HOW DO YOU MAKE BETTER DEVELOPMENT DECISIONS FASTER?

IMPLEMENTING ELEMENTAL IMPURITIES TESTING
ICH Q3D, USP <232> and <233> Requirements

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What is Driving the Change?

USP <231>

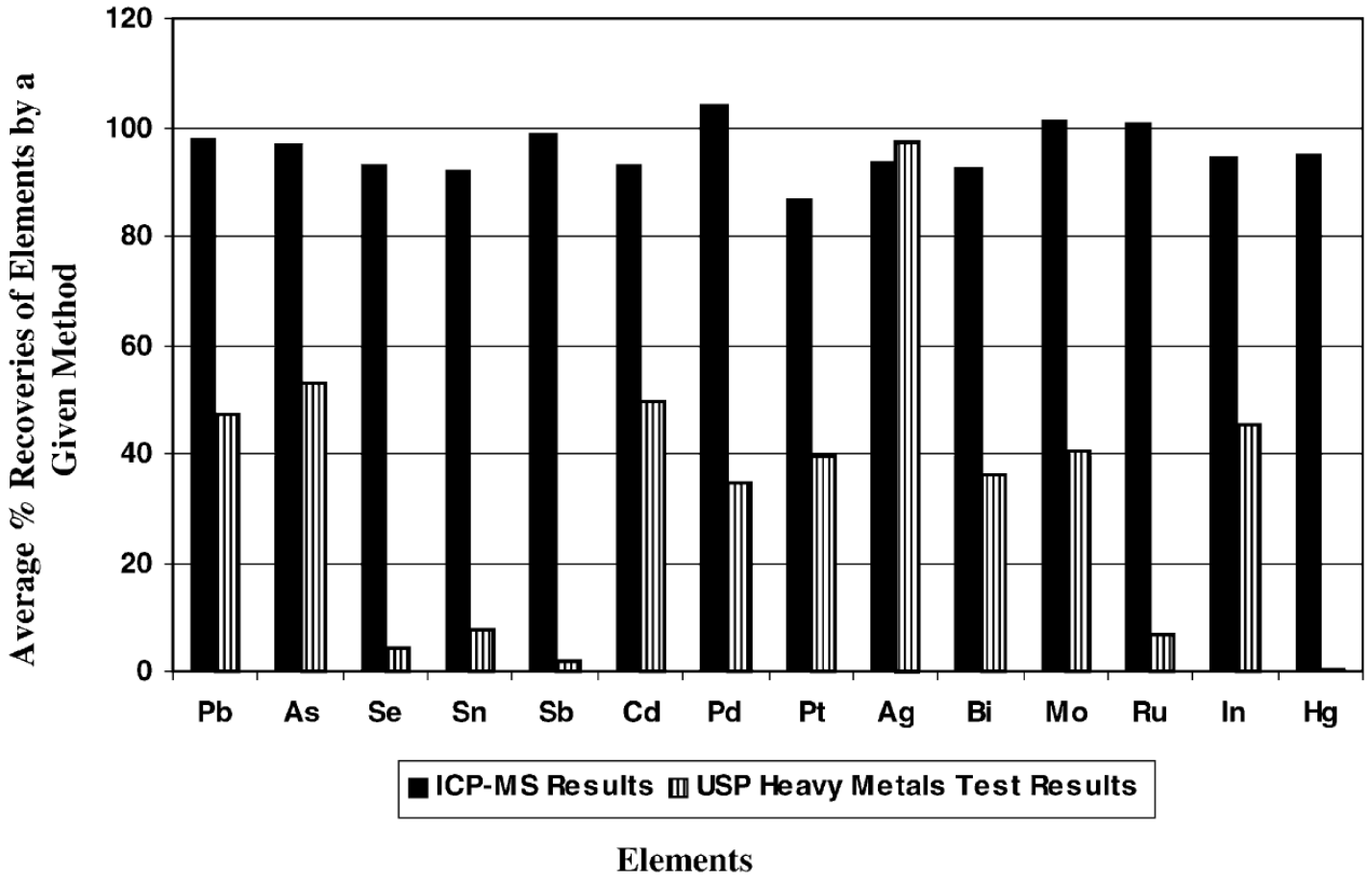
- Established in 1905
- Colorimetric limit test
- Limited scope:

