ICH Q3D Risk Assessment for New Filings – Recent Regulatory Experiences

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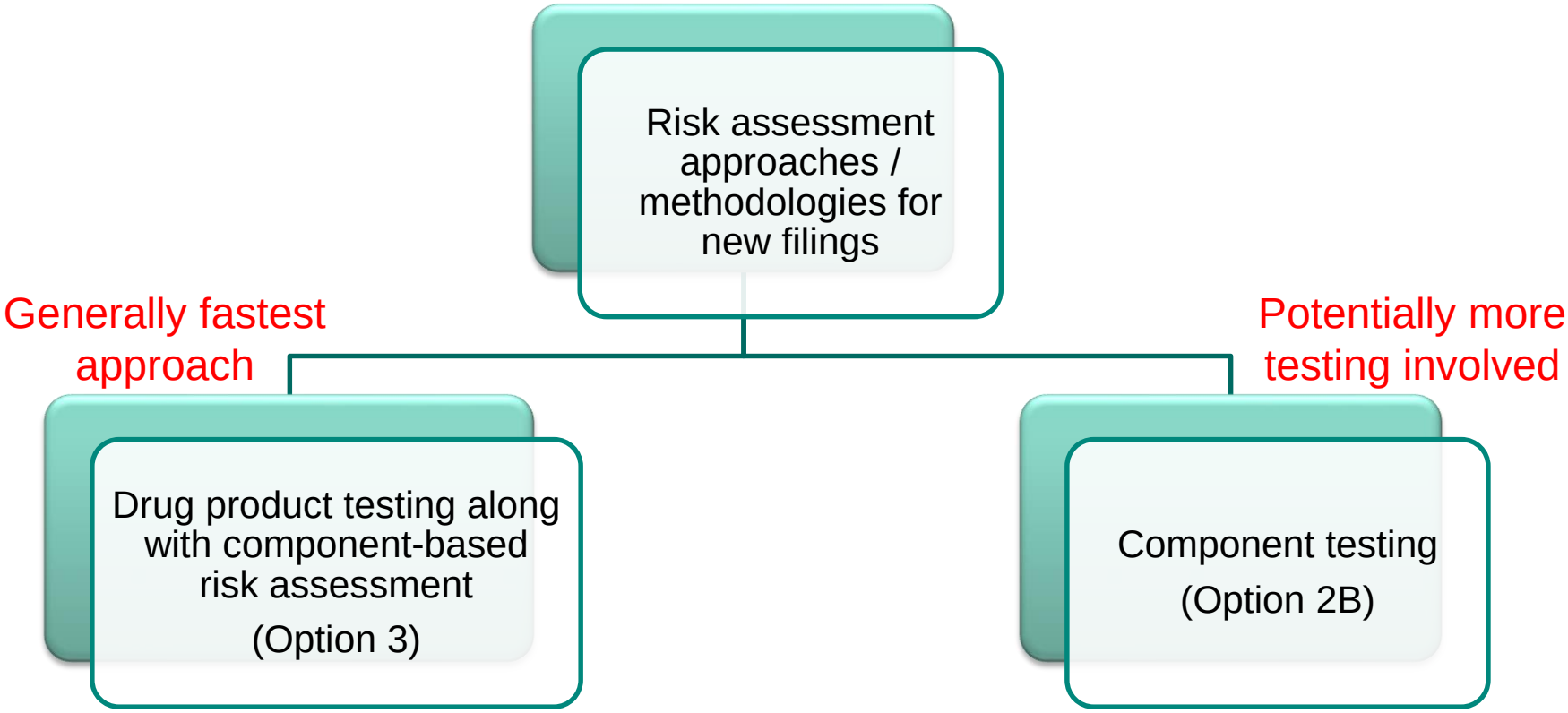
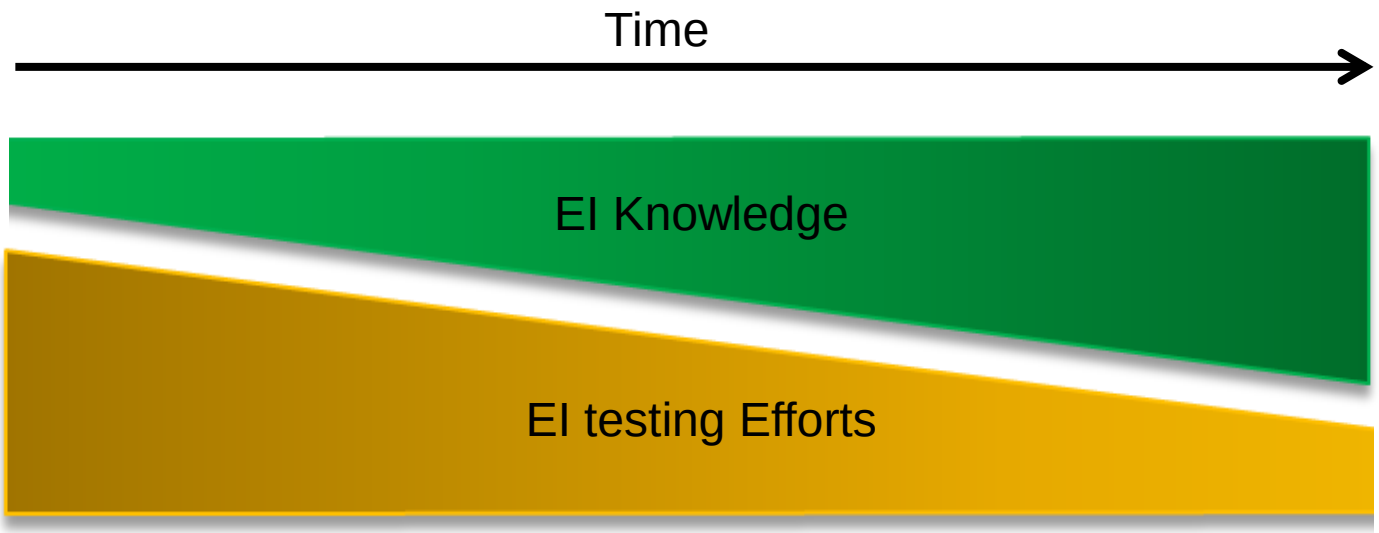
Risk Assessment Approaches



