A Supplier's Strategy for Elemental Testing and Risk Assessment

Katherine Ulman

Global Regulatory Compliance Manager

Dow Corning Corporation, a wholly owned subsidiary of The Dow Chemical Company

Overview

History of ICH Q3D and its implications for excipient suppliers

Understanding excipient sources, potential for elemental impurities/impurity variability and use of published data

Gathering relevant elemental impurity data

A case study for one excipient supplier’s strategy

History of ICH Q3D and its implications for excipient suppliers

ICH Q3D Overview from an excipient supplier perspective

A Requirement for Drug Manufacturers:

- Requires an assessment of the **potential elemental impurities present in drug products.**
  - Potential sources: Drug substance, **excipients**, manufacturing equipment and packaging.

ICH Q3D applies to:

- **All** human **drug products** - Emphasizes the use of risk assessment as opposed to testing wherever possible

Does not apply to:

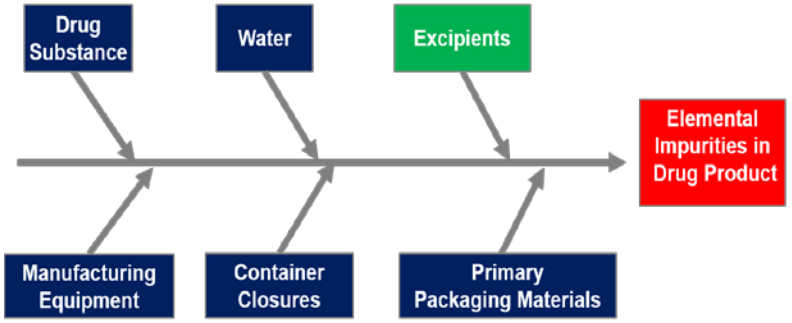
- Components, i.e. drug substance/ **excipients**
- **No compliance requirement for excipient suppliers other than to share what they may know and what they do not know about EI in their excipients – will often vary from supplier to supplier and possibly for different excipients from the same supplier!**

ICH Q3D – Risk Assessment for potential sources of EI – need to assess excipients

ICH Q3D advocates a risk assessment approach to determine the level of elemental impurities in drug products and the risk posed to patients.

"The data that support the risk assessment can come from:

- Prior knowledge,
- Published literature,
- Information provided from suppliers
- Data generated from testing of components of the drug product,
- Data generated from testing the drug product"