  Only works with sulfide precipitating metals
- Non-Specific:

  Cannot determine individual metals which are present
- Robustness is lacking

  Method performance can vary
- Solution stability is lacking
- Matrix interferences

USP <231> Recovery Issue



N. Lewen, S. Mathew, M. Schenkenberger, T. Raglione, *Jounal of Pharmaceutical and Biomedical Analysis, 35 (2004) 739-752*

New Testing Requirements

New USP Chapters

- <232> Elemental Impurities – Limits
- <233> Elemental Impurities – Procedures
- <2232> Elemental Contaminants in Dietary Supplements
- Effective on January 1st, 2018

ICH Guidance

- Q3D
- Effective for new NDA/ANDA: June 1st, 2016.
- Effective for all marketed products January 1st, 2018

FDA Guidance

- Elemental Impurities in Drug Products

Who is the USP?

United States Pharmacopeia

- Legally recognized standard setting organization
- Sets standards for Drugs, API's, etc. via Monographs/Chapters
- Does not enforce its standards – Enforced by the FDA

Who is the ICH?

International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- **Japan:** Ministry of Health, Labour and Welfare, and Japan Pharmaceutical Manufacturers Association
- **Europe:** European Union and European Federation of Pharmaceutical Industries and Associations
- **USA:** Food and Drug Administration and Pharmaceutical Research and Manufacturers of America
- **Members:** Health Canada, Swissmedic, ANVISA (Brazil), CFDA (China), MFDS (Korea), BIO, IGBA, WSMI

What Is the Goal of ICH?

To increase international harmonization of technical requirements through technical guidelines

- Reduce unnecessary duplication
- Aid in development of new medicines
- Guidelines for registration and supervision of new medicines

ICH ISSUES *GUIDANCE—NOT* REGULATIONS

USP <232> vs. ICH

Which applies to your product?

USP

- Drug products which have a monograph, unless the monograph specifically states otherwise

ICH

- New drug products (NDA/ANDA) which do not have a monograph.
- All marketed products that were approved via NDA/ANDA which do not have a monograph
- All marketed products which were not approved via NDA/ANDA (ex. OTC)

USP

<232> - Limits

Recommends a risk based approach

- *But doesn't make any recommendations on the approach*

Specifies 24 Metals

- *Now harmonized with ICH*

Permissible Daily Exposure (PDE) values

- Based on route of administration
- Now harmonized with the ICH

USP/ICH – Risk Assessment Table

Element CU	Class	If Intentionally Added *(All Routes)*	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cadmium	1	YES	YES	YES	YES
Lead	1	YES	YES	YES	YES
Arsenic	1	YES	YES	YES	YES
Mercury	1	YES	YES	YES	YES
Cobalt	2A	YES	YES	YES	YES
Vanadium	2A	YES	YES	YES	YES
Nickel	2A	YES	YES	YES	YES
Thallium	2B	YES	NO	NO	NO
Gold	2B	YES	NO	NO	NO
Palladium	2B	YES	NO	NO	NO
Iridium	2B	YES	NO	NO	NO
Osmium	2B	YES	NO	NO	NO
Rhodium	2B	YES	NO	NO	NO
Ruthenium	2B	YES	NO	NO	NO
Selenium	2B	YES	NO	NO	NO
Silver	2B	YES	NO	NO	NO
Platinum	2B	YES	NO	NO	NO
Lithium	3	YES	NO	YES	YES
Antimony	3	YES	NO	YES	YES
Barium	3	YES	NO	NO	YES
Molybdenum	3	YES	NO	NO	YES
Copper	3	YES	NO	YES	YES
Tin	3	YES	NO	NO	YES
Chromium	3	YES	NO	NO	YES

