ICH Q3D Guideline
Impact on the Users: Perspective of a Finished Product Manufacturer
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Outline

• Implications for a Global Company
• Infrastructure and Business Processes
• An Example
• Meeting Regulatory Expectations
• Complying with the Pharmacopoeias
• Regulatory Uncertainties (‘Grey Areas’)
• Summary
• Conclusions
• Acknowledgements
ICH Q3D Elemental Impurities Timelines

Implementation Timelines

**June 2016**
- FDA implement ICH Q3D for New Products

**June 2016**
- EMA regions implement ICH Q3D for New Products

**January 2018**
- FDA will implement ICH Q3D for Existing Products
- USP <232>, <233> & <2232> effective
- USP<231> removed from individual monographs

**January 2018**
- Ph. Eur 5.20 effective
- Ph. Eur 2.4.8 removed from individual monographs

**April 2017**
- JP to implement Q3D for New Products

**December 2017**
- EMA regions implement ICH Q3D for Existing Products (EMA/CHMP/QWP/109127/2015)

**Q2 2017**
- Risk Assessments for Existing Product at GSK Sites

**2021**
- JP to implement Q3D Existing Products in JP18

**JP will retain** their Heavy Metal test

**GSK is taking a proactive approach to implementation to ensure there is a buffer before the deadline:**

- To allow time to develop control strategies (if required)
- Address unforeseen issues/delays
GSK is a Large Company – Pharmaceuticals, Vaccines and Consumer Health

- Global – Supplying both ICH and Non-ICH Regions
- Need to evaluate large number of existing products
  - > 1000!

- Solid Oral Dosage Forms - 70%
- Dermatological products - 20%
- Inhalation products - 5%
- Parenteral products - 5%

- GSK Manufacturing Sites in-scope = 59
  - Includes 6 API sites
- And lots of CMO’s
Infrastructure

• Initially established a multi-disciplinary team to consider implications of ICH Q3D across the whole business
  ➢ Representatives from Pharma, Consumer Healthcare and Biopharm organisations
  ➢ Included analytical, pharmaceutical, CMC regulatory, quality and engineering disciplines

• Infrastructure created and business processes developed to support implementation
  ➢ Covers both new and existing products
  ➢ Common process and tools being used across R&D and Manufacturing
**Infrastructure**

**R & D Core Team**
- Risk assessment process has been incorporated into pharmaceutical development
- Linking to CMC project teams to train and provide guidance on generating the risk assessment during the path to submission,
- Hand off to manufacturing Organization

**Manufacturing Central Team**
- Coordinating generation of risk assessments for existing products
- For products manufactured by GSK Sites
- For products manufactured by CMOs

**CMC Regulatory**
- Considering regulatory expectations for Q3D in ICH and non-ICH regions
- Requirements still evolving and not always aligned
- Provide advice on requirements for global submissions on new products and variations to existing products

**Tools developed to support the risk assessment process, including:**
- Product Risk Assessment Process Guide
- Product Assessment Spreadsheet
- Product Assessment Documentation Template

**Training**
- Internal training modules developed
- Extensive training conducted for personnel at both R&D and Manufacturing sites

**Analytical Capability**
- ICP-MS introduced at a number of GSK sites
- Other analytical capability being introduced e.g. Atomic Absorption
- Use of several contract laboratories
An Example
OSD Product – Daily Dose >10g; 2 main ingredients are “Natural”

- 2 Main Natural Ingredients
  1 Mined, 1 Plant

- Review Existing Limits vs PDE

- Theoretically, there could be an Issue

- Screen Product

- 2 x Class 1 EIs
  CT < EI < PDE
  • Main Natural Ingredients
    90% of formulation
  • Other ingredients unlikely to be major source of EI

- Control Strategy
  - Mined Material:
    Every Batch Tested by Supplier to a defined Specification
  - Plant Material:
    Depending on Results:
    • No Testing
    • Periodic testing
    • Test Every Batch

