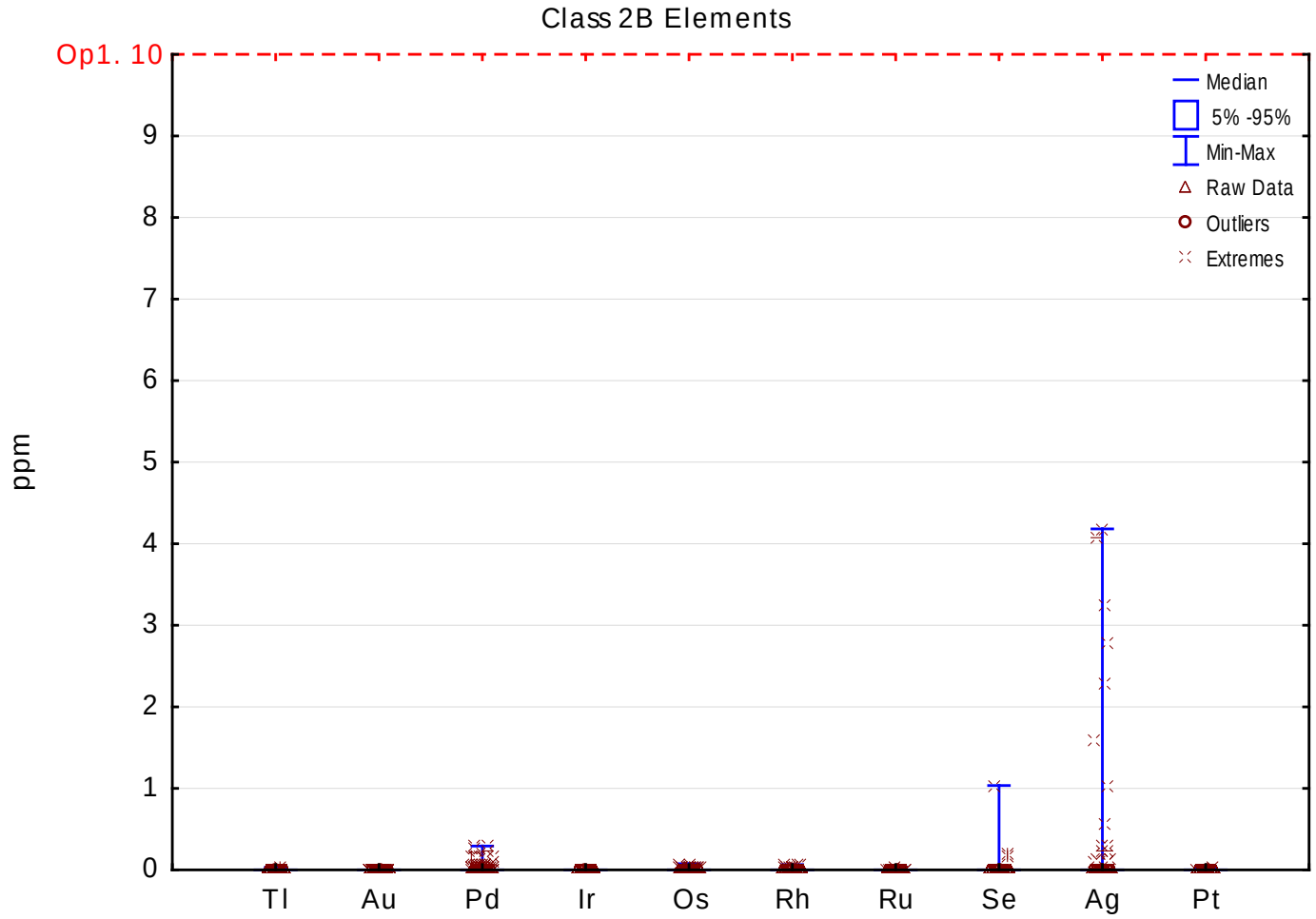