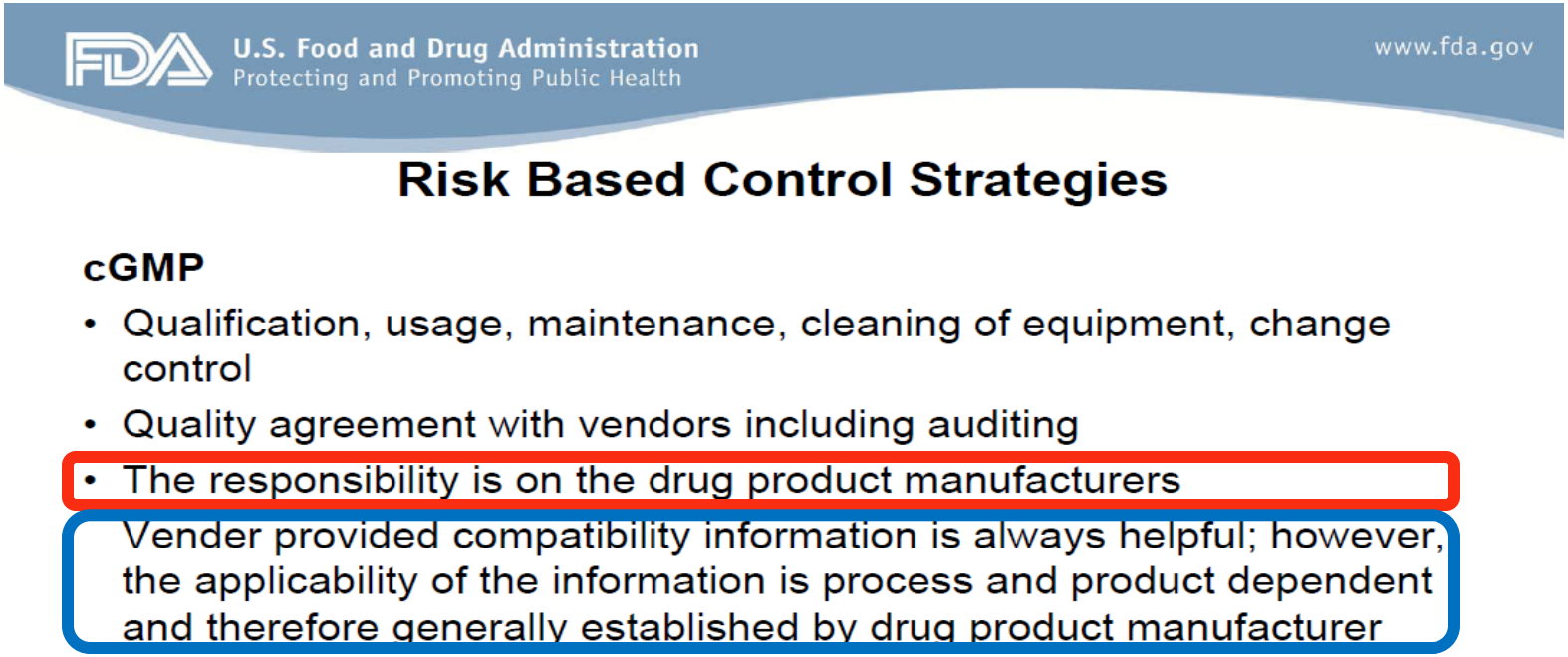


USP – US Pharmacopeal Convention

The intention is to use testing to evaluate risk…….not test every batch…..unless needed due to unpredictability

ICH Q3D Workshop – FDA/OPF's Perspective

Edwin Jao, Ph. D.
Acting Branch Chief FDA/CDER/OPQ/DIVIII/Branch VII



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Q3D Table 5-1:
Elements considered in the risk assessment

Elements	Class	If Intentionally added	If not intentionally added		
			Oral	Parenteral	Nasal
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

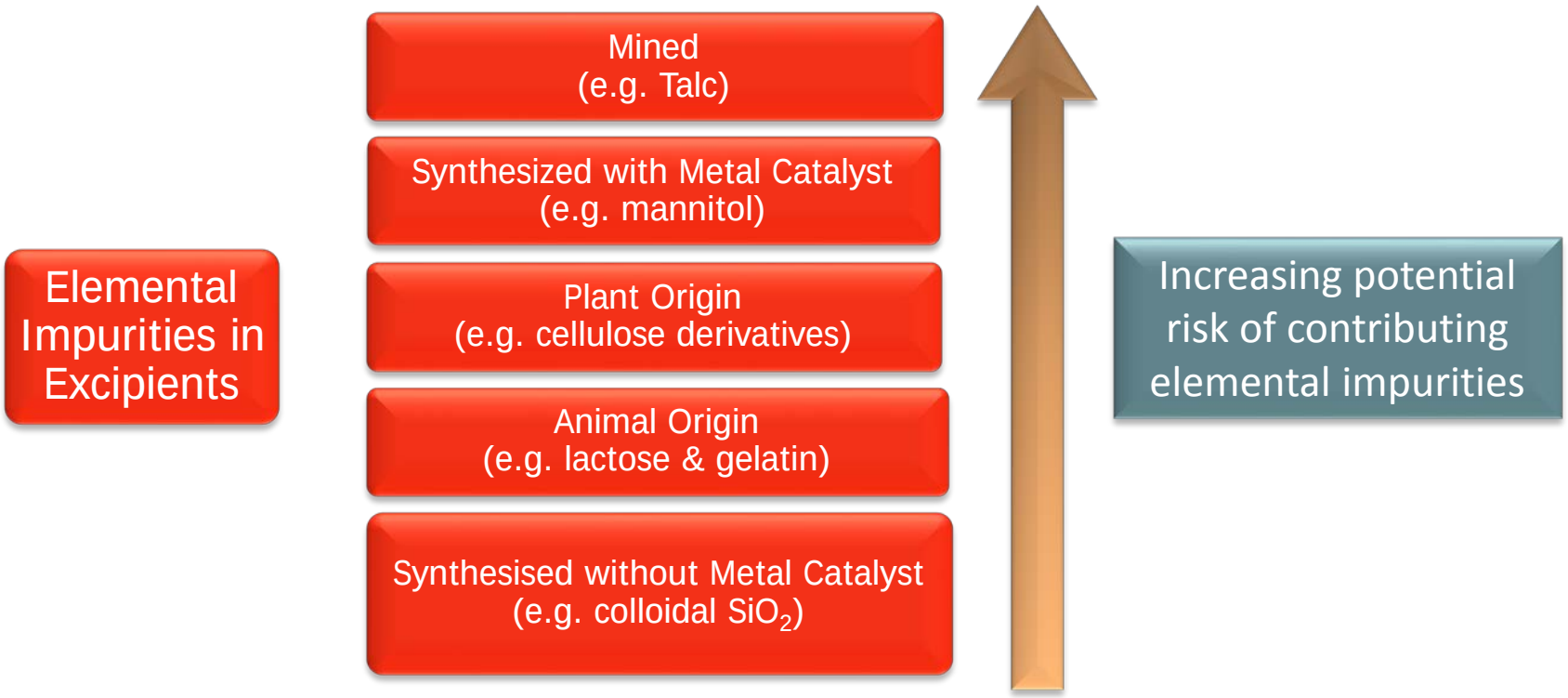
- **Understanding excipient sources, potential for elemental impurities/impurity variability and use of published data**