Table derived from ICH Q3B

Metal Classification from Q3D

Class 1

- "Big four"
- Limited or no use in production of products
- Known toxicity issues
- Must be included in risk assessment

Class 2A

- High probability if they will occur
- Must be included in risk assessment

Class 2B

- Low probability
- Can be excluded from risk assessment unless intentionally added
  - *Ex. Catalysts*

Class 3

- Low oral toxicity
- May require assessment for Inhalation and Parenteral dosing

USP/ICH – PDE

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalation PDE (µg/day)
Cadmium	1	5	2	2
Lead	1	5	5	5
Arsenic	1	15	15	2
Mercury	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5
Thallium	2B	8	8	8
Gold	2B	100	100	1
Palladium	2B	100	10	1
Iridium	2B	100	10	1
Osmium	2B	100	10	1
Rhodium	2B	100	10	1
Ruthenium	2B	100	10	1
Selenium	2B	150	80	130
Silver	2B	150	10	7
Platinum	2B	100	10	1
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Molybdenum	3	3000	1500	10
Copper	3	3000	300	30
Tin	3	6000	600	60
Chromium	3	11000	1100	3

Table derived from ICH Q3B

Compliance with USP

Drug Product Testing

- Test the drug product and compare against PDE values

Summation Method

- Add all contribution from excipients, API, etc. and compare against PDE values

Component option

- Testing each component material and compare against the referenced PPM levels
- Table 3 in <232>

ICH Q3D

As noted Elements and PDE are harmonized with USP

Contains recommendations for how to treat other routes of administration and PDE levels

Has detailed information on performing the Risk Assessment

ICH has published training modules for implementation

- Modules 0 – 9 are available for download

ICH Q3D Training Modules

- **Module 0:** Overview
- **Module 1:** Developing Acceptable Levels for Other Routes of Administration
- **Module 2:** Justification for Exceeding a PDE
- **Module 3:** Developing Acceptable Levels for EI not in Q3D
- **Module 4:** Considerations for Large Volume Parenterals
- **Module 5:** Risk Assessment
- **Module 6:** Controls on Elemental Impurities
- **Module 7:** Calculations Options
- **Module 8:** Case studies
- **Module 9:** Consolidated FAQs

ICH Q3D – Other Elements

Elements not included in Q3D

- Low inherent toxicity or differing regulations
- No PDE's have been established
- May require testing/control

Should be included in the overall risk assessment if needed

- Module 3

Potential elements include: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

ICH Q3D – Other Routes of Administration

PDE's are stated only for Oral, Parenteral and Inhalation products
Can/Should be included in the overall risk assessment if needed

- Oral, Parenteral or Inhalation PDE's may be used is appropriate or modified
- Items to consider
  - *Local vs. Systemic affects*
  - *Bioavailability for route of administration*
  - *Formulation affects*
    - *Ex. Dermal products*

ICH – Risk Assessment Table

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Table derived from ICH Q3B

Risk Assessment

Determine potential sources of elemental impurities

Risk assessment approach

- Drug product based
- Drug product component based

Output of the risk assessment

- Control strategy
- Routine testing

Risk Assessment - Considerations

Intentionally added elemental impurities (catalysts)