Decision between option 2b and option 3 based on:

- Development timelines
- Available data

ICH Q3D Risk Assessments– Evolution over time



Limited Excipient / Drug Substance EI Data

Some Excipient EI data available. Drug Substance EI information built during development

Most Excipient and DS EI data available.

Drug product testing is favored (Option 3)

Component based RA is favored (Option 1,2)

Implementation of ICH Q3D during drug development --- Two Stages

Formulation Development

- No formal risk assessment will be performed
- Consider high risk excipients and drug substance contributions during formulation selection
  - Calculate worst case levels of EI based component contribution
    - Opportunity to adjust formulation if needed

Scale-up / Site transfer

- Formal Elemental Impurities Risk Assessment will be performed
  - Based on final formulation, process, and manufacturing equipment

Note: Solid knowledge management is crucial for successful implementation

Example 1 : Drug Product testing for solid oral dosage form (Option 3)

Rationale for Selecting Option 3

- Drug product testing enabled speed and certainty to evaluate risk for EI in drug product
- At least 3 commercial drug product batches were available for testing at the time of risk assessment

Elemental Impurities Risk Assessment was conducted along with Drug Product Testing

- Extensive EI data was available for several developmental and commercial drug substance lots
- Vendor EI data for excipients available

Example 1 : Drug Product testing for solid oral dosage form (Option 3) - Results

Elemental Impurity Limit Test by ICP-MS on Stability Drug Product Batches Manufactured at the Commercial Site									
Element	Class	Permitted oral conc. (µg/g) Daily dose = 2.2 g	30% Permitted oral conc. (µg/g) Daily dose = 2.2 g	Found in each batch (µg/g)					
				Batch A	BatchB	Batch C	Batch D	Batch E	Batch F
Cd	1	2.3	0.7	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Pb	1	2.3	0.7	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
As	1	6.8	2.0	< 1	< 1	< 1	< 1	< 1	< 1
Hg	1	14	4.1	< 1	< 1	< 1	< 1	< 1	< 1
Co	2A	23	6.8	< 1	< 1	< 1	< 1	< 1	< 1
V	2A	45	14	< 1	< 1	< 1	< 1	< 1	< 1
Ni	2A	91	27	< 10	< 10	< 10	< 10	< 10	< 10

- No Elemental impurities Found in 6 Stability Batches
- No intentionally added Elements
- Risk assessment for each component accompanied along with Drug product testing
  → No high risk flagged

Example 2: EI Risk Assessment for injectable large molecule (Hybrid Approach)

Rationale for Selecting Option 2b:

- Data on components available at the time of risk assessment
- Possible to conduct worst case calculation for elemental impurities based on available data

Elemental Impurities Risk Assessment was conducted based on:

- Extractable profiling data of product contact materials used during DS manufacturing
- Specifications for elemental impurities of excipients and water
- Extractable profiling data of product contact materials used during DP manufacturing
- Data of extraction studies on the primary packaging components and supplier information of silicone oil.
- Excipient testing data and/or vendor data for excipients was found sufficient

Example 2: EI Risk Assessment for injectable large molecule (Hybrid) - Results

- Main risks identified based on elemental impurity data for each component and equipment contribution

Element	Class	Intentionally Added	Excipient Impurity	Water Impurity	Manufacturing Equipment	Leached from Container Closure Systems
Pb	1	No	Low risk in 4 excipients	Low risk	No	No
As	1	No	Low risk in 4 excipients	No	No	No
Hg	1	No	Low risk in 2 excipients	No	No	No
Ni	2A	No	No	Low risk	Low risk	No
Cu	3	No	Low risk in 2 excipients	No	No	No

- Worst case calculation was conducted based on available data according to option 2b
- Drug Product testing on 3 commercials lots confirmed no detectable EI levels

Implementation Strategy

Boehringer Ingelheim

- Control of intentionally added elements
  - Each API GMP-batch throughout development should be evaluated
- Screening for not-intentionally added ICH Q3D elements
  - In early development stages (phase I/II supplies), a screening for ICH Q3D elements has to be performed for all API GMP-batches
  - In late development stages (phase III/IV), a reduced testing of at least three batches out of GMP campaign may be considered
- Externally sourced APIs
  - Information on potential EIs in the API should be collected from suppliers

Current Practice

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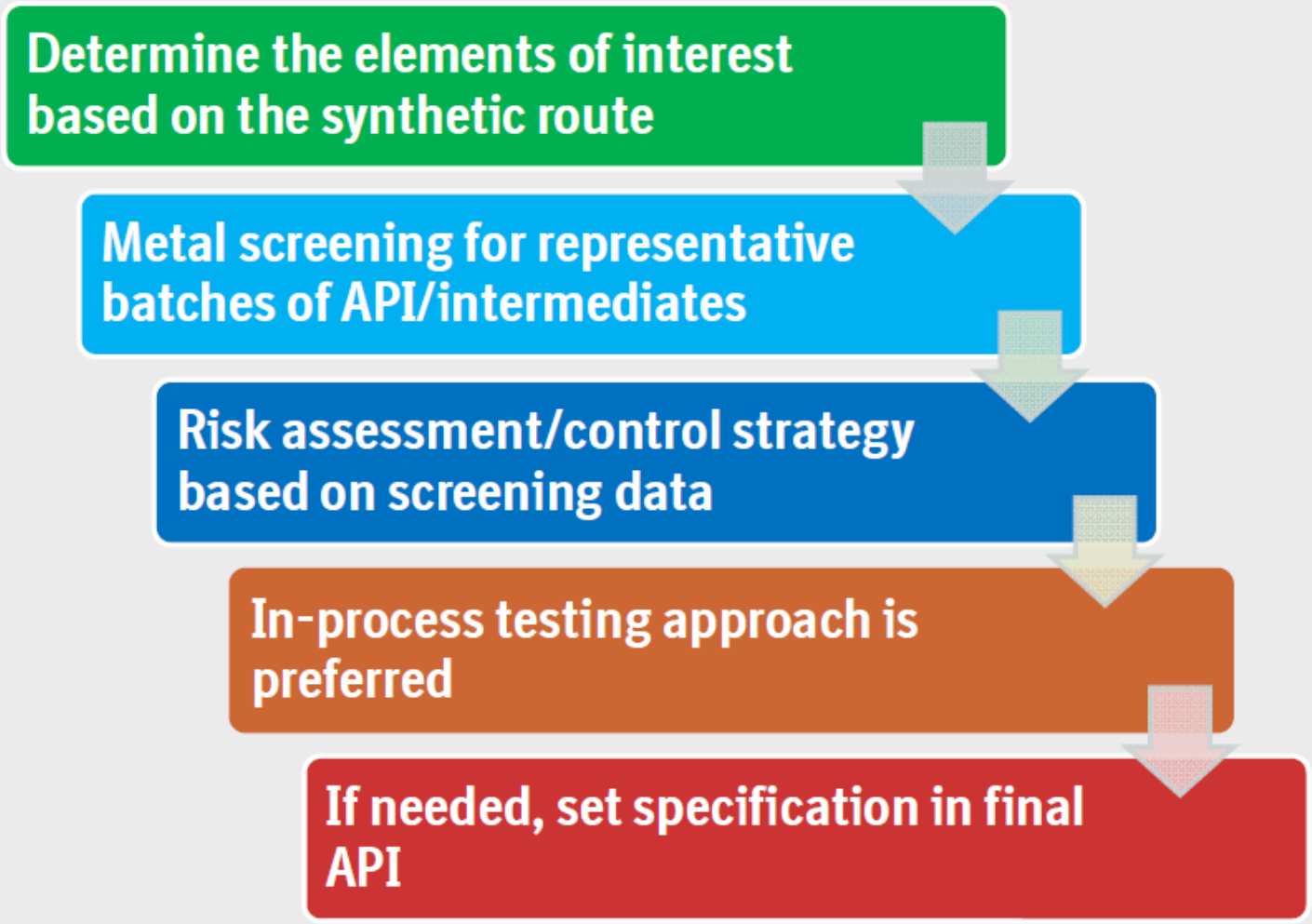