Potential sources of excipients

- **Chemical synthesis**
  - polymer mixtures derived through synthetic processes (colloidal SiO_2)
  - may use metal catalysts (e.g. povidone, PEG, silicones)
- **Mined minerals**
  - Conversion of ores from mines (e.g. TiO_2)
  - **NOTE**: Many metal impurities naturally present (e.g. lead) in **mined excipients** and cannot be further processed out; therefore, it is important to understand the actual levels present and expect normal variation and **excursions** which **CANNOT be predicted!**
- **Harvested vegetation**
  - Grown in soil (e.g. cellulose derivatives)
  - Harvested from the ocean (e.g. alginates, carrageenan)
  - Need understanding of source variability and level of processing in order to accurately predict EI levels – MORE THAN 3-6 batches!
- **Formulated products**
- **Biotech & fermentation**
- **Genetic modification**
- **Animal by-products**
  - lactose & gelatin

Potential elemental impurities from excipients

How to decide what potential levels of risk an excipient might have



What does the evidence show?

Unknowns - Analysis by FDA lab

IPEC Americas
request for “blinded samples” to be tested by FDA lab

Q1 2012
Law office for IPEC – Americas collected, blinded and submitted excipient samples to FDA lab for analysis

Q1 2013
Law office un-blinded and sent results to original submitters.

2014
Study completed - Industry assessed FDA results vs industry results

FDA & IPEC published data in journal - Fall 2015

Q2-Q4 2012
FDA analyzed samples using ICP-MS

Q1 2013
Additional samples sent to FDA

RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Elemental Impurities in Pharmaceutical Excipients

GANG LI,[1] DAVE SCHONEKER,[2,5] KATHERINE L. ULMAN,[5,3] JASON J. STURM,[4] LISA M. THACKERY,[4] JOHN F. KAUFFMAN[1]

[1]U.S. Food and Drug Administration, Division of Pharmaceutical Analysis, St. Louis, Missouri 63110
[2]Colorcon Inc., Harleysville, Pennsylvania 19438
[3]Dow Corning Healthcare Business, Midland, Michigan 48686-0994
[4]Dow Corning Analytical Sciences, Midland, Michigan 48686-0994
[5]IPEC-Americas, Arlington, Virginia 22201

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The Problem with Available Data

Data in the literature (such as the FDA study) or that may exist from shared study information is general and not specific to the actual grade and supplier of an excipient used in your particular drug product!

This information may be useful to give the Drug Product manufacturer an idea of what elemental impurities **“might”** exist in the excipients they use, however, without knowing that the data applies **specifically to the grades used**, this data is fairly irrelevant for use in a drug product risk assessment!

Users must still do appropriate testing of their specific grades or get supplier specific information to properly conduct their risk assessments

The suppliers of the excipients which were included in the FDA study were provided with the results for their specific samples through the blinding exercise. Therefore, they have some good information about what might be present in the grades they supply

Limited Supplier EI Information

Some excipient suppliers are fully engaged with this initiative, while others will not engage at all.

This will depend on whether the pharmaceutical uses of the excipient make up a significant share of their business or not – **business potential will drive decisions, not regulatory requirements.**

Many suppliers will only have EI information for elements which may have previously been listed in a compendial monograph or is of interest to their other markets which usually will drive their testing (i.e.; food, electronics, industrial).

Many suppliers **do not** plan to do any additional routine testing for elemental impurities due to ICH Q3D and have no intention of agreeing to any new specifications – although there are some exceptions.