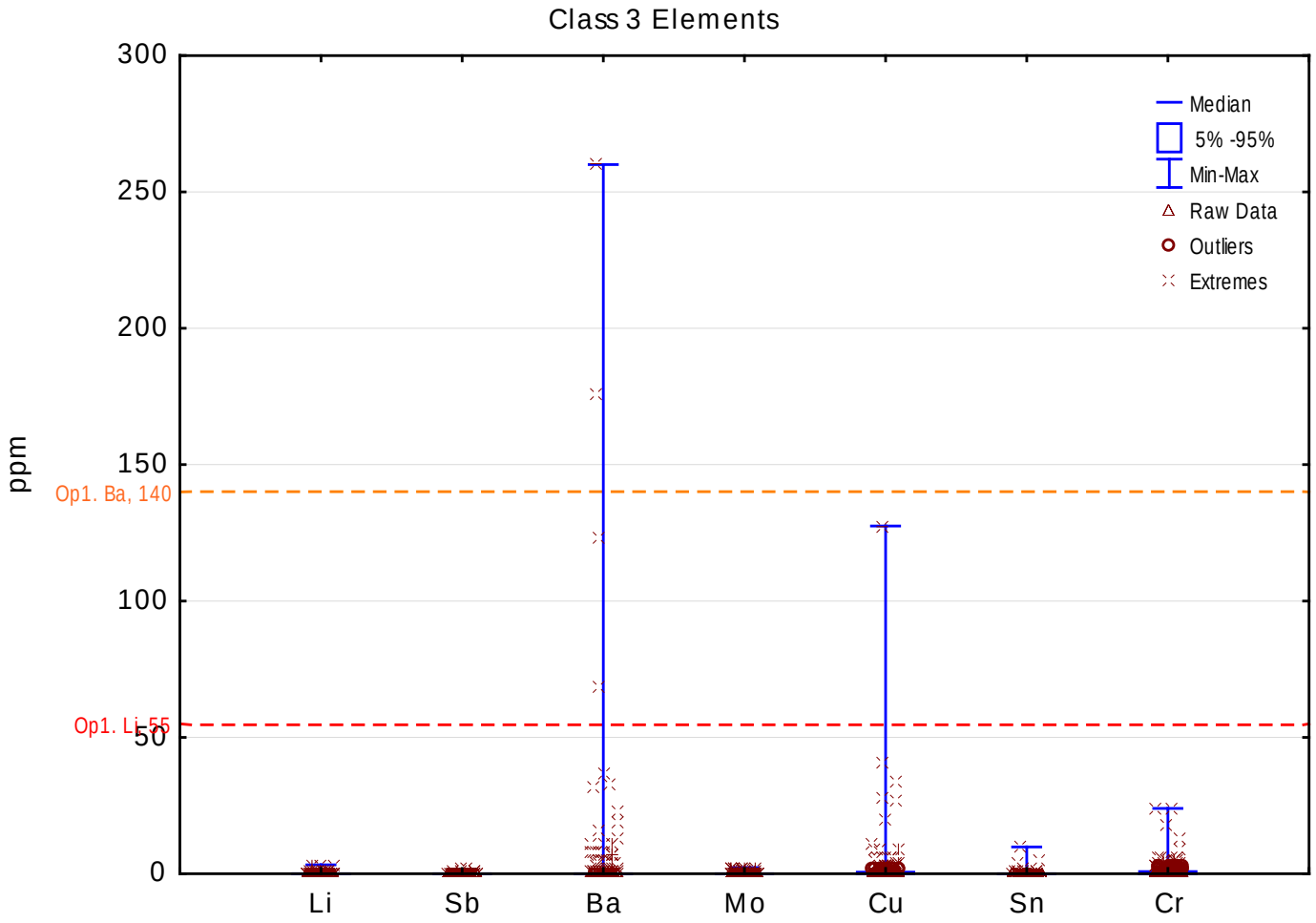
Data Review – Class 2B Elements



