Implementation of ICH Q3D in Product Development / Lhasa Database Update

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November 10th 2020

4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements

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Outline

- Very brief ICH Q3D **background** knowledge.
- **Excipients.**
  - Using prior knowledge (data) to make the risk assessment process more efficient.
  - **Lhasa Database.**
- **Case history.**
  - example risk assessment using Lhasa database.
- **Conclusions / Learnings.**

ICH Q3D background

- The guideline lists 24 elements that need to be considered in a drug product focussed risk assessment (RA).
- Applicable to new finished drug products (as defined in Q6A and Q6B) and new drug products containing existing drug substances.
- Does not apply to drug products used during clinical research stages of development.
  - applicable to the commercial product however, the principles can be usefully applied earlier in the development process.
- Approved guideline was published Dec 2014.
  - 3yr implementation timeline for existing marketed products (Dec 2017).
  - applicable to new drug products after ~18M (mid 2016).
- Useful resources;
  - FDA “Guidance for Industry” 2018.
  - ICH training modules.

Overview article: A. Teasdale et. al, Pharmtech Europe, 2015(3), p12ff

Elemental impurity PDEs

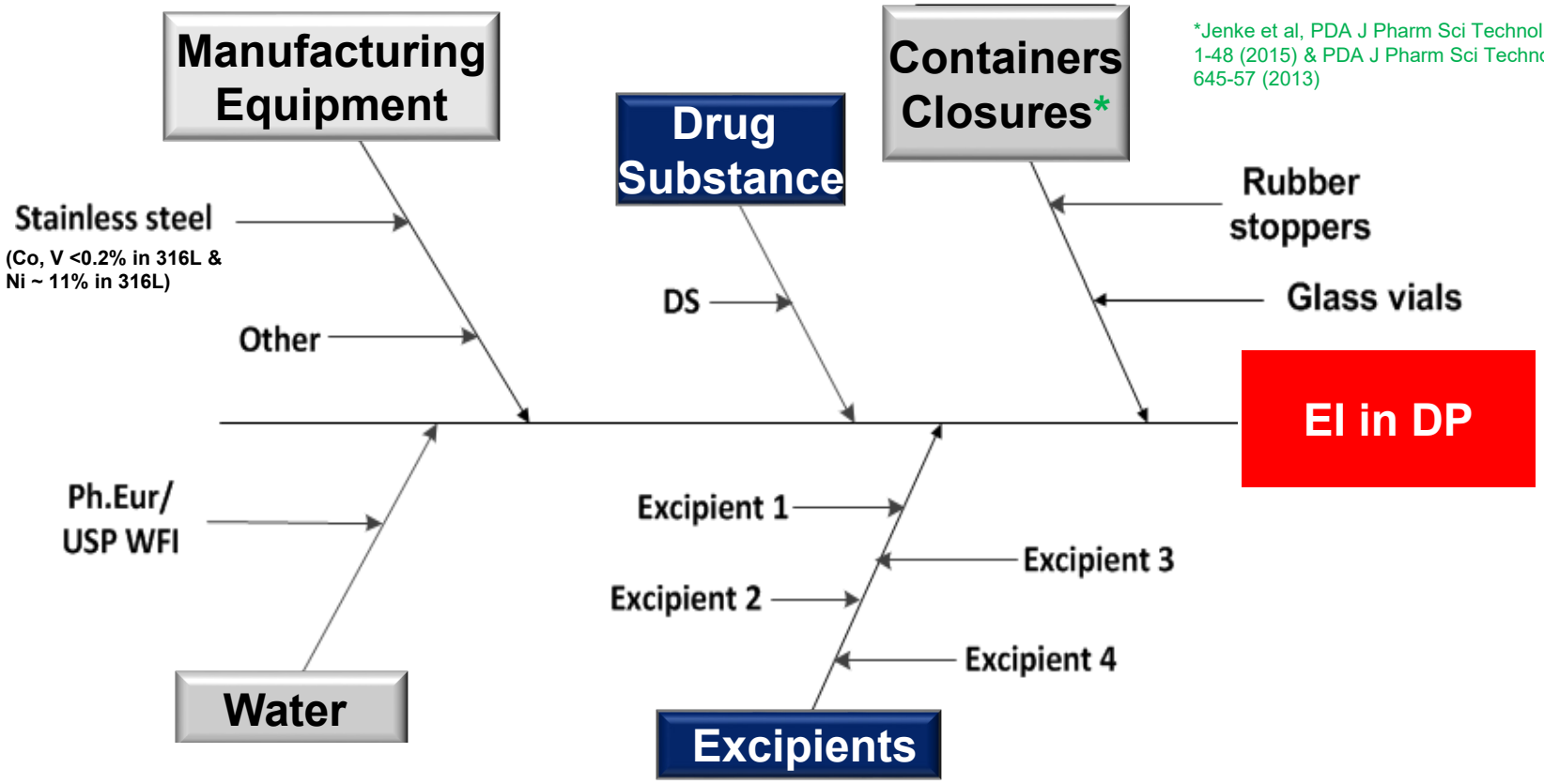
Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Elements to be considered in the RA

