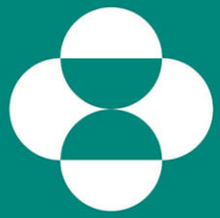
ICH Q3D RISK ASSESSMENT: REGULATORY SUCCESS AND STANDARDIZED METHODOLOGY FOR NEW FILINGS

WILLIAM STEVENS- MERCK & CO., INC.



MERCK

INVENTING FOR LIFE

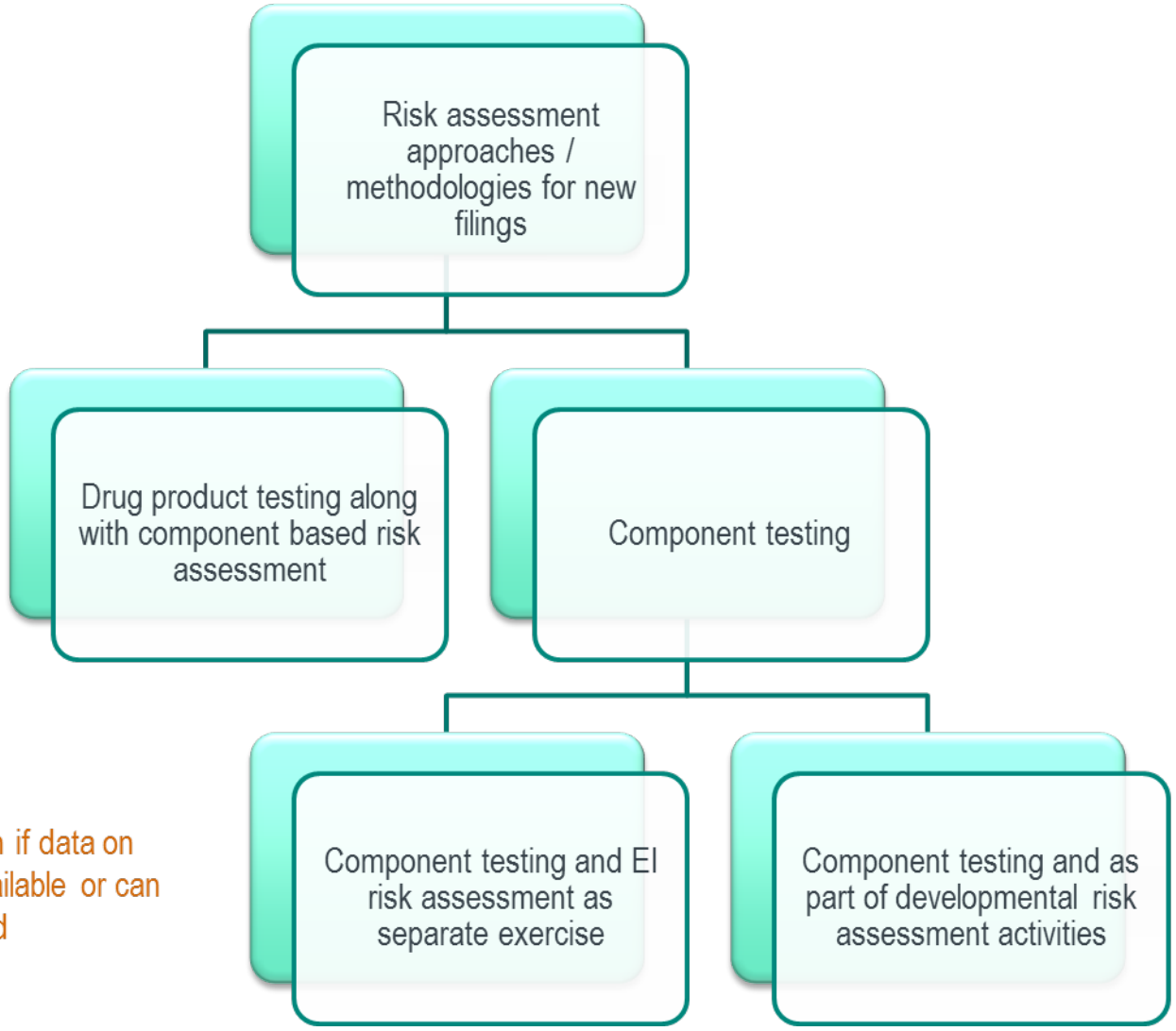
02 November 2017

PQRI/USP Elemental Impurities Workshop

Outline

- Review of Risk Assessment Approaches
- Standardized approach
  - Implementation, training, rollout, learning how to conduct assessments
- How much information included in filings?
- Cases studies and regulatory feedback
  - Combination Product
  - Sterile Liquid
- Testing- Analytical Considerations
  - Challenges of testing product
- Data Collection Experiences
- Food for Thought

Risk Assessment Approaches



Generally fastest approach

Only fast approach if data on components is available or can readily be retrieved

Timeline dictated by developmental timelines / activities

Approach 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
  - Appropriate risk evaluation on intentionally added impurities was possible
- Vendor information for Excipients available

Approach 2: EI Risk Assessment for injectable large molecule (Option 2b)

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

Approach 3: Incorporation of Elemental impurities into developmental risk assessment

Approach:

- Incorporation of EI as Critical Quality Attribute (CQA) into existing developmental product risk assessment
- Use of existing risk assessment process for manufacturing and raw materials

