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

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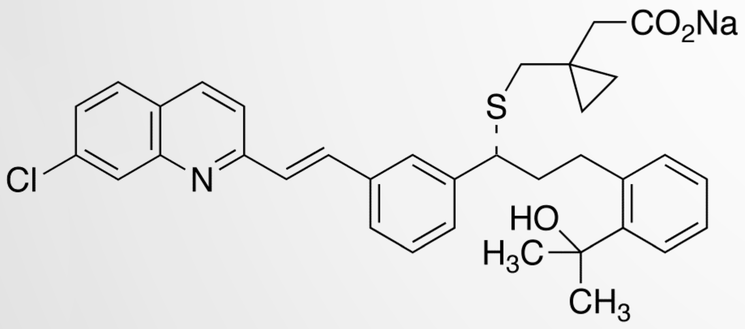
Introduction

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, D.R., et al., 2015; Li, G., et al., 2015; Rowe, R.C., 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 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, A.R., et al., 2022].



Montelukast sodium

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, H., 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 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. Moreover, data and specific evidences were reviewed from three commercial batches of the montelukast 10 mg film coated tablets manufactured in three successive years and the manufacturing equipment integrated in drug production process consists exclusively of stainless steel (mainly 316L grade steel).

Results and discussion

For this risk assessment study, the potential contribution from the API, excipients, manufacturing equipment, container closure system and used utilities are considered in order to determine the overall contribution of EIs to the finished drug product.

		Element Concentration (µg/g)						
		Cd	Pb	As	Hg	Co	V	Ni
Product batch number	Batch No.1	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
	Batch No.2	< 0.0005	< 0.001	< 0.0005	< 0.001	0.0016	< 0.001	< 0.005
	Batch No.3	< 0.0005	< 0.001	< 0.0005	< 0.001	0.0028	< 0.001	< 0.005
Max result		< 0.0005	< 0.001	< 0.0005	< 0.001	0.0028	< 0.001	< 0.005
Control threshold		7.211	7.211	21.635	43.269	72.116	144.231	288.461

Table 1. Evaluation of elemental impurities in drug product

The obtained results (Table 1.) 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.

Conclusion

The outcome of this risk assessment study 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 and the 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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Internal data of Manufacturer (available if necessary): statements received from suppliers, manufacturing instructions, packaging instructions, specifications, results of analysis.

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