Data Review – Class 3 Elements



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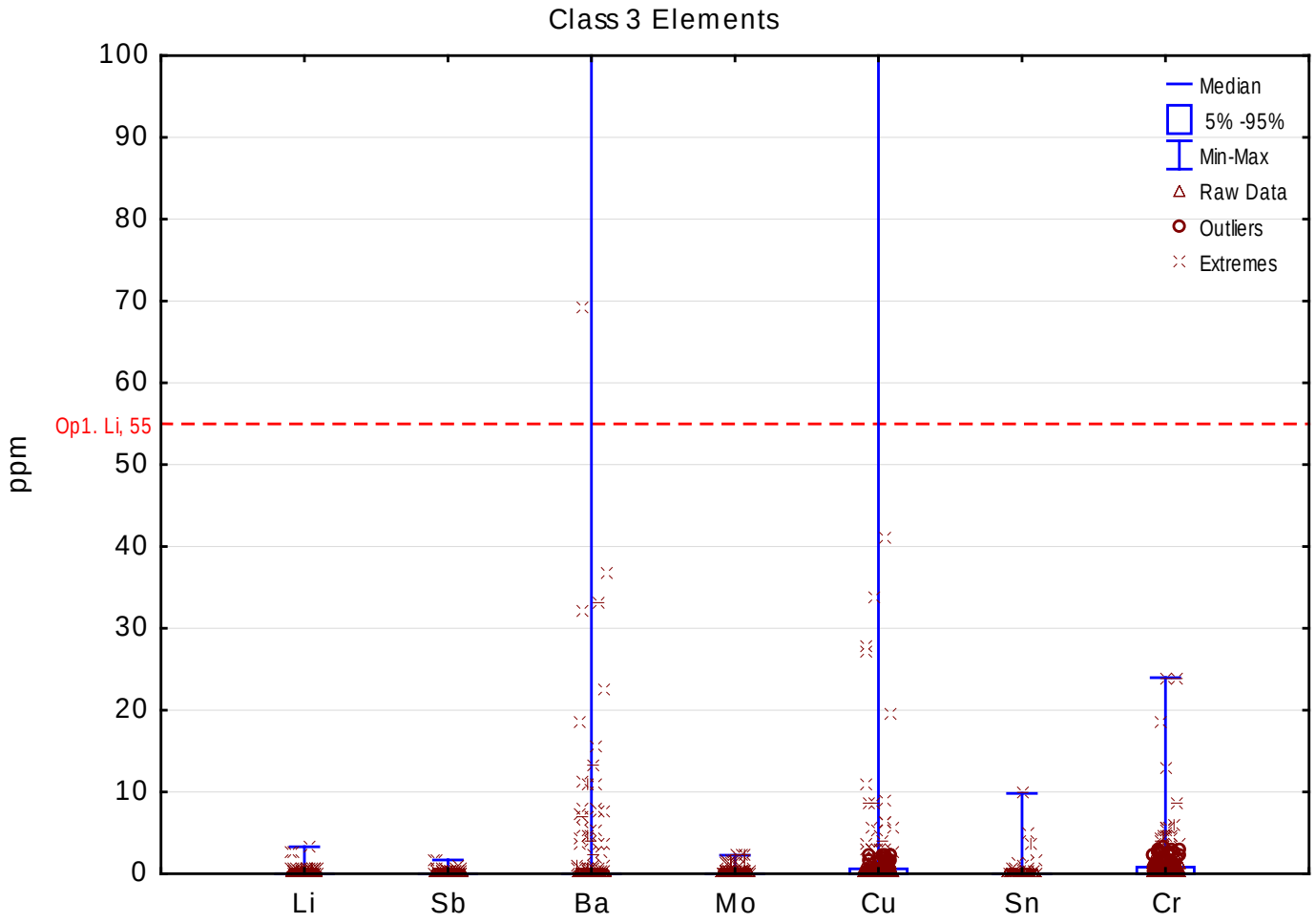
Data Review – Class 3 Elements

Zoomed in



Lhasa Elemental Impurities Database 2017.1

What Can We Learn From The Database?

Review of 5 major excipients

- Little evidence of substantive levels of Class 1 / Class 2A elements
- 'Highest' values often associated with LOD
  - Have seen limit test applied based on 30% of permitted concentration limit
  - In reality the actual content is likely to be significantly lower as demonstrated by measured values

