ELEMENTAL IMPURITIES RISK ASSESSMENT

Regulatory context

The issue of ICH Q3D “Guidelines for Elemental Impurities” on December 2014 and its following updates demanded the pharmaceutical companies to prove the compliance for existing Marketed Drug Products and for new Drug Products (DP) which requires new marketing authorization approval.

From the entry into force of EMA and FDA guidelines on December 2017 and January 2018 respectively, the compliance with ICH Q3D requirements for both commercialized and new DPs is required. The Marketing Authorization Holder (MAH) is responsible for the ICH Q3D product compliance.

vqms

Elemental Impurities
Risk Assessment

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ELEMENTAL IMPURITIES RISK ASSESSMENT

PTM approach & RA execution

The Elemental Impurities (EI) Risk Assessment (RA) aims to guarantee the compliance of the pharmaceutical products to the Permitted Daily Exposure (PDE) limits established for the 24 elements considered in the ICH Q3D and to define an adequate control strategy, if necessary.

Risk Assessment execution consists of several activities which can be customized considering the client needs: the way for implementation can be product specific or by means of platform to optimize the data gathering.

ELEMENTAL IMPURITIES RISK ASSESSMENT

Steps

DATA COLLECTION & EVALUATION

1 DEFINITION OF THE APPROACH FOR EI EVALUATION

The EI potential contribution to the DP is evaluated for each component. During this phase, PDE limits are set.

2 POTENTIAL SOURCES OF EI IDENTIFICATION

The identification of potential sources of EI in the final DP, allows to focus the RA on specific components by means of a Preliminary Risk Analysis (PRA) and a component mapping (base on IDEF0 techniques).

3 ASSESSMENT EXECUTION

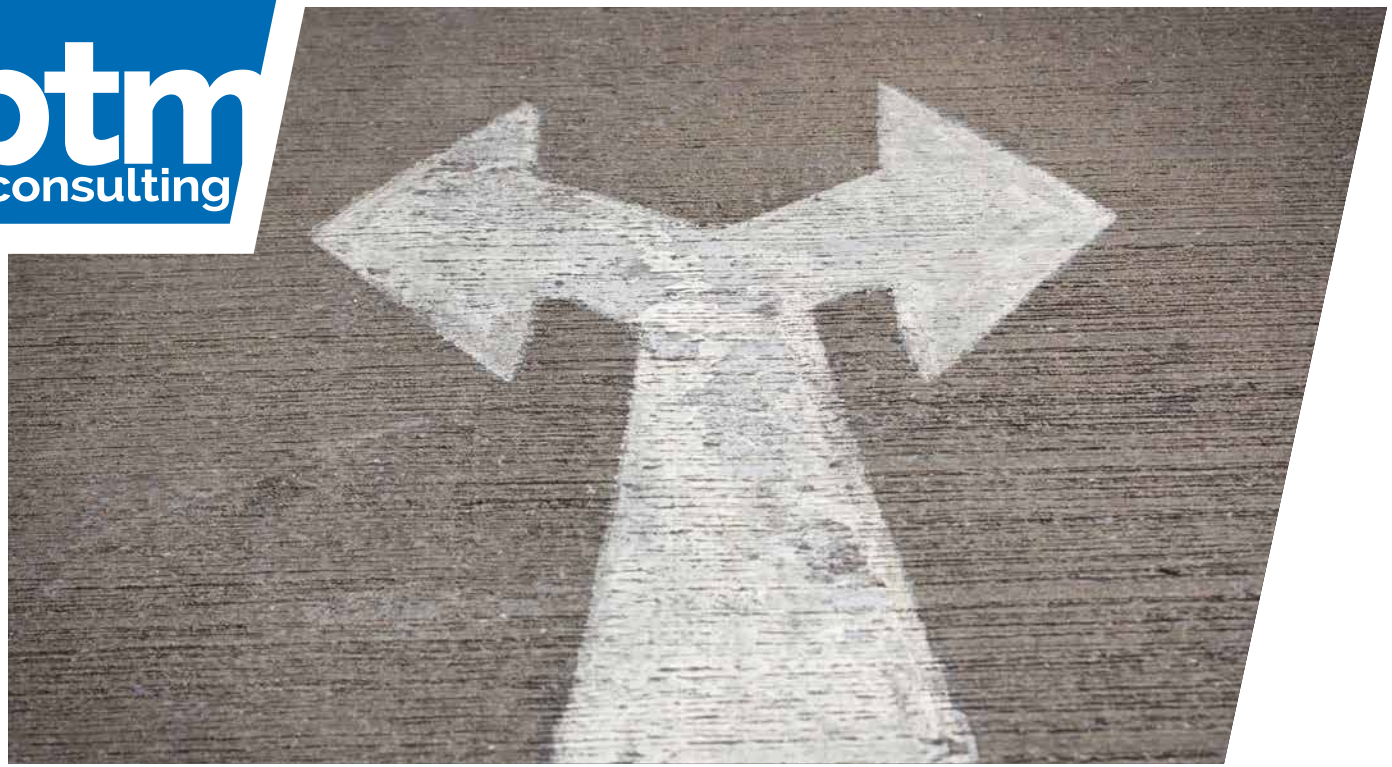
All the components are evaluated as potential cause of EI contamination in terms of severity and probability of contamination by means of the risk analysis tools FMEA.

4 COMPARISON OF EI LEVEL WITH THE ICH Q3D ESTABLISHED PDE

In this step, a comparison of EI levels with the ICH Q3D established PDE for the specific route of administration is carried out to understand if control measures are required in case of EI content higher than the ICH Q3D PDE control threshold.

5 RISK ASSESSMENT FORMALIZATION

The outcomes of the Risk Assessment (RA) activity are formalized in a specific report.



WHICH APPROACH?
Component VS drug product

The "**Component Approach**" allows to estimate the EI content in the finished product starting from each component contribution identified from ICH Q3D (API, excipient, equipment, utilities, CCS). This approach:

- ✓ Is recommended in case of missing or limited knowledge of EI levels in the finished product;
- ✓ Is the Regulatory Authorities "favourite" approach.

The "**Drug Product Approach**" allows, using the EI data gathered on the finished product, to identify the EI content. This approach:

- ✓ Requires the availability of representative batches to perform the analysis (from 3 to 6 batches) and adequate analytical methods;
- ✓ Can require additional data if there are excipients from mineral origin and the evaluation of CCS contribution.

ELEMENTAL IMPURITIES
RISK ASSESSMENT
Approach Description

The ICH Q3D approaches are based on the Quality Risk Management (ICH Q9) principles and, according to the information available from the Marketing Authorization Holder (MAH), allow choosing the better approach between those proposed by the guideline or the combination of approaches in order to demonstrate the product safety through the EI level control in the final DP.

Combined approaches are allowed by the ICH Q3D as complementary.

ELEMENTAL IMPURITIES RISK ASSESSMENT

Assessment results and Support for Control Strategy definition

The assessment completion allows to verify the compliance of the DP towards ICH Q3D limits (PDE threshold limits and/or PDE limits) and to understand if it is necessary to implement a specific Control Strategy in order to mitigate the EI levels in case the ICH Q3D limits were exceeded.

In case of new DP, the assessment results are generally compared with the EI data gathered by ICP-MS on at least three representative DP batches to present a supportive confirmation of the compliance to ICH Q3D requirements and of the safety of the administration of the assessed DP.