Case Study
Control Strategy for Compound X

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- **Inorganic Impurities based on synthetic route**
  - — **Iron (Fe), Titanium (Ti), Lithium (Li), Palladium (Pd) & Aluminum (Al)**

Element	Control limit (ppm)	Regulatory/toxicology guideline/information
Fe	1300	EMA
Pd	10	ICHQ3D
Li	55	ICHQ3D
Ti	200	Toxicology information from literature
Al	1300	Toxicology information from literature

Elemental Screening

Boehringer Ingelheim

Metals (ppm)#	Representative batches of APISM			Representative Batches of Compound X	
	Lot#1	Lot#2	Lot#3	Batch#1	Batch#2
Fe	Not tested	Not tested	Not tested	1	3.1
Ti	2.8	4.0	2.7	<1	<1
Pd	<1	<1	<1	<1	<1
Li	<1	<1	<1	1.3	1.2
Al	<1	<1	<1	Not tested	Not tested

Risk Assessment and Proposed Control Strategy

Boehringer Ingelheim

- Proposal:
  - In-process testing in API starting material
- Rationale:
  - Fe, Ti, Pd, Li, and Al are used several steps upstream of the final Compound X
  - After they are introduced, there are acidic and basic wash and crystallization steps
    - ➢ Sufficient purge
  - Representative batches of APISM and Compound X were analyzed
    - ➢ The results indicate that these metals do not carry through to the final API

Regulatory Filing Experiences

EI risk assessments submitted in 15+ new filings

- Most filings have received no questions at all → SUCCESS
  - No elemental impurities >30% PDE limit were identified in any of the risk assessments *
  - In cases where drug product testing was performed, the EI levels found in drug product were below the worst-case calculation from individual components

- EI data for excipients from vendor and published literature accepted

- Paper arguments on low risk drug product manufacturing equipment, water, and container closure systems accepted

Regulatory Filing Experiences

Location of EI information in filings

Based on FDA draft guidance: Risk assessment summary should be located in 3.2.P.2 (Pharmaceutical Development), regardless uncertainty persists:
Health Canada Notice: "*The locations where the elemental impurities-related information can be found in Module 3 should be clearly summarized in Module 2.3.P.5: Control of Drug Product of the Quality Overall Summary. The overall risk assessment summary for elemental impurities should be placed in Module 3.2.P.5.6 Justification of Specifications*"

Internal debate on including EI risk assessment in P.2.2, P.2.3, P.5.5. or P.5.6.

Standardization – P.5.5

Regulatory Filing Experiences

"Confirmatory" testing data on drug product

Agency considered the component-based risk assessment acceptable, but requested actual testing data on drug product batches

Interpretation: the agency's intention is to see "confirmatory" results supporting EI risk assessment, not to force routine EI control or testing in drug product

Provided testing data from 1 DP batch which was accepted.