Naturally sourced excipients materials

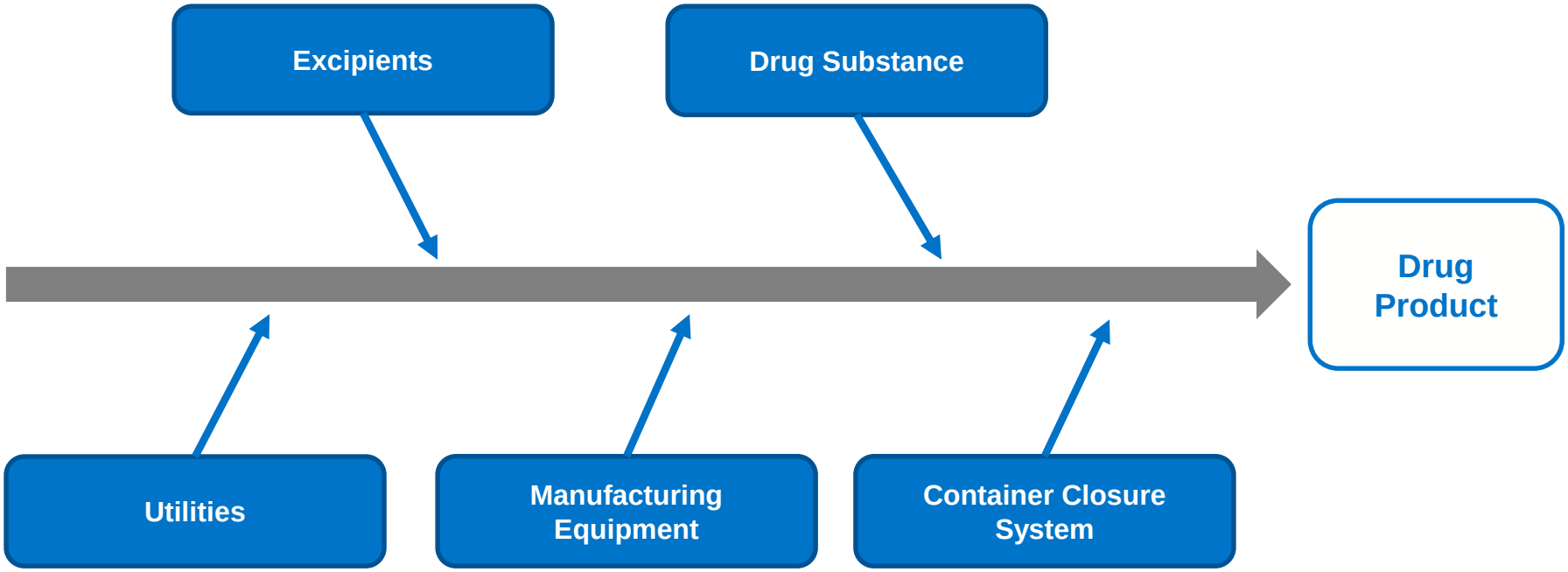
- Animal sourced, vegetable sourced, mined