Some suppliers have done some designed studies on a limited number of batches to improve their knowledge of potential EI in their products so they can provide some risk assessment assistance to their customers

Gathering relevant elemental impurity data

Sharing Information between Makers & Users

An industry “Coalition for the Rational Implementation of Elemental Impurities Requirements” developed a **standardized request letter and form templates** to help facilitate industry communication between users and makers of APIs and excipients. The template was created and designed to help pharmaceutical companies:

- **Gather information from suppliers pertaining to potential metals/concentrations (and the potential for excursions) in both APIs and excipients used in the production of drug products.**
- **Use information from suppliers (when available) to determine potential presence / concentration of each metal in the assessment of a finished drug product Permitted Daily Exposure (PDE) level.**

NOTE: both API and excipient manufacturers were encouraged to utilize the Information Exchange request template form to **proactively develop** their own product documentation/information.

Sharing Information between Makers & Users Information Exchange Request Template

Supplier Name:	Supplier Phone Number:
Supplier Address:	Supplier Email Address:
Manufacturer (if different than Supplier):	Date Form Filled Out:

Directions:
Identify elemental impurities in (Material Name) that are likely to be present. If likely to be present, identify expected concentration (or range), analytical method used and limit of detection, if known. Please note if any metals catalysts or reagents are intentionally used in the manufacturing process in the Comments column.

Please complete a separate form for each material

Material Name_____

Source/Type of Excipient: ___Mineral ___Mineral derived ___Plant ___Plant derived ___Synthetic ___Fermentation derived

Other (explain):_____

Elemental Impurity		Class	Likely to be Present			If Known, Please Identify the Expected Concentration /Units (or Range)	Analytical Method Used (and Limit of Detection if Available)	Comments regarding source of information (i.e.; frequency of testing, process understanding, etc.)
Arsenic (inorganic)	As	1	Yes ☐	No ☐	Unknown ☐			
Cadmium	Cd	1	Yes ☐	No ☐	Unknown ☐			
Mercury (inorganic)	Hg	1	Yes ☐	No ☐	Unknown ☐			
Lead	Pb	1	Yes ☐	No ☐	Unknown ☐			
Cobalt	Co	2A	Yes ☐	No ☐	Unknown ☐			
Nickel	Ni	2A	Yes ☐	No ☐	Unknown ☐			
Vanadium	V	2A	Yes ☐	No ☐	Unknown ☐			

IDEAL WORLD….

Pro-actively completed by suppliers and sent to users

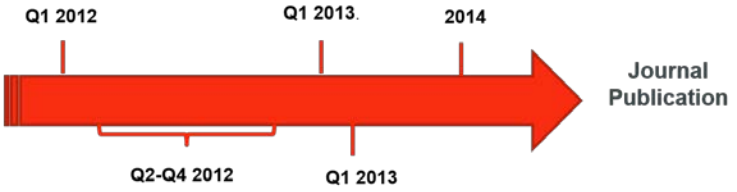
REAL WORLD…

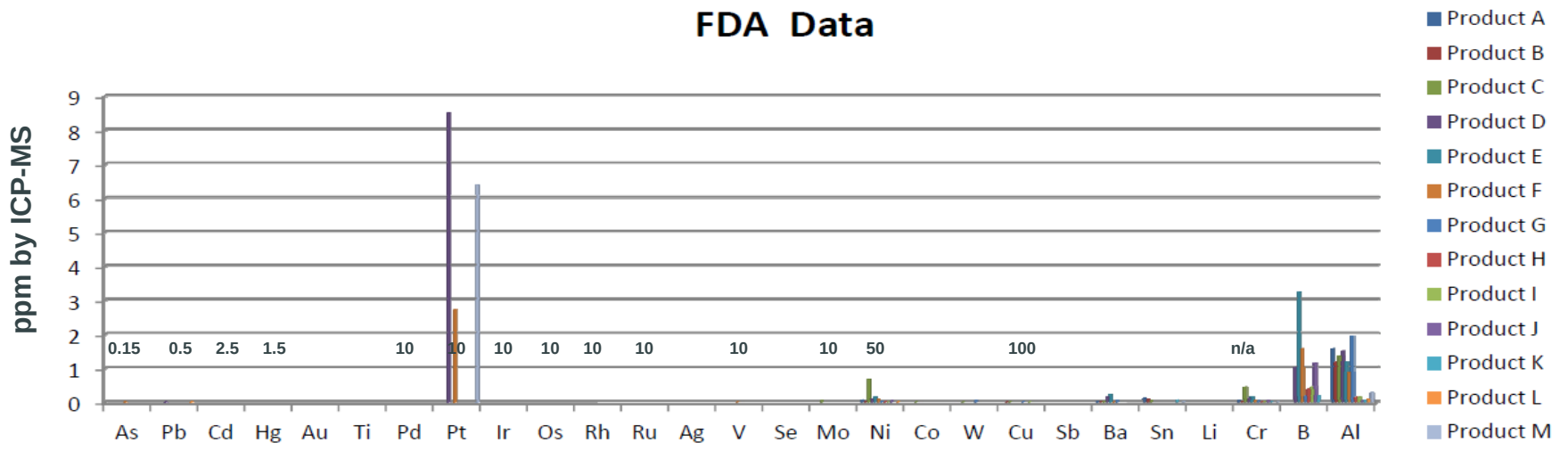
A limited number of suppliers have data or will complete and return the form to users

