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Comparative Risk Assessment Study of Elemental Impurities in Montelukast Chewable Tablets and Film-coated Tablets

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Abstract

It is well documented that elemental impurities (EIs) are critical in the field of pharmaceutical development since they could affect the quality, efficacy and safety of the finished dosage form (FDF). The responsibility of pharmaceutical manufacturers is to demonstrate via assessment approach, risk-based control strategy and/or required data analysis that the FDFs are compliant with ICH Q3D (R2). The aim of this research is to conduct a comprehensive comparative EIs risk assessment study of three different Montelukast dosage forms produced as chewable tablets (4 mg and 5 mg) and film-coated tablets 10 mg. The inductively coupled plasma-mass spectrometry (ICP-MS) system was used for the determination of EIs in samples of Montelukast sodium as the active pharmaceutical ingredient (API), placebos for all FDFs, and FDFs. Moreover, the analyses were also conducted on three batches from all three studied FDFs. Based on ICH Q3D (R2) guidelines, the tested products for EIs Class 1 and Class 2A showed that EIs levels in the API and placebos are well below the ICH Option 1 oral and parenteral limits. For the examined batches of each FDF strength (total of 9), none of the EI exceeds their concentration limits.

Key words: elemental impurities, Montelukast, risk assessment, ICH Q3D (R2), comparative study

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Introduction

Elemental impurities (EIs) in the finished dosage form (FDF) originate from versatile potential sources. Actually, EIs can be: 1) natively present in the entity of pharmaceutical interest; 2) added purposely as residual catalysts during synthesis processes; 3) the result of interaction between contact surfaces of used industrial equipment in the FDF production phase; 4) from the utilities in the pharmaceutical industry (e.g. steam, heating and air conditioning systems, water and other utilities), and 5) from primary packaging material and/or closure system. The interest in EIs is also because, apart from having an impact on the quality and efficiency of the FDF, they present potential health risk factors (1, 2). Hence, when assessing the risk of EIs in the FDF, the ICH Q3D (R2) identifies three steps: 1) toxicity evaluation of potential EIs; 2) establishing a Permitted Daily Exposure (PDE) for each element of toxicological interest and 3) an approach based on risk assessment in the control of EIs in FDF. In more detail, ICH Q3 places the focus on an extensive list of 24 chemical elements divided into three main classes (Class 1, Class 2: 2A and 2B, and Class 3) based on their toxicity, probability of occurrence, and the PDE for each EI (1). Classification is intended to focus the interest on elements with high toxicity and those that have a real possibility of being present in the FDFs. In the case of the presence of elements other than those in the above classes, they are examined and evaluated according to other guidelines and regulatory requirements (1). As concerns the other elements, depending on whether or not an allowable daily intake has been established as a result of their low toxicity or due to different regulatory requirements in some regions, in general, they have not been considered in the test element classes (1, 3, 4). Some of those chemical elements are Al, B, Ca, Fe, K, Mg, Mn, Na, W, and Zn. (1).

From a pharmaceutical point of view, it is evident that the EIs-profile of each diverse type of FDF differs, as well as the PDE of each EI, which is a specific challenge and must be defined according to the administration route. As concerns the approach of the industry regarding the ICH Q3D (R2) application, it is desirable to develop and implement a systematic risk assessment and control strategy. Once a control strategy is determined, it should be supported with validated methods.

Currently, to the best of our knowledge, published scientific data on EIs and risk assessment studies of EIs in Montelukast FDFs are still lacking (5), and factually, specific impurities have been dominantly concerned (6, 7). Hereby, this research is based on the ICH Q3D (R2) guidelines for EIs in FDF along with its practical implementation and a risk assessment study of potential EIs in three different formulations of Montelukast FDF produced as chewable tablets (4 mg and 5 mg) and film-coated tablets (10 mg). For the purpose of this research, the inductively coupled plasma-mass spectrometry (ICP-MS) system was utilised to perform EIs determination in samples of Montelukast sodium as API, placebos for all different types of FDFs, and FDFs. To achieve this goal, a reliable, consistent, and accurate analytical method is used that has been validated for the determination of a broad range of elements in various samples (8).