Inorganic excipients/materials

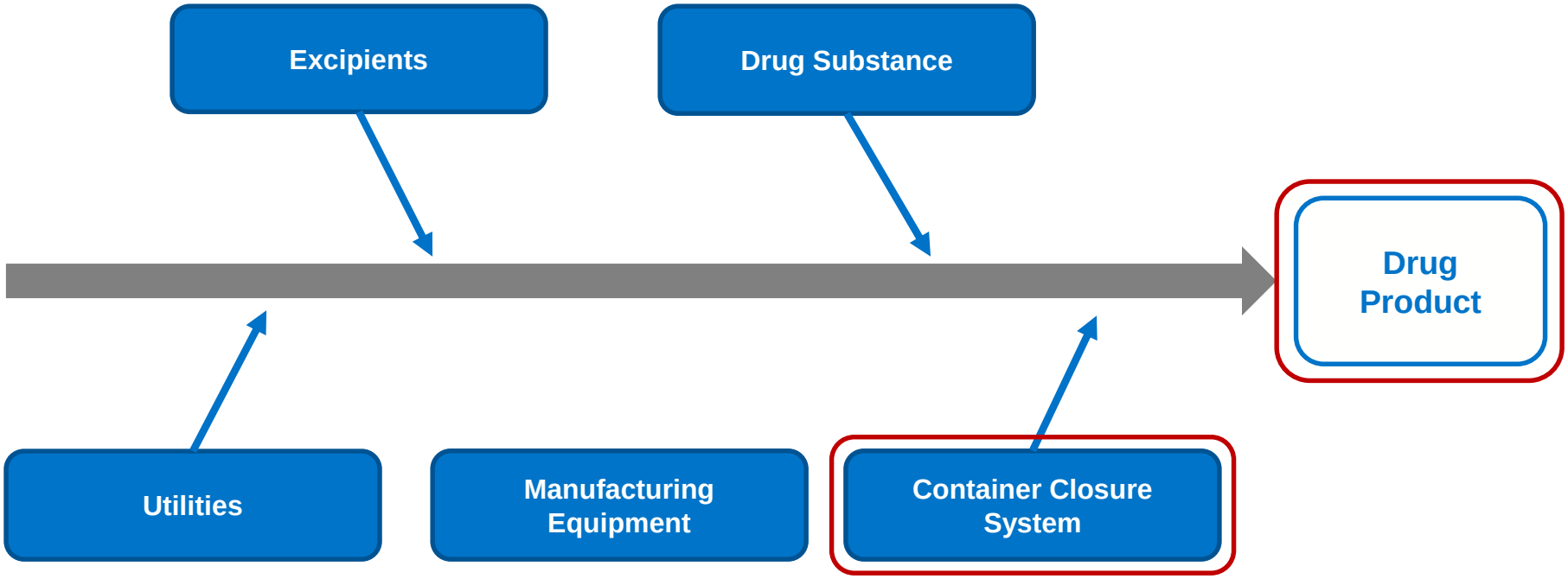
Manufacturing process

- Manufacturing solvents (water is likely source)
- Contact surfaces
  - *High shear systems*
  - *Leachables*

