

## Risk assessment study of potential elemental impurities in montelukast film coated tablets

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### Introduction

The elements listed in the ICH guideline Q3D are classified into three main categories (1, 2A, 2B and 3) according to their toxicity (PDE - established permitted daily exposure), likelihood of occurrence in the final drug product and their toxicity considering the particular route of administration (EMA ICH Q3D Elemental Impurities, 2019). Development of risk-based control strategy for potential elemental impurities (EIs) assessment in drug development and manufacturing is challenging for the pharmaceutical industry since there are multiple potential sources of EIs contamination (Jenke et al., 2015; Li et al., 2015; Rowe et al., 2009). In general, the EIs risk assessment approach, as an integral part of the overall drug product control strategy, involves four steps: 1) identification of known and potential sources of EIs, 2) evaluation of observed or predicted levels of EIs in drug product, 3) comparison of evaluated levels of EIs with PDE values and 4) definition of the control strategy. The drug product risk assessment study is also focused on impurity levels determination and assessing the levels of EIs in relation to the established PDEs (Ph. Eur. 10th Edition, 2019; Teasdale et al., 2015).

The global impact of the COVID-19 pandemic has urged the pharmaceutical industry to provide a worldwide supply of drugs that comply with legislation and international safety standards. One of the drugs that gained attention in COVID-19 treatment management is montelukast (Khan et al., 2022).

As acknowledged, montelukast is a selective cysteinyl leukotriene 1 (CysLT1) receptor antagonists (LTRA) with bronchodilator effect. Montelukast 10 mg

film-coated tablets are indicated in the treatment of mild to moderate persistent asthma and can be added to another patient's existing treatment regimen for asthma (Wermuth et al., 2021).

The aim of this research is to conduct detailed EIs risk assessment study of Montelukast 10 mg film coated tablets in accordance with the ICH guideline Q3D on EIs.

### Materials and methods

The method used for determination of elements (Cd, Pb, As, Hg, Co, V and Ni) from class 1 and class 2A, was inductively coupled plasma-mass spectrometry (ICP-MS) system (Agilent 7500 Series). The analyses were carried out on montelukast sodium (active pharmaceutical ingredient-API), finished dosage form (Montelukast 10 mg film coated tablets) and placebo dosage form. Each film-coated tablet contains montelukast sodium 10.4 mg equivalent to 10 mg montelukast. Moreover, data and specific evidences were reviewed from three commercial batches of the montelukast 10 mg film coated tablets manufactured in three successive years.

The manufacturing equipment integrated in drug production process consists exclusively of stainless steel (mainly 316L grade steel). [Internal data of Manufacturer).

### Results and discussion

For this risk assessment study, the potential contribution from the API, excipients, manufacturing equipment, container closure system and used utilities are

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considered in order to determine the overall contribution of EIs to the finished drug product. Thus, taking into consideration the manufacturing of Montelukast 10 mg film coated tablets and life cycle management, there are several broad categories of potential sources of elemental impurities. The quality procedures that ensure control of EIs include: equipment design and installation qualification, compatibility studies for the production process, equipment cleaning verification and validation, and visual inspection/line clearance procedures.

The control of the manufacturing equipment is done according to the standard operating procedures and manuals, and the risk assessment is represented with a risk factor number to identify the critical steps in which EIs could be present in the finished drug product.

The PDE values of potential elemental impurities have been calculated for the oral routes of administration. These PDE values were established following element-specific health-based risk assessments, which are available in the ICH Q3D guideline. Since the PDE reflects only the total exposure of the drug product, for the objectives of this study, PDE values were converted into concentrations as a tool in evaluating elemental impurities in the drug product of interest. The calculations are based on the following assumptions: a) the maximum concentration level (MCL) of particular elemental impurity in 1g of the product is calculated using the maximum daily dose of product, b) the control threshold (CT) is established as 30% of the MCL value.

The obtained results show that concentration levels of all examined elements are well below the CT value which is defined as 30% of the maximum concentration level of particular EI in the drug products. Based on ICH Q3D guideline, the results for EIs Class 1 and Class 2A showed that EI levels are well below the ICH Option 1 oral and parenteral limits.

If any changes are introduced to the manufacturing process or components of the drug product across the life-cycle, the risk assessment should be reviewed and existing controls may need to be re-evaluated.

## Conclusion

The outcome of this risk assessment study of potential EIs in Montelukast 10 mg film coated tablets is that no additional controls are required, since the current control strategy developed for the raw materials, finished dosage form and manufacturing process are sufficient to guarantee that the levels of EIs are consistently below their PDE values. It also confirmed that the current quality system has been designed to prevent, minimize and control any potential EIs contribution from the manufacturing equipment and utilities.

Additional considerations of the container closure system ascertain that it meets specific requirements regarding the EIs. Furthermore, it is recognized that the probability of elemental leaching into this solid dosage forms does not require additional step in the risk assessment.

Overall conclusions based on the conducted risk assessment study, as well as testing results are the following: the concentration of EIs is controlled within the acceptable limits and there is no risk associated to EIs for patients taking Montelukast 10 mg film coated tablets according to patient information leaflet.

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