In addition, an analysis of seven (Cd, Pb, As, Hg, Co, V, and Ni) EIs in three batches from all three studied types of FDFs (a total of 9) is presented. Moreover, the levels of designated EIs of interest in relation to the established PDEs for each impurity according to the administration route were evaluated.

We also present a discussion considering the potential risk of elemental contamination, taking into account: the origin of starting materials and raw materials, inter-surface contact of production equipment and pharmaceutical materials, industrial utilities, packaging materials, and containers.

The study is also used to evaluate the risk assessment pattern, as well the efficacy of an ICH Q3D (R2) compliance-designed strategy tailored to the studied FDFs.

Materials and methods

The maximum concentration level (MCL) of impurities from a certain element in one gram (g) of a product is calculated in relation to the maximum daily intake (MDI); the control limit value – Control threshold (CT) represents 30% of the MCL.

The inductively coupled plasma-mass spectrometry (ICP-MS) system (Agilent 7500cx Series, California, USA) equipped with a glass concentric nebulizer was used to determine EIs (Cd, Pb, As, Hg, Co, V, and Ni) in the samples of Montelukast sodium (active pharmaceutical ingredient-API, Table 1), placebos for all FDFs, and three commercial batches of all three different Montelukast FDFs (Montelukast chewable tablets 4 mg, Montelukast chewable tablets 5 mg, and Montelukast film-coated tablets 10 mg). The EIs analyses were conducted in a contract quality control (Unilab, Campus 2, Shtip, Republic of North Macedonia) MKC EN ISO/IEC 17025:2018 accredited laboratory. The digestion of the samples was performed in the Microwave Accelerated Reaction System, Model MARS5 (CEM Corporation, Matthews, NC, USA) with a mixture of HNO3 (69.0 %, w/w, trace select, Sigma Aldrich, Munich, Germany) and H2O2 (69.0 %, w/w, trace select, Sigma Aldrich, Munich, Germany) in a ratio of 5:2 (8). The microwave-assisted digestion parameters were optimized.

All measurements were performed in either the normal or helium collision tune mode of the instrument. The calibration range and approximate detection limits and quantification limits were acceptable for the intended analysis. The linearity of the validation method for the instrument was with a correlation factor $R > 0.999$. The test of reproducibility from two different analysts showed no significant difference between measurements, and the value of precision through RSDs for none of the analysed elements was less than 10%. The operating conditions used in ICP-MS were previously established, and the full method validation results are published by Balabanova et al. (8).

Results and discussion

Practical implementation of the ICH Q3D (R2) EIs guidelines and compliance of FDP with ICH Q3D (R2) are always challenging for the pharmaceutical industry. This

comparative study is basically focused on assessing the risk factors and the levels of designated EIs of interest in relation to the established Permitted Daily Exposure (PDEs).

Risk assessment strategy

The conducted risk assessment study of potential EIs in all three studied FDFs has identified several points that may represent potential risk factors for the transfer of EIs in the studied FDF, namely:

- potential risk related to the origin of starting materials and raw materials,

- potential risk of inter-surface contact of production equipment and pharmaceutical materials,

- potential risk originating from industrial utilities, and

- potential risk associated with packaging material and containers.

The designed product's risk assessment is focused on assessing the levels of EIs in an FDF in relation to the established PDEs. The information for this risk assessment includes data generated by manufacturers, information supplied by manufacturers of FDF components, and data available in the published literature (10, 11). It has been revealed that the following EIs risk assessment strategy is an integral part of the overall FDF control strategy, and it involves four steps:

1. identification and analysis of known and potential sources of EI,
2. evaluation of observed or predicted levels of EI in the FDF,
3. comparison of evaluated levels of EI with established PDE values, and
4. definition of the control strategy.