Potential Sources of Elemental Impurities



Risk Assessment – Drug Product Based

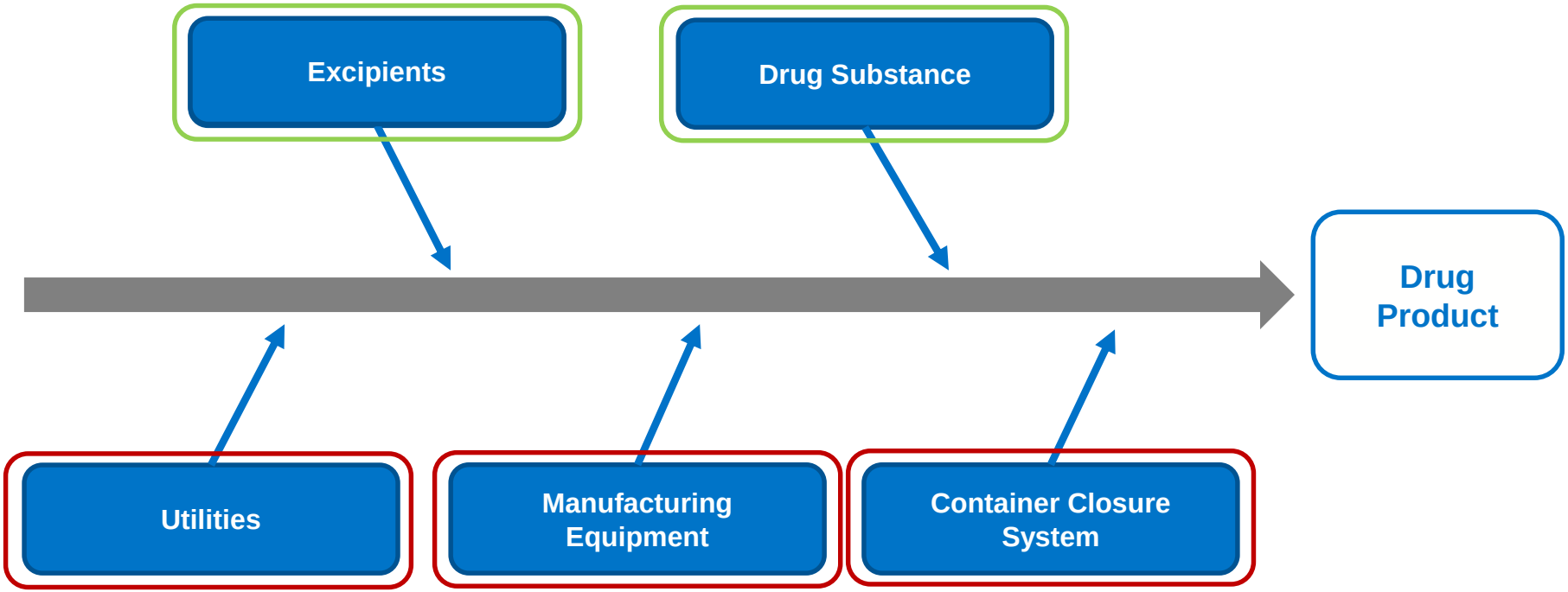


Risk Assessment – Drug Product Based

Drug Product Based

- **Determine elemental impurities**
  - Knowledge of manufacturing process
  - Initial lot screens
- **Validation of methods**
- **Perform lot survey (if needed)**
  - 3 lots of registration quality batches (or)
  - 6 lots of pilot scale
- **Evaluate risk associated with container closure**
  - i.e. leachables
- **Evaluate results against PDE and risk assessment**

Risk Assessment – Component Based



Risk Assessment – Component Based

Drug product component approach

- **Gather information on elemental content of components**
  - Literature
  - Manufacturer
  - Testing
  - Etc.
- **Components include**
  - Formulation components
  - Manufacturing specific materials
    - *Solvents (water, etc.), reagents, catalysts, etc.*
  - Container closure

Gathering Data from Manufactures

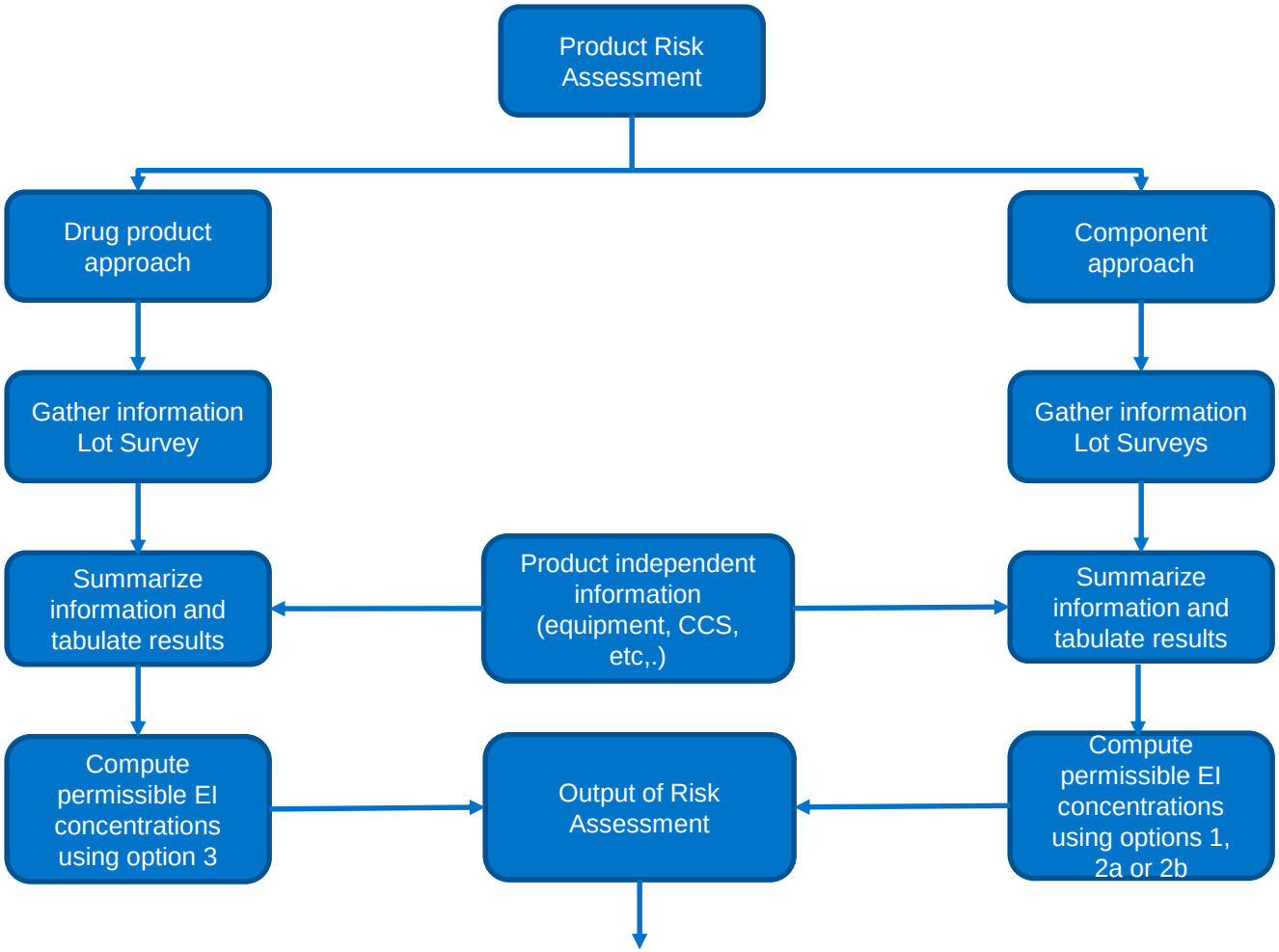
Gathering information from manufacturers can be problematic