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

The risk assessment

- The RA drives the decision to analyse components of the DP or the DP itself.
- A combination of risk analysis and available supportive data leads to a robust control strategy.
- Don't test the drug product for all 24 EIs and then consider risks!



*Jenke et al, PDA J Pharm Sci Technol Vol. 69(1), p 1-48 (2015) & PDA J Pharm Sci Technol Vol. 67(4), p 645-57 (2013)

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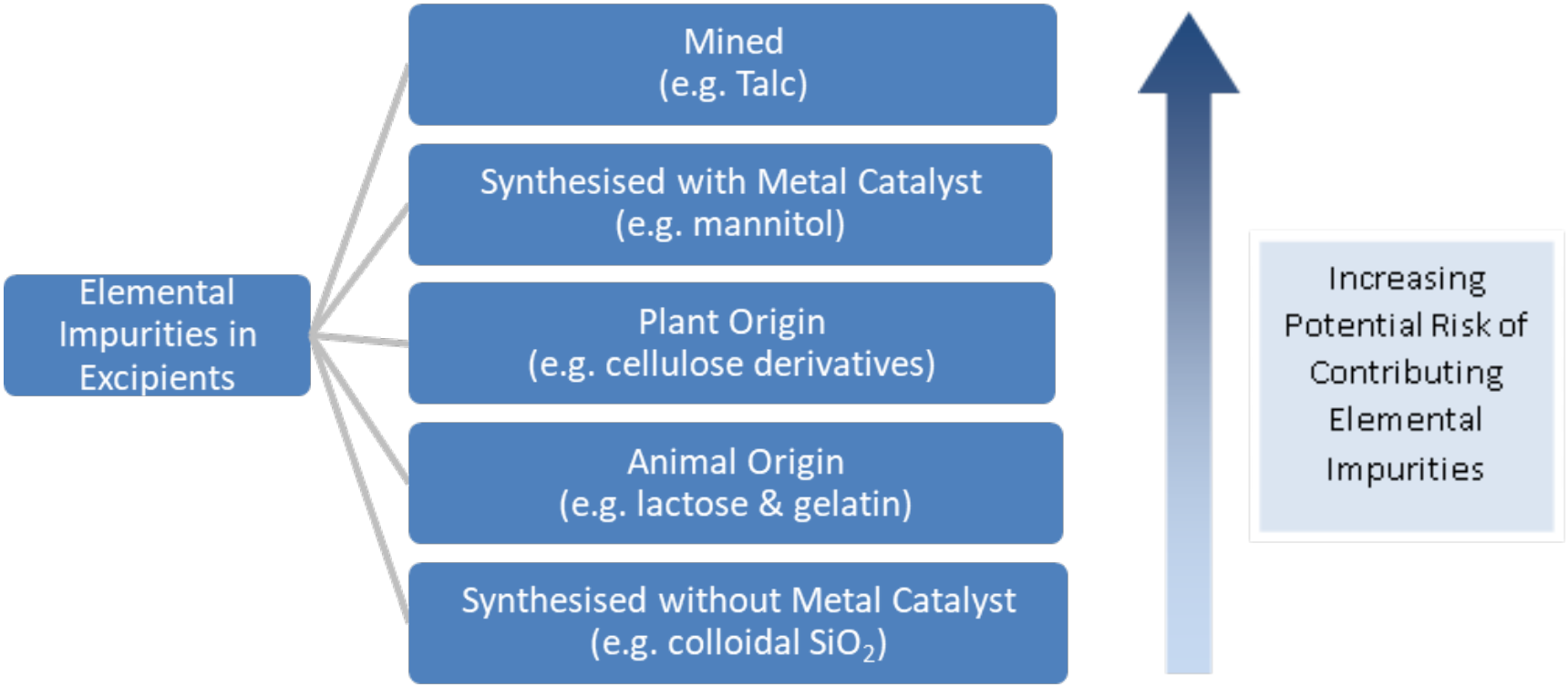
Excipients – the greatest unknown?