The allowed daily intake is calculated for an oral route of FDF administration. These values are set according to specific elemental health-risk assessments that are specified in the ICH Q3D (R2) guide. Since the PDE represents the maximum exposure to the product, in this paper the values are converted into concentrations to calculate the data for the evaluation of EI in the FDF. The data are presented in Table I.

Based on the regulatory requirements (2), along with their significant toxicity in humans and/or relatively high probability of occurrence in the studied montelukast FDFs, as presented in Table I, the elements included in the risk assessment are the elements of class 1 and class 2A. Thus, the elements Cd, Pb, As and Hg from class 1 are selected because of their significant toxicity in humans. They may appear in the used raw materials, for example, in the mined excipients as the colorants present in the formulation for montelukast FDF. On the other hand, the elements Co, Ni, and V (class 2A) have a relatively high probability of occurrence in the FDF (2); thus, the manufacturing equipment, the compressed air during manufacturing, and the packaging material can be their potential sources. Therefore, there is a requirement for risk assessment and control across all potential sources of EIs from class A2.

The PDE (µg/g) of each entity applies to FDF whose maximum daily intake does not exceed 10g, as it is in this case, and that is why the value is divided by a factor of 10.

Table I Permitted concentration limits of EIs in FDF of Montelukast chewable tablets (4 mg and 5 mg) and Montelukast film-coated tablets 10 mg

Tabela I Dozvoljene granice koncentracije EN u FOL Montelukast tablete za žvakanje (4 mg i 5 mg) i Montelukast filmom obložene tablete 10 mg

Element	Class	Oral PDE µg/day	MCL (µg/g)	CT (µg/g)	MCL (µg/g)	CT (µg/g)	MCL (µg/g)	CT (µg/g)
			4 mg tablet		5 mg tablet		10 mg film-coated tablet	
Cd	1	5	20.83	6.249	16.67	5.001	24.04	7.211
Pb	1	5	20.83	6.249	16.67	5.001	24.04	7.211
As	1	15	62.50	18.75	50.00	15.00	72.12	21.635
Hg	1	30	125.00	37.50	100.00	30.00	144.23	43.269
Co	2A	50	208.33	62.499	166.67	50.001	240.39	72.116
V	2A	100	416.67	125.001	333.33	99.999	480.77	144.23
Ni	2A	200	833.33	249.999	666.67	200.01	961.54	288.46

PDE - Permitted Daily Exposure; MCL - maximum concentration level; **CT -** Control threshold

PDE – dozvoljeno dnevno izlaganje; MCL- maksimalni nivo koncentracije; **CT-** kontrolni prag

The calculated PDE of EIs from classes 1 and 2A, for all examined FDFs considering the route of administration, are also shown in Table I. Moreover, a control limit value was calculated concerning the maximum concentration level. Additional amounts of EIs that may come from inter-contact surfaces with production equipment can also be limited in terms of the type of elements that should be included in the comprehensive risk assessment. The approach depends on the manufacturing equipment used in the production process of the PDFs.

Risk assessment of potential EIs in starting and raw materials

The raw materials used for manufacturing of the FDFs were Montelukast sodium by Morepen Laboratories Ltd. (Gurgaon, Haryana India), Mannitol, Sorbitol and Sodium starch glycolate by Roquette Frères (France), Low-substituted hydroxypropyl cellulose, Cellulose microcrystalline and Croscarmellose sodium by JRS PHARMA Gmbh & Co.KG (Germany), Sodium cyclamate by Golden Time Enterprises Limited (Hong Kong, China), Magnesium stearate by Mosselman oleochemicals (Belgium), Lactose monohydrate by Molkerei MEGGLE Wasserburg GmbH & Co. (Germany), Silica, colloidal anhydrous by Cabot Corporation, Boston, Massachusetts, USA, Cherry powder nat. 09192PD flavour by Curt Georgi GmbH & Co. Ltd. (Germany), Pregelatinized starch, Opadry® white 03F28342, Iron Oxide Yellow (E172) and Iron Oxide red (E172) by Colorcon (Europe).