Example Inclusion of EI as CQA in raw materials risk assessment

Initial risk assessment

CQA \ Components	Drug Substance	Excipient 1	Excipient 2	Excipient 3	Excipient 4
Assay	•	•	○	○	
Content Uniformity	○	○	○	○	○
Impurities and Degradation Products	•	○	○	○	○
Appearance/Elegance	○	○	○	○	○
Dissolution/Disintegration			○	○	○
Elemental Impurities	○	•	○	•	○

Final risk assessment

CQA \ Components	Drug substance	Excipient 1	Excipient 2	Excipient 3	Excipient 4
Assay	○	○	○	○	
Content Uniformity	○	○	○	○	○
Impurities and Degradation Products	○	○	○	○	○
Appearance/Elegance	○	○	○	○	○
Dissolution/Disintegration			○	○	○
Elemental Impurities	○	○	○	○	○

Legend

	No impact to CQA
○	Suspected / Confirmed impact to CQA. Existing Controls Adequate to meet CQA
•	Suspected / Confirmed impact to CQA. Existing controls or understanding not adequate to meet CQA

Approach 3: Incorporation of Elemental Impurities into Manufacturing Risk Assessment

Pros	Cons
Streamlined procedure →Time savings	Difficult to score Risk Priority Number (RPN) for Elemental Impurities
One workflow and methodology for all developmental quality risk assessments	Developmental risk assessment methodologies are not necessarily aligned across developmental areas
EI risk assessment fits into the developmental timeline as part of site transfer activities to supply site	EI risk does not evolve during development unless additional data becomes available or additional controls are needed

Internal feedback

-EI should NOT be considered a CQA to be assessed with the product manufacturing process, rather - best conducted as a separate risk assessment

-unique topic, assemble specialists for reviews

-since standard scoring did not readily translate to elementals, separate knowledge has evolved

Rollout of Standardized Approach

SOP based (GMP) --→ one approach

- Allows some flexibility for Development
- Links to Commercial Operations

- Provides
  - Clear strategy for conducting assessments through workflows
  - Team Structure
  - Defined set of tools for scoring risks
  - Training
- Additional Benefits of the standard approach
  - Data for New filings is standardized across programs
  - Implementation of ICH Q3D awareness and simplified
  - Efficiency- access to SMEs, method development requirements and routine scheduling

Risk Assessments for New Filings

Variety of Dosage Forms/ Modes Assessed

- Sterile liquid
- Combination Drug Product
- Oral Solid
- Small molecule
- Large Molecule

Regulatory Feedback

- ICHQ3D risk assessments completed for approximately 10 New Filings
- Most filings have received no questions at all → SUCCESS

- Initial questions regarding location of information in filing

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 CMC comment:
Debatable to be included in P.2.2, P.2.3./ P.5.5. or P.5.6.
Needs standardization

- One regulatory request to provide additional confirmation that the full risk assessment was completed per requirements for all impurities. Response with statement describing the extent of the assessment and a conclusion statement was accepted.

Learnings from individual drug product ICHQ3 assessments

Assessment 1: Sterile Liquid DP

Water evaluation- prospective testing of processed water needed. Data may not be available from initial water source depending on local region.

Assessment 2: Tablet DP

Contains process intermediate and requires evaluation of solvents

-consider levels used (excess)

-consider specific vendor and process used to manufacture the solvent

Assessment 3: Combination DP

Mix of new and existing drugs, legacy data

complication of obtaining historical elementals data (if old and commercial- adds complexity)

potential risk/ concern to existing product (especially in combination)

consider generating data early, mitigate risk

Very common excipient, however, bulk of volume used primarily ex-Pharma.

- elemental data not available from vendor or available databases
- prospective analysis was needed

Elemental Data - Testing

Analytical Testing to date

Global Testing,

Approximately 200 API, 3 batches each

40 unique excipients tested

Internal Feedback-

'In general, the supplier information for many excipients was very convincing' and held up to testing.

Relative Risk for excipients assessed thus far is low

Elemental Data - Collection from vendors/ suppliers

Activity: Elemental data for approximately 1100 excipients collected

Key challenges: of collecting data from vendors/suppliers

Obtaining correct contact information for the vendor/supplier to provide elementals information

Responsiveness

Questionnaires, data incomplete or incorrect

LOD levels from vendors can vary; this may impact the calculation of levels in an excipient

Tips:

Address vendors with clear questions to provide the required data first time, this will aid with potential language differences

Align with site quality to understand vendors in and out of scope

Food for Thought

Are there any experiences with ophthalmic or other dosage forms in USP <1059>?

Will future guidance contain rules for handling certain components known to be low risk?

- -e.g., rules for solvents manufactured by a certain process (condensation, with no catalysis).

Public and Database information for Elemental Impurities Risk Assessment is being generated

- -this sufficient for risk assessment ?
- -will low risk excipients be considered exempt from assessment?

Will certain manufacturing processes become considered low risk ‘across the board’, for example, tablet compression?

Acknowledgements

Andre Hermans

Terri Hennessy

Max Li

Xiaoyi Gong

Phyllis Walsh

Frans Maris

David Goldfarb

Peter Colvin

Jenny Drake

John Carboy

Angela Kuhn

THANK YOU

MERCK