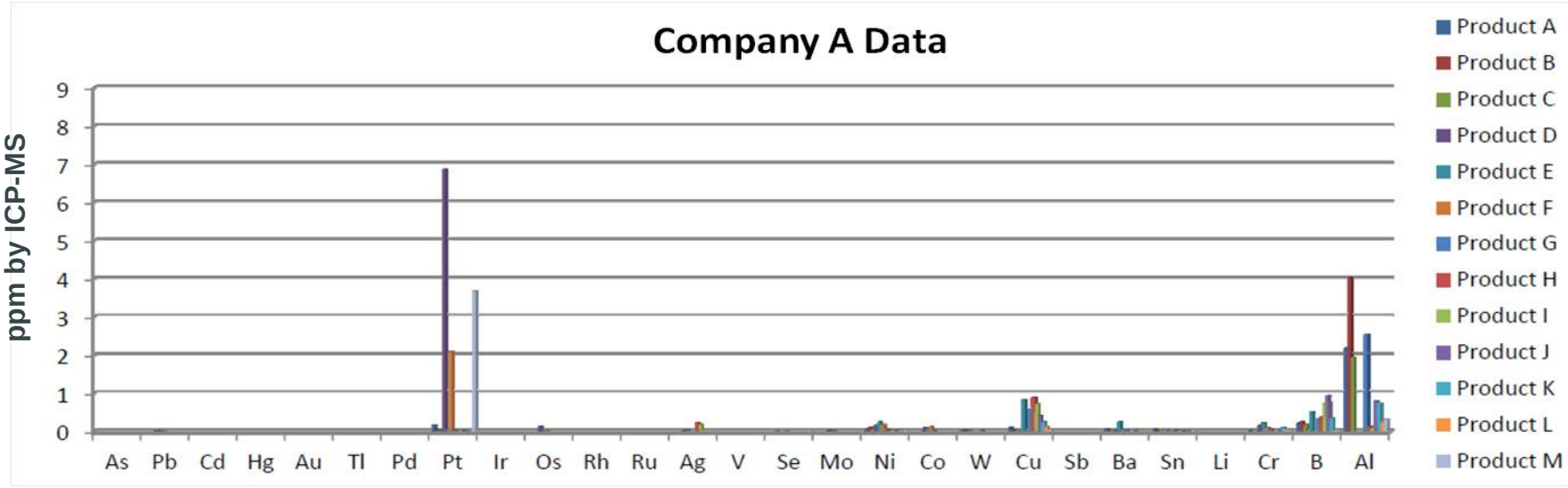
Download IPEC-Americas Links:	
Letter	PDE Calculator Instructions
Template	Daily Intake Calculator

A case study for one excipient supplier’s strategy

FDA Analytical Lab Project







Established/validated equipment and testing strategy

Clearly defined goal of testing

- Screening for risk assessment or **formal control**

Clearly defined type of digestion

- **Total metal extraction** or acid leach

Developed understanding for how materials and matrix could affect analysis

- Dissolved solids, undigested carbon, etc.

Established level of validation/verification needed and completed validation activities

Developed and follow established protocols

- “sample preparation” and “analysis” methodologies

Developed overall testing and communication strategy

Defined products to test

Trained personnel

Developed base-line elemental impurity levels for each ingredient identified for use in a drug product – where necessary, monitored for excursions

Performed testing

Developed future testing / reporting strategy for each product.

Created and communicated reports to share *elemental impurity* data for excipient products per USP <232> and ICHQ3D

Current communication strategy

While USP <232> and ICH Q3D are not mandatory for excipients, finished drug manufacturers and authorization holders must assess all sources of elemental impurities in their finished drug product. This letter is intended to provide elemental impurity data for SENTRY™ POLYOX™ Water-Soluble Resins NF grade excipient products per USP <232> and ICH Q3D.

