Elemental Impurities

Inhalation grade Lactose (EU)

Product group: Inhalation

Brand name: Respitose®

Product description: Lactose Monohydrate
Lactose Anhydrous

Document No.: PD-0650

Dear Customer,

In framework of the ICH Q3D (R2) guideline, DFE Pharma tested batches of Respitose®, originating from the production site located in Veghel, The Netherlands representing the brand name mentioned above.

Neither the elements listed below, nor other elements classified as class 2B, are intentionally added during the production process.

DFE Pharma performed analysis on relevant elemental impurities categorized as class 1, class 2A and some class 2B, class 3 and other relevant elements by the ICH Q3D (R2) guideline (according to table 5.1: Elements to be considered in the Risk Assessment – Oral Dosage Form).
Analysis was performed using the analysis technique ICP-MS (Inductively Coupled Plasma-Mass Spectrometry) conforming to USP-NF <233> and Ph. Eur. 2.4.20.

Table 1: Table of elemental impurities following ICH Q3D (R2)

Metal	Class	Limit in ppm inhalation	Required for inhalation	Tested at DFE Pharma
Cadmium	1	0.3	Yes	Yes
Lead	1	0.5	Yes	Yes
Arsenic	1	0.2	Yes	Yes
Mercury	1	0.1	Yes	Yes
Cobalt	2A	0.3	Yes	Yes
Vanadium	2A	0.1	Yes	Yes
Nickel	2A	0.6	Yes	Yes
Selenium	2B	13	No	Yes
Lithium	3	2.5	Yes	Yes
Antimony	3	2	Yes	Yes
Barium	3	30	Yes	Yes
Molybdenum	3	1	Yes	Yes
Copper	3	3	Yes	Yes
Tin	3	6	Yes	Yes
Chromium	3	0.3	Yes	Yes
Aluminium	None	-	No	Yes
Strontium	None	-	No	Yes

*[1]: Limits are based on option 1 of the ICH Q3D (R2) guidelines, based on administration of not more than 10g of drug product per day (stated in table A.2.2).

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Table 2: Results of elemental impurities in Respitose® produced in Veghel, The Netherlands

Metal	Batch Limit (ppm)	Batch Report limit (ppm)	Respitose® 109WNMS (ppm)	Respitose® 10BXK1M (ppm)	Respitose® 10F8M6N (ppm)
Cadmium	0.3	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	<0.01	<0.01	<0.01
Arsenic	0.2	0.005	<0.005	<0.005	<0.005
Mercury	0.1	0.006	<0.006	<0.006	<0.006
Cobalt	0.3	0.005	<0.005	<0.005	<0.005
Vanadium	0.1	0.002	0.006	<0.002	<0.002
Nickel	0.6	0.030	<0.03	<0.03	<0.03
Selenium	13	0.004	<0.004	<0.004	<0.004
Lithium	2.5	0.004	<0.004	<0.004	0.005
Antimony	2	0.005	<0.005	<0.005	<0.005
Barium	30	0.005	0.015	0.010	0.013
Molybdenum	1	0.020	0.046	0.038	0.045
Copper	3	0.010	<0.010	<0.010	<0.010
Tin	6	0.25	<0.010*	<0.25	<0.25
Chromium	0.3	0.030	<0.03	<0.03	<0.03
Aluminium	None	0.200	0.84	0.45	0.39
Strontium	None	0.005	0.020	0.016	0.016

*At time of measurement the reporting limit was different

A risk assessment was performed. This document and raw data are available for review during audits. Conclusion of the risk assessment is that all values obtained are below 30% of the limits and thus do not need additional control, the change control procedure is the key to maintain this situation. The levels of ICH Q3D (R2) relevant elemental impurities are monitored on regular basis.

This statement substitutes all previous versions issued for the brand names mentioned above.
We trust this information, which is made up to the best of our knowledge, will be helpful to you.

With kindest regards,

Name : Peter Ebben
Job title : Global Quality Control Manager
Signature :

This document is controlled by a validated, electronic system and is valid without signature.
The above facsimile signature is only for display.

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