The risk assessment of potential EIs in starting and raw materials was performed in order to compile a representative document for all FDFs series. Upon request, analyses

performed by the materials' manufacturers were provided. Overall, the data obtained for starting and raw materials reveal that elements are rarely added to the target of interest unless they are catalysts or are involved in chemical reactions of synthesis. The results obtained from the manufacturers are below the permitted present level (PPL) in starting and raw materials, and even below the limit of quantification for the used methods of determination, showing that they were produced by using a quality-controlled approach (9, 12). According to these values, if the final mass of the product is known, it is relatively easy to assume the amount of EI in the "ideal" conditions of FDF production.

Risk assessment of EIs in packaging material and industrial containers used for Montelukast FDFs

An assessment of the packaging material (contact packaging) was performed in order to identify whether certain parameters and additional requirements should be followed (11). Since the possibility of transfer of EI in the FDF is insignificant in all three studied FDFs (Montelukast chewable tablets – 4 mg and 5 mg, and Montelukast film-coated tablets 10 mg), there is no justified reason for additional steps in the assessment strategy. Aluminum foil and PA/AI/PVC foil were used as packaging material. The listed materials meet the regulatory requirements (13-17).

The risks associated with the allowable daily intake related to the above-mentioned materials are low and no additional control activity is required. In addition, due to the nature of the FDFs themselves, in this case, chewable tablets and film tablets (solid dosage forms), there is no significant mechanism that would limit the transfer of EIs from the container/packaging material to the FDFs.

Risk assessment of EIs in compressed air

As acknowledged, the HVAC (Heat, Ventilation, and Air-Conditioning) system also plays a major role in ensuring the quality production of pharmaceutical products. Temperature, air humidity and ventilation should be adequate and in no case should they have an impact on the quality of the FDFs during the production process, packaging process, or on industry equipment and machinery operation (18).

Another component used in the production of Montelukast chewable tablets and film-coated tablets is the compressed air, which was the reason for taking it into account during the risk analysis. The installation is fully qualified, and as a preventive measure, flow controls are installed to minimize the risk of failure of the equipment. In addition, the system contains a central pre-filter and a sterile filter (0.2 μm), and additional sterile filters (0.2 μm) at each outlet where the contact of the compressed air with the product is possible. Filters are qualified before placement/installation. Moreover, the air quality is managed to comply with the standards of good manufacturing practice (GMP). Equipment and process qualification, validation and installation, basic equipment controls, routine analysis and monitoring guides further contribute to the air quality used in the manufacturing process; therefore, no specific additional risk assessment is required.

Industrial manufacturing equipment used in the Montelukast-FPDs production process and risk assessment of EIs

The risk assessment affecting the industrial equipment, used during the production process of Montelukast FDFs, is represented by a numerical risk factor (RF) to identify critical steps in which EIs may be present in an FDF. The risk assessment is based on three criteria: "seriousness", "possibility" and "detection". Each criterion is evaluated with risk levels such as level 1 – low risk, level 2 – medium to high risk, and level 3 – high risk (Table II). The seriousness criterion takes into account the class of the material which the equipment is made of, and the "possibility" criterion takes into account the conditions of the production process and the stress, while the "detection" criterion takes into account the possibility of a failure in the production machinery and equipment. The comprehensive assessment ranks the critical risk with 13-27, medium risk with 8-12, and low risk with 1-7 of EIs originating from production equipment. Production equipment can represent a potential source and risk of EIs during production, but in the case of Montelukast chewable tablets (4 mg and 5 mg, and 10 mg film-coated tablets), the production system has shown that it was designed so as to minimize and control the additional possibility of any potential source of impurities.