- In 2014 there was very little data available and excipients were considered to be a significant risk



According to ICH Q3D, information and data used in the risk assessment can be derived from numerous sources

- Prior knowledge;
- Published literature;
- Data generated from similar processes;
- Supplier information or data;
- Testing of the components of the drug product;
- Testing of the drug product.

However, in the case of excipients, supplier information relating to elemental impurities can be limited and published literature is also sparse.

- *Li et al., J.Pharm.Sciences, Sept. 2015, DOI 10.1002/jps.24650* (FDA/IPEC/Industry study).
  - 24 Elements, 205 excipients samples, > 4900 determinations, overall low EI levels.

Consortium membership

Lhasa Limited

Elemental Impurities Data Sharing Initiative

Facilitate more scientifically driven **elemental impurities risk assessments under ICH Q3D**, and **reduce unnecessary testing** as part of the elemental impurities risk assessment efforts.

Vei Vitic elemental impurities

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The Initiative

- The data shared is analytical data generated to establish the levels of elementals within batches of excipients.
- Lhasa acts as the ‘honest broker’ and facilitates the data sharing.
- A database of shared excipient elemental impurity determinations with equivalent provenance to published literature, can be used as an additional source of information.
- This aims to save time and reduce the amount of testing required for ICH Q3D risk assessments.
- Data is accessible to industry and regulators and can be used to make it clear why specific excipients are regarded as low (negligible) or higher risk in a particular formulation at a given daily intake.

The Initiative

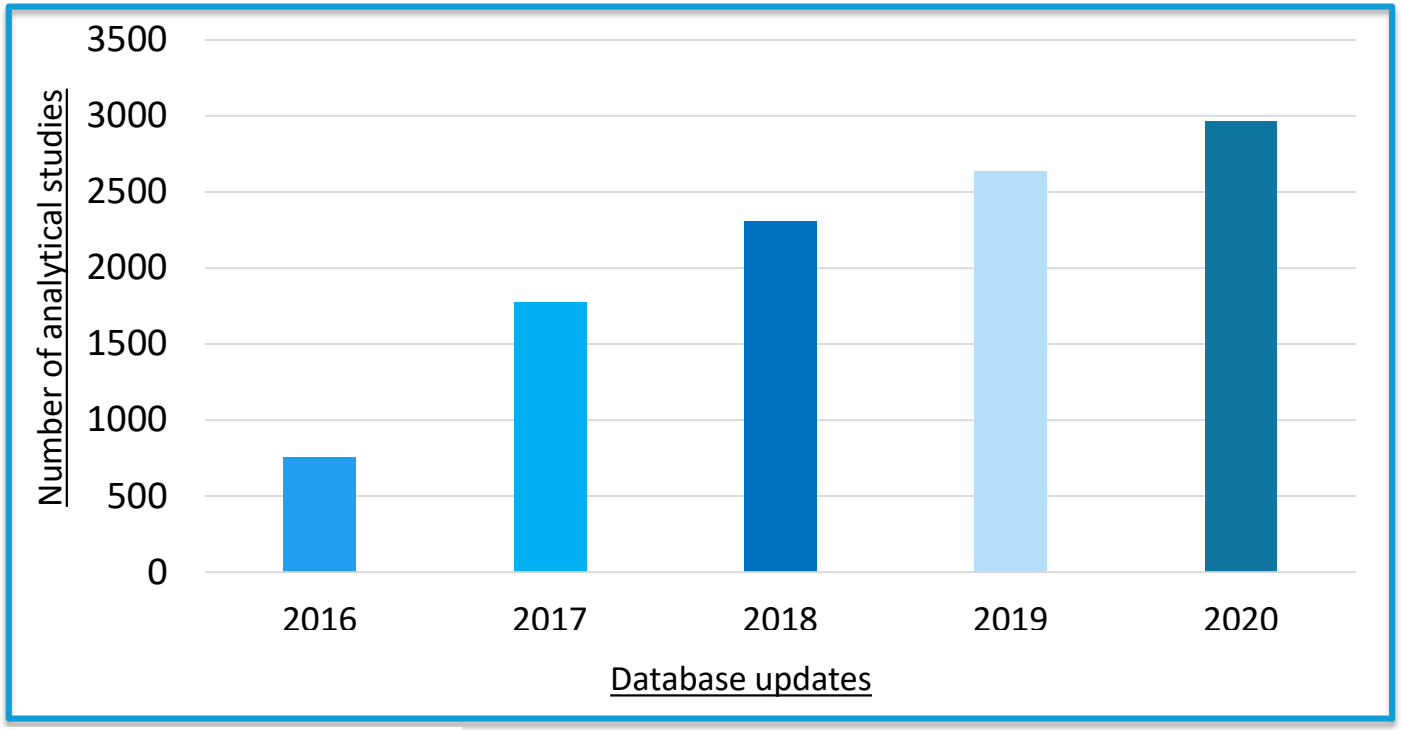
- **Integrity** of the data is very important!
  - data is blinded by the third party (Lhasa)
  - data on excipients NOT suppliers
- **Quality** is critical
  - standards (“acceptance criteria”) for method validation
  - active data management (outliers etc.)
- **Relevance**
  - sufficient number of relevant excipients
  - data for relevant elements
  - multiple excipient samples, from a range of suppliers