Class	1	1	1	1	2A	2A	2A
Element	Cd	Pb	As	Hg	Co	V	Ni
MAGNESIUM STEARATE							
Max	0.2	0.2	1	0.5	0.8	2	5
Min	0.02	0.05	0.02	0.01	0.03	0.01	0.14
Mean	0.08	0.1	0.25	0.13	0.19	0.57	1.32
MICROCRYSTALLINE CELLULOSE							
Max	0.2	0.2	1	0.5	0.8	2	3
Min	0.003	0.01	0.02	0.01	0.02	0.01	0.03
Mean	0.04	0.07	0.19	0.11	0.18	0.43	0.68
LACTOSE							
Max	0.2	0.21	0.23	0.5	0.8	2	3
Min	0.003	0.04	0.01	0.01	0.03	0.01	0.03
Mean	0.07	0.08	0.11	0.12	0.15	0.33	0.47
STARCH							
Max	0.1	0.1	0.2	0.1	0.1	0.15	0.3
Min	0.02	0.05	0.02	0.01	0.03	0.01	0.03
Mean	0.03	0.07	0.14	0.04	0.06	0.11	0.21
CELLULOSE DERIVATIVES							
Max	0.2	0.2	0.2	0.2	0.2	0.56	1.04
Min	0.02	0.02	0.02	0.01	0.01	0.01	0.09
Mean	0.05	0.08	0.11	0.05	0.07	0.16	0.34
Option1 Oral	0.5	0.5	1.5	3	5	10	20
Option1 Oral 30%	0.15	0.15	0.45	0.9	1.5	3	6

What Can We Learn From The Database?

What about common mined excipients?

e.g. calcium phosphate

- Couple of examples where level exceeds Option 1 Permitted Concentration Limit.
  - Ni in anhydrous calcium phosphate
  - Hg in sodium phosphate

	1 Cd	1 Pb	1 As	1 Hg	2A Co	2A V	2A Ni
ANHYDROUS DIBASIC CALCIUM PHOSPHATE							
Max	0.20	0.20	1.00	0.20	0.60	10.00	21.84
Min	0.05	0.10	0.10	0.01	0.07	0.04	0.27
Mean	0.11	0.16	0.38	0.08	0.31	2.06	7.72
DIBASIC SODIUM PHOSPHATE							
Max	0.20	0.20	0.41	10.00	0.20	0.20	3.06
Min	0.004	0.01	0.10	0.003	0.03	0.01	0.05
Mean	0.04	0.07	0.17	1.46	0.08	0.08	0.72
DIBASIC CALCIUM PHOSPHATE DIHYDRATE							
Max	0.04	0.27	0.37	0.02	0.51	0.02	15.97
Min	0.04	0.10	0.20	0.01	0.34	0.01	13.47
Mean	0.04	0.21	0.28	0.01	0.41	0.01	14.52
SODIUM CHLORIDE							
Max	0.20	0.20	0.20	0.20	1.00	0.20	1.00
Min	0.01	0.01	0.05	0.05	0.01	0.05	0.04
Mean	0.05	0.10	0.08	0.13	0.15	0.09	0.17
Option1Oral	0.5	0.5	1.5	3	5	10	20
Option1Oral30%	0.15	0.15	0.45	0.9	1.5	3	6

Ultimately these levels are unlikely to to pose a risk.
IT DEPENDS HOW THE EXCIPIENT IS DOSED

What Can We Learn From The Database? *Summary*

- Overall results showed little evidence of substantial levels of the 'big 4' **Class 1** elements in excipients.
  - Concluded that it was highly unlikely these levels would adversely impact on the overall quality of a typical drug product

- Generally, metal impurities were found where they might be expected.
  - **Class 2A** metals were detected at appreciable levels in some mined excipients,
  - ferric oxide samples were seen to contain Ni, Co at approximately 100 ppm,

In all cases, the level at which the excipient is used becomes important

Database – Conclusions

- The feasibility of sharing excipient elemental impurity data has been successfully demonstrated
- Pooling and publishing data can help to improve the ease with which risk assessments can be completed
- Ultimately it will give a much better picture of which materials represent a more significant risk than others
  - Indicate where the risk is real & where it is negligible
- Reduce the amount of testing that is needed to be done moving forward to support implementation
- We expect the EI database to be seen as key supportive information that is used routinely **in conjunction** with some product specific test data in the risk assessment.

Database – Conclusions

- ***In the short-term***
  - supportive drug product testing may be used to confirm any conclusions derived from information in the Database and ensure that appropriate controls have been established.
- In the longer term,
  - it is envisaged that drug product testing itself will also not be necessary under certain circumstances
    - For example, oral drug products where sufficient data exist to support a conclusion of low elemental impurity risk

Acknowledgements

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Questions?