The production tools and equipment listed in Table II are specifically made of stainless steel (generally 316L steel) which contains a lower content of carbon atoms in the structure than regular steel, minimizing the chance of corrosion or elemental breakdown. Furthermore, during quality assurance in the control of EIs, the following are included: equipment design and installation qualification, equipment compatibility studies during the production process of the specific dosage pharmaceutical form, equipment validation and cleaning validation, visual inspection, and production clearance. In general, compliance with GMP standards, processes, and procedures, overall contributes to a low level of EI.

Analyses were performed on placebo powder and API for all three different FDFs of Montelukast (Table III). Using these concentrations (Table III) taken as absolute values and the individual component percent for the MDI of the product, levels of EIs in the drug product can be determined and compared to the established PDE and MPC (Table IV, V, VI). Calculations presented in Tables IV, V and VI demonstrate that no EIs were detected in the placebo and API individually and altogether exceed their concentration limits.

The obtained results (Table VII) show that the concentration levels of all the examined elements are well below the CT value, which is defined as 30% of the MCL of a particular elemental impurity in the FDFs.

Based on ICH Q3D (R2) guidelines, the tested products for EIs Class 1, Class 2A showed that EI levels in the API and placebos are well below the ICH Option 1 oral and parenteral limits. In the examined batches of each tablet strength (a total of 9), none of the individual limits of each component was equal to or higher than the CT value, which means that no EI exceeds their concentration limits. The calculated daily intake of EIs according to the ICH requirements, for all three different FDFs, confirmed that in all

tested formulations, the MDI is significantly lower and below the control value (30% of the PDI – permitted daily intake), which is prescribed in ICH Q3D (R2) class 1 and class 2 guidelines. The different mass of the three tested formulations is not a key factor and there is no proportional increase in the concentration of EIs in the finished drugs.

Table II Summarized risk assessment for industrial manufacturing equipment and machinery used during the production process of Montelukast-FDFs

Tabela II Sumirana procena rizika za industriisku opremu i mašine koje se koriste tokom proizvodnog procesa Montelukast-FOL

Equipment	Material properties	Risk assessment Numerical risk factor				Control	Final risk assessment Numerical risk factor			
		S	P	D	RF		S	P	D	RF
Vibration sieve	- elements made of stainless steel - smooth surface, not abrasive - dry working environment - low kinetic energy	1	2	2	4	standard operating procedures and manuals	1	2	1	2
Vertical granulator		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Wet sieve		1	2	2	4	standard operating procedures and manuals	1	2	1	2
Fluid bed processor		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Fluid bed containers		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Dry sieve		1	2	2	4	standard operating procedures and manuals	1	2	1	2
Dry sieve		1	2	2	4	standard operating procedures and manuals	1	2	1	2
Machine for dry mixing		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Container for the mixer		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Suitably equipped tableting machine		2	3	1	6	standard operating procedures and manuals	1	3	1	3
De-duster		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Metal detector		1	1	1	1	standard operating procedures and manuals	1	1	1	1
Suitably equipped tableting machine		1	3	2	6	standard operating procedures and manuals	1	3	1	3

S – Severity; P – Possibility; D – Detection; RF – risk factor (RF = S x P x D)

S – ozbiljnost; P – verovatnoća; D – detekcija; RF – factor rizika (RF = S x P x D)

Table III Concentrations of EIs (µg/g) in API and excipients determined in the placebos

Tabela III Koncentracije elementarnih nečistoća (µg/g) u aktivnoj komponenti i ekscipijenti koji se nalaze u placebo prahu