- **Elemental impurities for compendia raw materials will no longer be required**
- **Manufactures may or may not institute testing**
  - *Not required for "USP" designation so why do it?*
  - *Will likely depend on client need/influence*
- **Manufactures to date appear to be behind the curve**
  - *Sponsors in many cases are performing the testing as needed*

Container/Closure Elemental Impurities

- **Extractable/Leachable elemental impurities from container/closure**
  - For parenteral and inhalation products this is typically performed during the products E&L larger studies
- **Extraction studies**
  - Solvent(s) extraction
    - Need to factor in formulation specifics
      - *pH, solubility enhancers, etc.*
  - Can be used for component or drug product risk assessment
- **Leachable studies**
  - Requires “aged” product at end or beyond shelf life
    - *May be timing prohibitive*

Risk Assessment Approaches



Permissible Concentrations Calculations

- **Option 1**
  - Applies to individual components
  - Assumes 10 gram dosing
  - Elemental impurities present equally in all components
- **Option 2a**
  - Similar to option 1
  - Assumes less than a 10 gram dosing
  - Elemental impurities present equally in all components
- **Options 2b**
  - Apply differing permitted levels in component based on the mass distribution
    - *Higher levels for some components*
- **Options 3**
  - For use with drug product route.
  - $permissible\ concentration\ \left(\frac{ug}{g}\right) = \frac{PDE}{DP\ in\ gram\ per\ day}$

Risk Assessment Output

1. **Elemental impurities which are excluded**
   - Based on the risk assessment table
   - Detail out which elements are not required
2. **Elements which are present but are below control threshold**
   - Routine testing typically not required
   - Control strategy may not be required if data indicates limited variability
     - Naturally sourced (mined) components need special consideration
3. **Elements which exceed the control threshold but below the PDE**
   - Routine testing may be required
     - *Drug product or individual components*
   - Control strategy is likely needed to ensure safety
     - *Control at incoming materials?*
4. **Elements which exceed the PDE**
   - Justification for exceeding the PDE
     - *Module 2*
   - Alteration of process to lower below the PDE
   - Control procedures to ensure compliance

Control Threshold

Defined in ICH as 30% of the PDE for any particular elemental impurity in the drug product

- **If all my result are below the control threshold, am I done?**
  - Not necessarily
  - Depends on the larger risk assessment
    - *Variability*
    - *Controls on incoming materials*

Test Methods/Techniques

ICH does not detail any testing specifics

- Instrumentation
- Method

USP <233> Elemental Impurities – Procedures

Contains two specific procedures

- Procedure 1 – *ICP-OES*
- Procedure 2 – *ICP-MS*

USP Procedures

Procedure 1 and 2

- **Quantitative in nature**
- **Two standards present at 0.5J and 1.5J**
    - ***Note:*** *USP range does not cover the 30% PDE control threshold as defined in the ICH*
- **Compare sample result against PDE value**