Regulatory Filing Experiences

"Worst-case calculation"

Element	Class	Permitted Daily Exposure (µg/day)	API -1 (µg/g)	API-2 (µg/g)	API -3 (µg/g)	Excipient (µg/g)	Total EI (µg/day)*	%PDE
Cadmium (Cd)	1	2	0.1	0.1	0.1	2	0.69	34.5
Lead (Pb)	1	5	0.1	0.1	0.1	2	0.69	13.8
Arsenic (As)	1	15	0.1	0.1	1	2	1.64	10.9
Mercury (Hg)	1	3	0.1	0.1	0.1	2	0.69	23.0
Cobalt (Co)	2A	5	0.1	0.1	1	2	1.64	32.7
Vanadium (V)	2A	10	0.1	0.1	1	2	1.64	16.4
Nickel (Ni)	2A	20	0.1	0.1	2	2	2.69	13.4
Lithium (Li)	3	250	5	5	10	2	31.90	12.8
Antimony (Sb)	3	90	0.1	0.1	10	2	11.10	12.3
Copper (Cu)	3	300	0.1	0.1	10	2	11.10	3.7
Palladium (Pd)	2B	10	Not Tested	Not Tested	0.1	Not Tested	0.11	1.1

- LOQ's were used as worst-case values for calculating EI levels in components
- Poor testing sensitivity in excipient led to total calculated EI > 30% PDE
- "worst-case" argument provided and accepted

- **< LOQ results can be treated as 0 in accordance with Appendix 4 (Tabe A4.8) of ICH Q3D**

Analytical Testing Experiences

Global testing to meet ICH Q3D requirements for marketed products

- ~ 350 APIs and drug products , ~ 1000 batches, ~ 50 unique excipients

Internal Feedback

- A lot of work but minimum technical issues
  - Full digestion or exhaustive digestion were employed
  - Method validation / spike and recovery meet typical requirements
  - Inter-laboratory comparison not performed but no issue reported
- The supplier EI data for most excipients held up to internal testing
- EI risk in excipients is **low**

STIMULI TO THE REVISION PROCESS

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Technical Guidance for the Preparation and Analysis of Pharmaceutical Materials for Compliance with Elemental Impurities—Limits ⟨232⟩

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)[a]

ABSTRACT

This *Stimuli* article provides a general analytical guideline in sufficient detail to assist analytical laboratories engaged in elemental impurity analyses of drug products, drug substances, and excipients per Elemental Impurities—Limits ⟨232⟩ and *Elemental Impurities—Procedures* ⟨233⟩. The objective is to promote discussion of the inclusion of a general information chapter, similar to ⟨*233*⟩, to assist stakeholders with overcoming technical challenges of elemental impurity analyses.

INTRODUCTION

The control of elemental impurities (EIs) in drug products is demonstrated through risk assessment of all contributing sources, which includes drug substance, excipients, container–closure, and production equipment. The analysis of representative source materials and/or final drug products to demonstrate control of EIs is generally required to support a robust risk assessment (*1*,*2*).

The objective of this *Stimuli* article is to provide a general analytical guideline in sufficient detail to assist analytical laboratories engaged in EI analyses. The technical guidance provided in this article may be appropriate content for a general information chapter in *USP*.

BACKGROUND

This *Stimuli* article is written specifically for those with a high-level working knowledge of atomic spectrometric analyses, which includes inductively coupled plasma (ICP) mass spectrometry (MS), optical emission spectroscopy (OES), and microwave digestion. Particular emphasis is placed on applications of ICP-MS.

SMALL MOLECULE DRUG SUBSTANCE ANALYSIS

Small molecule drug substances (APIs) are considered to be at high risk for EI contamination. This is due to application of metallic catalysts during synthesis, corrosive or high temperature reaction mixtures, and/or contact with metallic surfaces during processing or particle size reduction (milling, high-shear blending). In some circumstances, the ICH Q3D 30% control threshold for 10 g/day dosing is applied to small molecule drug substance analyses. Throughout this article, 10-g dosing will be applied to illustrate analytical challenges. This is not to imply that option 1 dosing is required for EI compliance testing (*2*).

Generally, the Class 1, 2A, and 2B (as included in the process) EI concentrations are measured for oral dosage drug substances (arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), cobalt (Co), nickel (Ni), and vanadium (V)). The Class 1, 2A, and 2B (as included in the process) EIs as well as Class 3 elements copper, lithium, and antimony are measured for parenteral dose drug substances. For drug products administered via inhalation, the Class 3 elements barium, molybdenum, tin, and chromium are included to the elements to be included for a parenteral drug product (*2*).

Although drug substances are often digested with a strong acid to prepare aqueous sample solutions for EI analysis, small molecule drug substances are somewhat unique in that they lend themselves well to direct dissolution in organic solvents for ICP-based analyses.

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