Component	**Maximum Permitted Concentration-MPC (µg/g) Montelukast chewable tablets 4 mg**						
	Cadmium Class1	Lead Class1	Arsenic Class1	Mercury Class1	Cobalt Class2A	V Class2A	Ni Class2A
Montelukast sodium	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.0001	< 0.005
Placebo powder	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
PEC (µg/g)	0.5	0.5	1.5	3	5	10	20
Component	**Maximum Permitted Concentration-MPC (µg/g) Montelukast chewable tablets 5 mg**						
	Cadmium Class1	Lead Class1	Arsenic Class1	Mercury Class1	Cobalt Class2A	V Class2A	Ni Class2A
Montelukast sodium	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.0001	< 0.005
Placebo powder	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
PEC (µg/g)	0.5	0.5	1.5	3	5	10	20
Component	**Maximum Permitted Concentration-MPC (µg/g) Montelukast film-coated tablets 10 mg**						
	Cadmium Class1	Lead Class1	Arsenic Class1	Mercury Class1	Cobalt Class2A	V Class2A	Ni Class2A
Montelukast sodium	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.0001	< 0.005
Placebo powder	< 0.5	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.0001	< 0.001
PEC (µg/g)	0.5	0.5	1.5	3	5	10	20

PEC – permitted element concentration

PEC – dozvoljena koncentracija elementa

Table IV Calculated EI values determined in API and placebos; compared with PDE for Montelukast chewable tablets 4 mg

Tabela IV Izračunate vrednosti EN sadržane u aktivnoj komponenti i placebu i upoređene sa PDE za Montelukast tablete za žvakanje 4 mg

Component	**MDI (g)**	**Cd**		**Pb**		**As**		**Hg**		**Co**		**V**		**Ni**	
		C	**MDI * C**	**C**	**MDI * C**	**C**	**MDI * C**	**C**	**MDI * C**	**C**	**MDI * C**	**C**	**MDI * C**	**C**	**MDI * C**
Montelukast sodium	4.16×10^{-3}	5×10^{-4}	2.08×10^{-6}	1×10^{-3}	4.16×10^{-6}	5×10^{-4}	2.08×10^{-6}	1×10^{-3}	4.16×10^{-6}	5×10^{-4}	2.08×10^{-6}	1×10^{-4}	4.16×10^{-7}	5×10^{-3}	2.08×10^{-5}
Placebo	2.36×10^{-1}	5×10^{-4}	1.18×10^{-4}	1×10^{-3}	2.36×10^{-4}	5×10^{-4}	1.18×10^{-4}	$1 \times 10\text{-}3$	2.36×10^{-4}	5×10^{-4}	1.18×10^{-4}	1×10^{-3}	2.4×10^{-4}	5×10^{-3}	1.18×10^{-3}
Total intake (µg/day)	/	1.2×10^{-4}		1.2×10^{-4}		1.2×10^{-4}		2.4×10^{-4}		1.2×10^{-4}		2.4×10^{-4}		1.2×10^{-3}	
PDE-Oral (µg/day)		5		5		15		30		50		100		200	

MDI – maximum daily intake; PDE-Oral - Permitted Daily Exposure-Oral exposure

MDI – maksimalni dnevni unos; PDE-Oral – dozvoljeno dnevno izlaganje oralnim putem

Table V Calculated EI values contained in API and placebo; compared with PDE for Montelukast chewable tablets 5 mg

Tabela V Izračunate vrednosti EN sadržane u aktivnoj komponenti i placebu i upoređene sa PDE za Montelukast tablete za žvakanje 5 mg

Component	MDI (g)	Cd		Pb		As		Hg		Co		V		Ni	
		C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C
Montelukast sodium	5.2×10^{-3}	5×10^{-4}	2.6×10^{-6}	1×10^{-3}	5.2×10^{-6}	5×10^{-4}	2.6×10^{-6}	1×10^{-3}	5.2×10^{-6}	5×10^{-4}	2.6×10^{-6}	1×10^{-4}	5.2×10^{-7}	5×10^{-3}	2.6×10^{-5}
Placebo	2.95×10^{-1}	5×10^{-4}	1.47×10^{-4}	1×10^{-3}	2.95×10^{4}	5×10^{-4}	4.7×10^{-4}	1×10^{-3}	2.95×10^{-4}	5×10^{-4}	1.47×10^{-4}	1×10^{-3}	2.9×10^{-4}	5×10^{-3}	1.47×10^{-3}
Total intake (µg/day)	/	1.50×10^{-4}		3.00×10^{-4}		1.50×10^{-4}		3.00×10^{-4}		1.50×10^{-4}		3.0×10^{-4}		1.50×10^{-3}	
PDE-Oral (µg/day)		5		5		15		30		50		100		200	