ICP-OES

Inductively Coupled Plasma – Optical Emission Spectroscopy

Monitors the wavelength emissions from excited atoms

Issues:

- Sensitivity can be an issue
  - *ppb+*
- Specificity can be a challenge
- Low dynamic linear range
- Slower sample analysis for multiple methods

Pros:

- More robust sample capabilities
  - *Higher organic/total undissolved solids*
- Lower cost
- Easier instrument maintenance

ICP-MS

Inductively Coupled Plasma – Mass Spectroscopy

Monitors the mass responses of elemental impurities

Issues

- Low tolerance on sample organic/total dissolved solids
- Higher cost/maintenance
- Specialized staff

Pros

- High sensitivity
  - *ppt or lower*
- High level of specificity (low interferences)
- Wide dynamic linear range
- Can monitor for all species simultaneously

ICP-MS is the preferred technique

J-Value

Defined in USP as the analytical equivalent of the PDE

$$J = \frac{PDE}{Total\ Dilution\ x\ Max\ Daily\ Use}$$

Element	PDE (µg/day)	Dilution Factor	J – Value (µg/L)
Cd	5	1000	5
Hg	5	1000	5
As	15	1000	15
Hg	30	1000	30

For doses with ≤10 gram dose

Sample Preparation

Neat Analysis

- Analyzes the samples directly (organic or Aqueous)

Indirect Solution Analysis

- **Closed Vessel Digestion**
  - *Wet chemistry based*
    - Has potential for loss of volatiles
  - **Microwave Digestion**
    - *Completely sealed*
    - *Preferred for volatile Metals*

Sample Preparation – Known Issues

- **Multiple elements require stabilizers to be present for long term stability**
  - Os – *May form OsO_4*
  - Sn and Sb – *Fluoride*
  - Au, Ir, Ru – *may require Chloride*
- **Matrix affects**
- **Solubility issues in various digestion solvents**
- **Ensuring complete digestion**
- **Volatility of elemental impurities**

Do the Analytical Methods Need to be Validated?

“Analytical Procedures for both risk assessments and routing testing should be validated”

- FDA draft guidance

“Validation Criteria…..can depend on the analytical procedure’s intended purpose”

- FDA draft guidance

Risk Assessments

- Methods should be demonstrated to give the required level of confidence in the results
  - *Accuracy, Precision, Specificity*

Routine Testing

- Methods should comply with ICH Q2(R1) guidelines

USP defines criteria for validations for alternate methods

Typical Elemental Impurities Program

Method Feasibility/Development

- Evaluate digestion conditions
- Matrix interferences

Method Validation

- For risk assessments: *Accuracy, Precision, Linearity, LOD/LOQ, Specificity*

Lot Survey

Risk Assessment

Specification Setting (if required)

Method Validation

- ICH Q2(R1) compliant

Routine testing

- Batch release, lot release, stability testing (leachables)

Case Study 1

Product is a tablet with various strengths/colorants

- No data is available on the individual components of the tablet

Will be filed as an NDA subject to ICH Q3B

Obtained all excipients and drug products

Method evaluated for use on all excipients used in the process

Method validation performed covering all of the excipients and the final drug products

- Combined validation

Lot survey performed on multiple lots of each

Risk assessment performed

- All metals were below the control threshold
- One excipient was a mined material with known variability of EI-X
- Testing established to monitor/control the level of EI-X in excipient

Case Study 2

Product is a pre-filled syringe

- Data available on API and formulation components

Will be filed as an NDA subject to ICH Q3B

Extractable testing performed on the container/closure system

- EI-X and EI-Y were found

Method developed and validated for drug product analysis

- Survey Performed
- EI-X and EI-Y were found in DP

Risk Assessment performed

- Determined potential for impurities to exceed control threshold in product

Routine testing initiated on drug product

Contact an EAG expert to learn more about elemental impurities testing:

www.eag.com/elemental