Growth of the database

A consortium was established in **2015** and the first release of the Elemental Impurities Excipient Database was in **2016.**

The database contains the results of **2,962 analytical studies and 40,574 elemental determinations, for 299 excipients.**

The next database release is planned for November 2020.



Currently the largest known collection of this type of data.

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An Elemental Impurities Excipient Database: A Viable Tool for ICH Q3D Drug Product Risk Assessment

Ruth Boetzel, Agnieszka Ceszlak, Christopher Day, Patrick Drumm, Joan Gil Bejar, John Glennon, Laurence Harris, Crina I. Heghes, Radu Horga, Peter L. Jacobs, Wilfried J.T.M. Keurentjes, Fiona King, Carlos W. Lee, Nancy Lewen, Carol A. Marchant, Frans A. Maris, William Nye, Samuel Powell, Helmut Rockstroh, Laura Rutter, Mark Schweitzer, Elaine Shannon, Lance Smallshaw, Andrew Teasdale, Sarah Thompson, David Wilkinson

PlumX Metrics

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Article Info

Abstract

Abstract

To support the practical implementation of the ICH Q3D guideline, which describes a risk-based approach to the control of elemental impurities in drug products, a consortium of pharmaceutical companies has established a database to collate the results of analytical studies of the levels of elemental impurities within pharmaceutical excipients. This database currently includes the results of 26723 elemental determinations for 201 excipients and represents the largest known, and still rapidly expanding, collection of data of this type. Analysis of the database indicates good coverage of excipients relevant to real-world drug product formulations and tested element profiles consistent with

Boetzel R *et al.*. An Elemental Impurities Excipient Database: A Viable Tool for ICH Q3D Drug Product Risk Assessment. Journal of Pharmaceutical Sciences 107 2335-2340 (2018). https://doi.org/10.1016/j.xphs.2018.04.009