MDI – maximum daily intake; PDE-Oral - Permitted Daily Exposure-Oral exposure

MDI – maksimalni dnevni unos; PDE-Oral – dozvoljeno dnevno izlaganje oralnim putem

Table VI Calculated EI values contained in API and placebo; compared with PDE for Montelukast film-coated tablets 10 mg

Tabela VI Izračunate vrednosti EN sadržane u aktivnoj komponenti i placebu i upoređene sa PDE za Montelukast filmom obložene tablete 10 mg

Component	MDI (g)	Cd		Pb		As		Hg		Co		V		Ni	
		C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C	C	MDI *C
Montelukast sodium	1.04×10^{-2}	5×10^{-4}	5.2×10^{-6}	1×10^{-3}	1.04×10^{-5}	5×10^{-4}	5.2×10^{-6}	1×10^{-3}	1.04×10^{-5}	5×10^{-4}	5.2×10^{-6}	1×10^{-4}	1.04×10^{-6}	5×10^{-3}	5.2×10^{-5}
Placebo	1.976×10^{-1}	5×10^{-1}	9.88×10^{-2}	5×10^{-4}	9.88×10^{-5}	5×10^{-4}	9.88×10^{-5}	5×10^{-4}	9.88×10^{-5}	5×10^{-4}	9.88×10^{-5}	1×10^{-3}	1.976×10^{-5}	1×10^{-3}	1.976×10^{-4}
Total intake (µg/day)	/	9.88052×10^{-2}		1.092×10^{-4}		1.04×10^{-4}		1.092×10^{-4}		1.04×10^{-4}		2.08×10^{-5}		2.496×10^{-4}	
PDE - Oral (µg/day)		5		5		15		30		50		100		200	

MDI-maximum daily intake; PDE-Oral - Permitted Daily Exposure-Oral exposure

MDI – maksimalni dnevni unos; PDE-Oral – dozvoljeno dnevno izlaganje oralnim putem

Table VII Evaluation of EI in three batches of three different Montelukast-FDFs
Tabela VII Procena EN u tri serije tri različita finalna proizvoda leka Montelukast

Montelukast chewable – **4mg**		**Element Concentration (µg/g)**						
		Cd	**Pb**	**As**	**Hg**	**Co**	**V**	**Ni**
Product batch number	**Batch 1**	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
	Batch 2	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
	Batch 3	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
MCL		< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
Control threshold - CT		6.249	6.249	18.75	37.5	62.499	125.001	249.999
Acceptable*		yes	yes	yes	yes	yes	yes	yes
Montelukast chewable – **5mg**		**Element Concentration (µg/g)**						
		Cd	**Pb**	**As**	**Hg**	**Co**	**V**	**Ni**
Product batch number	**Batch 1**	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
	Batch 2	< 0.0005	< 0.001	< 0.0005	< 0.001	0.00083	< 0.001	< 0.005
	Batch 3	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
MCL		< 0.0005	< 0.001	< 0.0005	< 0.001	0.00083	< 0.001	< 0.005
Control threshold - CT		5.001	5.001	50.00	30.00	50.001	99.999	200.01
Acceptable*		yes	yes	yes	yes	yes	yes	yes
Montelukast **film-coated– 10mg**		**Element Concentration (µg/g)**						
		Cd	**Pb**	**As**	**Hg**	**Co**	**V**	**Ni**
Product batch number	**Batch 1**	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.0005	< 0.001	< 0.005
	Batch 2	< 0.0005	< 0.001	< 0.0005	< 0.001	0.0016	< 0.001	< 0.005
	Batch 3	< 0.0005	< 0.001	< 0.0005	< 0.001	0.0028	< 0.001	< 0.005
MCL		< 0.0005	< 0.001	< 0.0005	< 0.001	0.0028	< 0.001	< 0.005
Control threshold - CT		7.211	7.211	21.635	43.269	72.116	144.231	288.461
Acceptable*		yes	yes	yes	yes	yes	yes	yes