Dow currently performs the following elemental testing on SENTRY™ POLYOX™ Water-Soluble Resins NF products:

- Heavy metals per the USP test method to demonstrate compliance with the USP, PhEur and JP Pharmacopoeia. The USP heavy metals test will give positive indication for the presence of Ag, As, Bi, Cd, Hg, Mo, Pb, Sb, and Sn.

ICH Q3D Class I and 2A elements

In anticipation of customer requests for Elemental Impurity data per USP <232> and ICH Q3D, Dow has completed an assessment of the manufacturing process and tested representative samples of SENTRY™ POLYOX™ Water-Soluble Resins NF representing all producing plants and production lines for batches produced over a multi-year time period. Conclusions of the manufacturing process assessment are as follows:

Risk Assessment considerations

Manufacturing process “Risk” Assessment

- Elemental impurities are not intentionally added to SENTRY™ POLYOX™ products.
- Calcium based catalysts are used in the SENTRY™ POLYOX™ manufacturing process.
- Dow has well-defined manufacturing processes and controls for SENTRY™ POLYOX™ production.
- The reaction vessels are stainless steel clad.

Analytical results for USP <232> and ICH Q3D elemental impurities are summarized in Table I.

- All Class 1 and Class 2A elements were quantified.
- Selenium and Cobalt were added to the USP list for testing due to ICH Q3D requirements.
- No Class 2B elements were intentionally added to Table I, but some Class 2B elements were tested due to USP <232> requirements.
- Chromium and nickel are components of stainless steel. These trace impurities, if present, are from the components of the POLYOX™ manufacturing equipment.

In conclusion, based on the product chemistry, raw materials, materials of construction and the manufacturing processes and controls, as well as results of recent screening tests, SENTRY™ POLYOX™ Water-Soluble Resins NF products do not contain the majority of elemental impurities listed below.

Manufacturing process “Risk” Assessment – a “Family Affair”

Since the “family” of SENTRY™ POLYOX™ WSR products all utilized the same:

- **raw materials**
- **chemistry**
- **manufacturing equipment, processing & quality system controls**
- **packaging materials of construction**

110,000 MW 500,000 MW 5,000,000 MW

Three grades of SENTRY™ POLYOX™ WSR were analyzed ***to cover the entire FAMILY*** of POLYOX™ polyethylene oxide.

Equivalent “non-detectable” results were obtained for all three grades.

Elemental impurity data

Elemental Impurity		Class	Likely to be Present			Concentration /Units (ppm) ND = Not Detected	Analytical Method Used (and Limit of Detection if Available)	Comments regarding source of information (i.e.; frequency of testing, process understanding, etc.)
Arsenic (inorganic)	As	1	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Cadmium	Cd	1	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Mercury (inorganic)	Hg	1	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Lead	Pb	1	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Cobalt	Co	2A	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Nickel	Ni	2A	Yes ☒	No ☐	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Vanadium	V	2A	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Silver	Ag	2B	Yes ☐	No ☒	Unknown ☐			Not tested
Gold	Au	2B	Yes ☐	No ☒	Unknown ☐			Not tested
Iridium	Ir	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Osmium	Os	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Palladium	Pd	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Platinum	Pt	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Rhodium	Rh	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Ruthenium	Ru	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Selenium	Se	2B	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Thallium	Tl	2B	Yes ☐	No ☒	Unknown ☐			Not tested
Barium	Ba	3	Yes ☐	No ☒	Unknown ☐			Not tested
Chromium	Cr	3	Yes ☒	No ☐	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Copper	Cu	3	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 1 ppm)	
Lithium	Li	3	Yes ☐	No ☒	Unknown ☐			Not tested
Molybdenum	Mo	3	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 0.1 ppm)	
Antimony	Sb	3	Yes ☐	No ☒	Unknown ☐			Not tested
Tin	Sn	3	Yes ☐	No ☒	Unknown ☐			Not tested
Aluminum	Al	4	Yes ☐	No ☒	Unknown ☐	ND	<233> Elemental Impurities (LOD 3 ppm)	

Conclusions

The level and type of information that excipient suppliers will provide to support drug product risk assessments to meet the ICH Q3D and compendial requirements will vary.

The key to success for both excipient suppliers and drug manufacturers will be for both parties to share information and understand the limitations of what each party may be dealing with.

Often time the dialog is what is most important to ensure that users have enough information to successfully complete their risk assessments

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Your Questions – Thank You!

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