Excipient relevance based on 2018 FDA novel approved drug list

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm592464.htm

US FDA novel drugs list 2018 label information			Database
Inactive ingredients	**No. of formulations**	**Administration**	**No. of records**
Acetic acid	2	IV	3
Anhydrous dibasic calcium phosphate	2	Oral	14
Ascorbic acid	2	Oral, IV	6
Calcium stearate	2	Oral	0
Citric acid/citric acid monohydrate	4	Inhalation, Oral, IV	22
Colloidal silicon dioxide	12	Oral	11
Colorant: red	2	Oral	1
Croscarmellose sodium	11	Oral	29
Crospovidone	4	Oral	32
Dibasic sodium phosphate dihydrate	3	IV, Topical	0
Edetate disodium	2	IV	9
Ferric oxide (Iron oxide red/yellow)	8	Oral	23
Gelatin	2	Oral	8
Glycine	2	IV	12
Histidine	7	IV	6
(L-Histidine monohydrochloride monohydrate	5	IV	7
Hydroxypropyl cellulose	3	Oral	36
Hypromellose	7	Oral, Topical	56
Hypromellose acetate succinate	4	Oral	2
Lactose monohydrate	8	Oral	80
Lecithin	3	Oral	0
Magnesium stearate	23	Oral	61
Mannitol	9	Oral, Topical, IV	58
Microcrystalline cellulose	24	Oral	107
Monobasic sodium phosphate	2	IV	19
Polyethylene glycol	4	Oral, Topical	12
Polysorbate 80	10	IV	24
Polyvinyl alcohol (Coating: polyvinyl alcohol)	3	Oral	104
Povidone	8	Oral	54
Pregelatinized starch	2	Oral	25
Silicified microcrystalline cellulose	2	Oral	1
Sodium chloride	8	IV, Inhalation	43
Sodium citrate	2	Oral, Inhalation	32
Sodium hydroxide	3	IV	34
Sodium lauryl sulfate	7	Oral	10
Sodium starch glycolate	6	Oral	13
Sodium stearyl fumarate	4	Oral	9
Sorbitol	2	Oral	16
Sucrose	7	IV	42
Talc	7	Oral	13
Titanium dioxide	11	Oral, IV	6
Triethyl citrate	2	Oral	6

49 novel drugs approved in 2018

42 excipients used > once

86% (36 of these 42) **have ≥ 3 studies in the database**

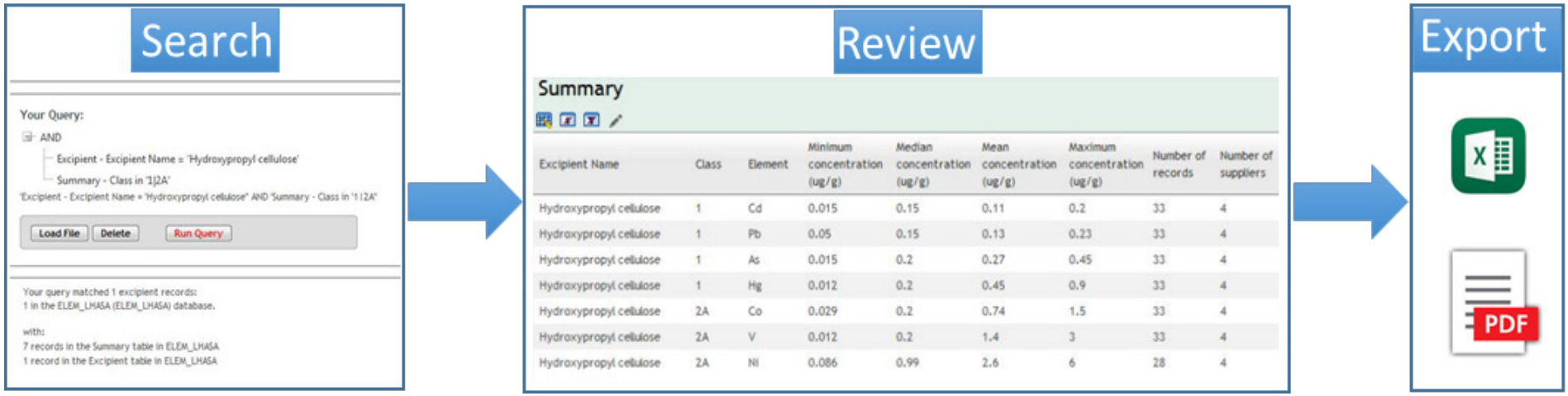
39 excipients (93%) used > once are covered in the database

Notes;

1. A list of excipients used in 49 novel drugs was generated using label information available through Drugs@FDA service.
2. These comprised of 30 oral, 17 parenteral, 1 topical and 1 inhaled formulation.
3. Water for injection and tablet coatings were not considered.

Retrieving data from the database is easy!

1. Identify all excipients in the drug product
2. Search the database for each excipient
3. Review and export relevant elemental impurity results



It is easy to export all data required to assess excipient risk in a new formulation in approximately 10 minutes.

Case History 1 – solid oral drug product

4 standard excipients, API (10%), film coat (EI data available from supplier), Pd used in the API synthesis.