MCL- Maximum concentration level of EI

MCL- maksimalni nivo koncentracije EN

*Acceptance criteria: None of the individual limits of each component is equal to or higher than the Control threshold.

*Ulazni kriterijumi: nijedna od individualnih graničnih vrednosti za svaku od komponenata nije jednaka ili viša od kontrolnog praga.

Conclusion

For the pharmaceutical industry, the implementation of the ICH Q3D (R2) EI guideline in practice is challenging. On the one hand, there are requirements that need to meet the limits for EI in FDF related to the route of administration, but on the other, the outcomes of the risk assessment study serve either to support the control strategy or to facilitate decisions in prioritizing the additional controls.

A comparative risk assessment performed on three different montelukast FDFs allows the identification of potential points of risk for EIs across potential sources of elemental impurities (raw materials, contact points of manufacturing machines and materials, the risk from utilities in the industry and packaging material).

The obtained results for all three studied Montelukast FDFs confirm that no additional actions are needed in the existing quality assurance and control system.

The overall risk assessment, according to the results of the screening analyses of all 9 batches from all three studied FDFs confirmed that there is no risk (related to EIs) for patients when the drugs are taken according to the recommendations specified in the instructions for drug use.

However, with every change in the manufacturing process, in the raw materials or in the use of a different manufacturing machine, an additional risk assessment analysis will be required in this dynamic cycle.

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Uporedna studija o proceni rizika elementarnih nečistoća u Montelukast tabletama za žvakanje i filmom obloženim tabletama

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Kratak sadržaj

Dobro je dokumentovano da su elementarne nečistoće (EN) kritične u oblasti farmaceutskog razvoja jer mogu uticati na kvalitet, efikasnost i bezbednost finalnog oblika leka (FOL). Odgovornost proizvođača farmaceutskih proizvoda je da pokažu, preko pristupa procene, strategije kontrole zasnovane na riziku, i/ili potrebne analize podataka, da su FOL usaglašeni sa ICH Q3D (R2). Bez obzira na to, praktična primena ICH Q3D (R2) smernice i usklađenost FOL-a sa ICH Q3D (R2) uvek predstavljaju izazov za farmaceutsku industriju. Cilj ovog istraživanja je da se sprovede detaljna komparativna studija procene rizika od EN za tri različita dozirana oblika Montelukasta proizvedenih kao tablete za žvakanje (4 mg i 5 mg) i film obložene tablete od 10 mg. Sistem induktivno spregnute plazma-masene spektrometrije (ICP-MS) korišćen je za određivanje EN u uzorcima montelukast natrijuma, kao aktivne komponente, placeba za sve FOL i FOL. Nakon toga, analize su takođe sprovedene na tri serije iz sva tri proučavana FOL-a. Na osnovu ICH Q3D (R2) smernice, testirani proizvodi za EN, klasa 1 i klasa 2A pokazali su da su nivoi EN u aktivnoj komponenti i placebu znatno ispod oralnih i parenteralnih granica ICH Opcije 1. Za ispitivane serije svake FOL jačine (ukupno 9), nijedan EN ne prelazi njihove granice koncentracije.

Ključne reči: elementarne nečistoće, Montelukast, procena rizika, ICH Q3D (R2), komparativna studija