- Finished product testing is not required
  - Control is achieved by testing highest risk input materials to limits
  - Risk based decisions are a key driver of ICH Q3D
Meeting Regulatory Expectations

**US**
- **FDA Guidance on Elemental Impurities** (Draft, June 2016)
  - Risk Assessment
    - Summary of the risk assessment should be provided in NDA/ANDA
    - Suggests P.2 Section as location
  - Analytical Procedures
    - Recommends procedures described in USP <233> (ICP-AES and ICP-MS)
    - Analytical procedures for risk assessments should be validated,
      - validation criteria “can depend on the analytical procedures intended purpose”

**Canada**
- **Health Canada Recommendations for implementation of ICH** (July 2016)
  - Risk Assessment
    - Requires summary of risk assessment to be included in Module 2.3.P.5 Control of Drug Product in QOS
    - Overall risk assessment summary should be placed in Module 3.2.P.5.6 Justification of Specifications
    - Detailed risk assessments and data should be documented and available upon regulatory request (e.g. at inspection)

**EU**
- **Implementation strategy of ICH Q3D guideline** (Draft, July 2016)
  - Risk Assessment
    - Summary of the risk assessment is expected in the MMA,
  - Calculation Options
    - Component Approach preferred
    - Application of Drug Product Approach needs to be supported by risk assessment
    - For catalyst used in last step of synthesis of drug substance
    - Specification normally expected

**EU**
- **Implementation of ICH Q3D in the Certification Procedure** (August 2016)
  - Provides high level guidance on expectations for analytical methods used for screening purposes and for control
  - Provides an example of how to present the Risk Management Summary (in tabular format)
  - Clarification regarding the Heavy Metals Test as per Ph. Eur. General Chapter 2.4.8 given

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Complying with the Pharmacopoeias

USP vs. Ph Eur vs. JP Policy on elemental impurities
• Not completely aligned

Analytical Methodology
• USP <233> describes 2 procedures (ICP-AES and ICP-MS)
• Alternative procedures can be used if meet validation requirements and then considered ‘equivalent’ to ICP procedures
• ICP not necessarily ‘best’ method for all applications - Industry needs flexibility

Removal of Heavy Metals Test
• Being handled differently across regions
• Need to consider both ICH and non-ICH regions
Regulatory Uncertainties (‘Grey Areas’)

Component Approach vs. Drug Product Assessment
- Q3D allows different options - Companies need flexibility

Analytical Methodology
- Validation requirements for screening and control methods
- Applicant should be able to justify methodology for application

Application of the Control Threshold Concept
- A pragmatic approach is needed

Risk Assessment
- Summary of Risk Assessment for submission
  - Level of detail, format and location in CTD
- Full Risk Assessment
  - Level of detail, supporting data/information and how to document
  - Should be documented and available upon regulatory request (e.g. at inspection)
Summary

- A significant infrastructure has been created by GSK to manage and maintain ICH Q3D globally

- Summary of Risk Assessment
  - Greater clarity on regulatory expectations on level of detail and location in CTD needed
  - Needs to be aligned across ICH

- A pragmatic approach to application of the control threshold concept is needed

- Need to understand regulatory implications of the deletion of the reference to the heavy metals test
  - <231> in individual monographs of the USP
  - (2.4.8) in individual monographs of the Ph. Eur.

- Progression of ICH harmonized pharmacopoeial general chapter on analytical methodology for EIs with greater sense of urgency would be welcomed
Conclusion

• The implementation of ICH Q3D provides an opportunity to put into practice a **risk and science based approach to the control of elemental impurities**

• **Some divergence in regulatory expectations is already emerging**
  - Need to continue dialogue to minimize opportunities for further divergence

• The observed elemental impurity content of most products is significantly below the control threshold (i.e. <30% PDE) for all elements, with few exceptions
  - Perceived risk is higher than actual risk of EI contamination in drug products
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk (ICH Q9, Principle 2)

**Greatest challenge is carrying out a risk assessment that meets regulatory expectations, rather than complying with Q3D!**
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Thank you for your attention

Any Questions?