Element	C_{max} for Excipient 1 (ppm)	C_{max} for Excipient 2 (ppm)	C_{max} for Excipient 3 (ppm)	C_{max} for Excipient 4 (ppm)
Cd				
Pb				
As				
Hg				
Co				
V				
Ni				

1. Identify the elements of concern based upon the risk assessment
2. Search for the excipients in the Lhasa elemental impurities excipients database
3. Confirm that each excipient in the formulation has been tested for each element of concern
4. Extract the maximum observed value from the database
5. Assess how much confidence to place in the data
   - How many batches tested?
   - From many different suppliers?
   - Is the highest value recorded sensible (not a sig. outlier)?

Element	C_{max} for Excipient 1 (ppm)	C_{max} for Excipient 2 (ppm)	C_{max} for Excipient 3 (ppm)	C_{max} for Excipient 4 (ppm)	µg/day from Excipient 1	µg/day from Excipient 2	µg/day from Excipient 3	µg/day from Excipient 4
	>76 lots tested 4 suppliers	18 lots tested 3 suppliers	9 lots tested 3 suppliers	≥50 lots tested 4 suppliers	Calculation based on: 4 x 25mg tablets (approx. 1 g of drug product) and composition of each tablet. *supplier data used			
Cd	0.2	0.2	0.2	0.2	0.115	0.057	0.006	0.002
Pb	0.2	0.27	0.2	0.2				
As	1	1	0.2	1				
Hg	0.9	0.2	0.2	0.9				
Co	1.5	0.6	0.2	1.5				
V	3	10	1	3				
Ni	6	22	1	6				

6. Calculate the maximum Cd contribution from excipient 1

convert micrograms per gram to grams per day

7. Repeat for all excipients
8. Repeat for all elements of concern

9. For each element sum the individual contributions across all excipients
10. Compare to the PDE and 30% control threshold

Element	C_{max} for Excipient 1 (ppm)	C_{max} for Excipient 2 (ppm)	C_{max} for Excipient 3 (ppm)	C_{max} for Excipient 4 (ppm)	µg/day from Excipient 1	µg/day from Excipient 2	µg/day from Excipient 3	µg/day from Excipient 4	µg/day Film coat*	Sum	% Oral PDE
	>76 lots tested 4 suppliers	18 lots tested 3 suppliers	9 lots tested 3 suppliers	≥50 lots tested 4 suppliers	Calculation based on: 4 x 25mg tablets (approx. 1 g of drug product) and composition of each tablet. *supplier data used						
Cd	0.2	0.2	0.2	0.2	0.115	0.057	0.006	0.002	0.015	0.195	4 %
Pb	0.2	0.27	0.2	0.2	0.115	0.077	0.006	0.002	0.015	0.215	4 %
As	1	1	0.2	1	0.573	0.287	0.006	0.010	0.045	0.921	6 %
Hg	0.9	0.2	0.2	0.9	0.516	0.057	0.006	0.009	0.090	0.678	2 %
Co	1.5	0.6	0.2	1.5	0.860	0.172	0.006	0.015	0.150	1.203	2 %
V	3	10	1	3	1.720	2.867	0.030	0.030	0.300	4.947	5 %
Ni	6	22	1	6	3.440	6.307	0.030	0.060	0.600	10.44	5 %

Test data on the finished drug substance & product was also generated

- 9 lots at commercial scale
- All class 1 and 2a elements < 30% of option 2A concentration limits
- Pd used in API synthesis routinely measured at <30% of control threshold
- No specification based controls proposed in the CTD

Element	C_{max} for Excipient 1 (ppm)	C_{max} for Excipient 2 (ppm)	C_{max} for Excipient 3 (ppm)	C_{max} for Excipient 4 (ppm)	µg/day from Excipient 1	µg/day from Excipient 2	µg/day from Excipient 3	µg/day from Excipient 4	µg/day Film coat*	Sum	% Oral PDE
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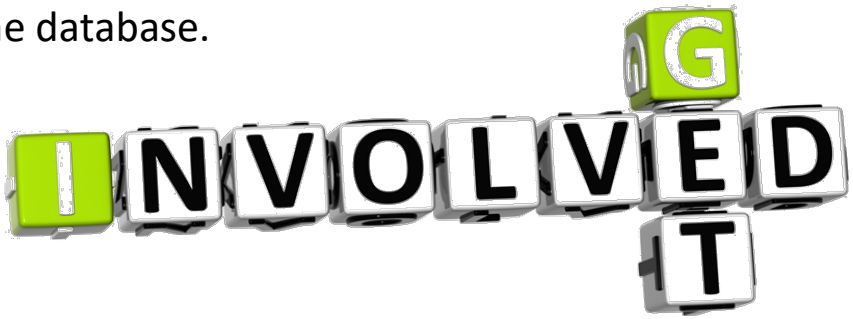
Pb	0.2	0.27	0.2	0.2	0.115	0.077	0.006	0.002	0.015	0.215	4 %
As	1	1	0.2	1	0.573	0.287	0.006	0.010	0.045	0.921	6 %
Hg	0.9	0.2	0.2	0.9	0.516	0.057	0.006	0.009	0.090	0.678	2 %
Co	1.5	0.6	0.2	1.5	0.860	0.172	0.006	0.015	0.150	1.203	2 %
V	3	10	1	3	1.720	2.867	0.030	0.030	0.300	4.947	5 %
Ni	6	22	1	6	3.440	6.307	0.030	0.060	0.600	10.44	5 %

The feasibility of sharing excipient elemental impurity data has been successfully demonstrated.

New consortium members (pharmaceutical organisations and excipient suppliers) are actively being sought to expand the database.



Member organisations participating in the data sharing initiative will join with the intent of regularly (e.g. annually) providing elemental impurity data on non-proprietary excipients.

https://www.lhasalimited.org/Initiatives/Elemental-Impurities.htm

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Acknowledgements

*The Elemental Impurities Database Consortium steering group in 2020 is chaired by **Laurence Harris** (Pfizer), and consists of the following representatives:*

***Grace Kocks** (Lhasa), **Fiona King** (GlaxoSmithKline), **Tim Cartwright** (GlaxoSmithKline), **Chris Jones** (GlaxoSmithKline), **Christopher Day** (AstraZeneca), **Andrew Teasdale** (AstraZeneca), **Lydria Breckenridge** (Bristol Myers-Squibb), **Sharla Wood** (Bristol Myers-Squibb), **Mark Schweitzer** (Novartis), **Lance Smallshaw** (UCB), **Juan Gil** (B.Braun), **Elaine Shannon** (Takeda), **Roman Lauchart** (Takeda), **Philip Lienbacher** (Takeda), **Agnieszka Ceszlak** (ZF Polpharma), **Valerie Chiva** (Sanofi), **Ruimin Xie** (Celgene Corporation), **David Liu** (Celgene Corporation), **Diego Zulkiewicz Gomes** (Ache), **Jessica Cunha** (Ache), **Enid Gatimu** (Abbvie), Holly VanMetre (Abbvie), **Ruth Boetzel** (Pfizer) and **Crina Heghes** (Lhasa Limited).*

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Back-Up

- ✓ Discuss and agree upon the scientific direction of the project.
- ✓ Contribute and share expertise and knowledge.
- ✓ Monitor the data provided by the member organisations and ensure it meets predefined quality standards.
- ✓ Identify data gaps and recommend priorities for work on the project.

- ✓ The consortium aims for the data to be accessible to industry, regulators and pharmacopeial bodies.
- ✓ We have introduced multiple regulatory bodies to the initiative.
- ✓ Two pharmacopeial bodies have access to the database. The data is used to review and update the monographs. Positive feedback has been received from both on the initiative and the data in the database.

ICH Q3D

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Excipient relevance based on 2016 FDA novel approved drugs list

excipients

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm592464.htm

Table 2
Excipients Found in More Than 1 Formulation of 22 Novel Drugs Approved by the FDA in 2016 and the Number of Corresponding Analytical Studies in the Database

Label Information		Database	
Name	Number of Formulations	Name	Number of Analytical Studies
Colloidal silicon dioxide	3		13
Copovidone	3	*Not present*	0
Croscarmellose sodium	3		22
Glacial acetic acid	2		5
L-Histidine	3	Histidine	4
Hydrochloric acid	6		11
Lactose monohydrate	2		65
Magnesium stearate	6		57
Mannitol	3		45
Microcrystalline cellulose	5		96
Polysorbate 20	2		5
Polysorbate 80	5		17
Potassium chloride	2	*Not present*	0
Sodium acetate trihydrate	2	Sodium acetate	3
Sodium chloride	8		18
Sodium citrate Sodium citrate dihydrate Trisodium citrate	4	Sodium citrate	13
Sodium hydroxide	8		20
Sodium phosphate dibasic anhydrous	3	Dibasic sodium phosphate	24
Sodium starch glycolate	2		9
Sucrose	2		28

22 Novel drugs approved in 2016
20 excipients used > once
90% (18 of these 20) **have ≥ 3 studies in the database**

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

An Elemental Impurities Excipient Database: A Viable Tool for ICH Q3D Drug Product Risk Assessment

Ruth Boetzel [1], Agnieszka Ceszlak [2], Christopher Day [3], Patrick Drumm [4], Joan Gil Bejar [5], John Glennon [6], Laurence Harris [1], Crina I. Heghes [7], Radu Horga [8], Peter L. Jacobs [9], Wilfried J.T.M. Keurentjes [9], Fiona King [10], Carlos W. Lee [11], Nancy Lewen [12], Carol A. Marchant [7,*], Frans A. Maris [9], William Nye [7], Samuel Powell [1], Helmut Rockstroh [13], Laura Rutter [14], Mark Schweitzer [4], Elaine Shannon [15], Lance Smallshaw [16], Andrew Teasdale [3], Sarah Thompson [3], David Wilkinson [7]

US FDA novel drugs list 2019 label information		Database	
Name	Number of formulations	Number of analytical studies	
Ammonium hydroxide	4	*Not present*	
Carnauba wax	2		9
Citric acid monohydrate	2		16
Colloidal anhydrous silica	14	Colloidal silicon dioxide	12
Croscarmellose sodium	10		34
Crospovidone	5		34
Ethanol, ethyl alcohol	4	Alcohol	14
FD&C blue No. 2 aluminium lake	2	Indigotine aluminium lake	10
FD&C yellow no. 6	2	Colorant: yellow	1
Gelatin	6		8
Glycerin	4		25
L-Histidine	2	Histidine	6
Hydroxypropyl cellulose	2		37
Hypromellose	11		68
Iron oxide red/black/yellow	18	Ferric oxide	34
Isopropyl alcohol	2		4
L-histidine hydrochloride monohydrate	2	L-histidine monohydrochloride monohydrate	7
Lactose monohydrate	9		87
Low-substituted hydroxypropyl cellulose	2		5
Magnesium stearate	20		67
Mannitol	7		59
Microcrystalline cellulose	16		114
Polyethylene glycol	12		12
Polysorbate 20	4		13
Polysorbate 80	5		25
Polyvinyl acetate phthalate	2		7
Polyvinyl alcohol	9	Coating: polyvinyl alcohol	108
Povidone	5		57
Propylene glycol	6		22
Sodium chloride	8		44
Shellac (shellac glaze)	3	*Not present*	
Sodium hydroxide	2		39
Sodium lauryl sulfate	8		10
Sodium starch glycolate	3		15
Sodium stearyl fumarate	2		11
Sorbitol	3		17
Sucrose	5		48
Talc	11		15
Tartaric acid	3		1
Titanium dioxide	20		6
Triacetin	2	*Not present*	
Trisodium citrate dihydrate	3	Sodium citrate	32

The **relevance of the excipients** within the database was confirmed by a review of novel drugs approved by the US FDA in 2019.

48 novel drugs approved in 2019

42 excipients used > once

88% (37 of these 42) **have ≥ 3 studies in the database**

39 excipients (93%) used > once covered in the database

https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

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Analytical methodology (ICP-MS)

implementation

- ICP-MS methodology has been extensively used within Pfizer.
  - generic method has been established aligned with USP<233>.
  - acid digestion (in microwave) is preferred approach to sample preparation.
  - internal Standards with similar ionization potential have been established for each Q3D element of concern.
  - minimum of a 3 point calibration curve established.
  - recovery established by use of spiked samples.

Analytical methodology (ICP-MS)

implementation

- FDA Guidance for Industry
  - https://www.fda.gov/media/98847/download

Validation is the process of demonstrating that an analytical procedure is suitable for its intended purpose. Analytical procedures for both risk assessments and routine testing should be validated, but the validation criteria (e.g., accuracy, precision, detection limits) can depend on the analytical procedure's intended purpose.

Manufacturers should establish that the analytical procedures used during risk assessments possess characteristics (e.g., accuracy, precision, specificity) such that the manufacturers can be reasonably certain (e.g., at the 95-percent confidence level) that the measurements can be relied upon to decide whether to include routine testing of materials in the control strategy. This decision depends on whether the amounts of the elemental impurities in the materials are consistently below control thresholds. The analytical procedures should be validated with this goal in mind.