Elemental Impurities

Lactose (EU)

Product group: Lactose

Brand name: Pharmatose®, SuperTab® , Lactochem®, Lactopress®

Product description: Lactose Monohydrate

Lactose Anhydrous

Dear Customer,

In framework of the ICH Q3D (R2) guideline, DFE Pharma tested batches of Pharmatose®, SuperTab®, Lactochem® and Lactopress® , originating from the production sites located in Europe (Veghel and Borculo, The Netherlands and Nörten-Hardenberg, Germany) representing the brand names 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 oral	Required for oral route	Tested at DFE Pharma
Cadmium	1	0.5	Yes	Yes
Lead	1	0.5	Yes	Yes
Arsenic	1	1.5	Yes	Yes
Mercury	1	3	Yes	Yes
Cobalt	2A	5	Yes	Yes
Vanadium	2A	10	Yes	Yes
Nickel	2A	20	Yes	Yes
Selenium	2B	15	No	Yes
Lithium	3	55	No	Yes
Antimony	3	120	No	Yes
Barium	3	140	No	Yes
Molybdenum	3	300	No	Yes
Copper	3	300	No	Yes
Tin	3	600	No	Yes
Chromium	3	1100	No	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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In Table 2 and 3 the data of Pharmatose® 80M and 200M is presented. These products serve as model products for all Pharmatose® products produced in Veghel, the Netherlands.
Pharmatose® is also used as raw material for all SuperTab® products produced in Nörten-Hardenberg, Germany.
Neither the elements listed in Table 1, nor other elements classified as class 2B, are intentionally added during the production process. Therefor the Pharmatose® data is also representative for all SuperTab® products.

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

Metal	Batch Limit (ppm)	Batch Report limit (ppm)	Pharmatose® 80M 109N6PM (ppm)	Pharmatose® 80M 10CRD04 (ppm)	Pharmatose® 80M 10FD01T (ppm)
Cadmium	0.5	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	<0.01	<0.01	<0.01
Arsenic	1.5	0.005	<0.010*	<0.005	<0.005
Mercury	3	0.006	<0.006	<0.006	<0.006
Cobalt	5	0.005	<0.005	<0.005	<0.005
Vanadium	10	0.002	<0.002	<0.002	<0.002
Nickel	20	0.030	<0.03	<0.03	<0.03
Selenium	15	0.004	<0.004	<0.004	<0.004
Lithium	55	0.004	<0.004	<0.004	<0.004
Antimony	120	0.005	<0.005	<0.005	<0.005
Barium	140	0.005	0.099	0.006	0.010
Molybdenum	300	0.020	0.030	0.050	0.045
Copper	300	0.010	<0.010	<0.010	<0.010
Tin	600	0.25	<0.010*	<0.25	<0.25
Chromium	1100	0.030	<0.03	<0.03	<0.03
Aluminium	None	0.200	0.44	0.52	0.29
Strontium	None	0.005	0.039	0.015	0.012

*At time of measurement the reporting limit was different

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Table 3: Results of elemental impurities in lactose produced in Veghel, The Netherlands

Batch			Pharmatose® 200M 10B3RJJ (ppm)	Pharmatose® 200M 10BPVPF (ppm)	Pharmatose® 200M 10FL5R8 (ppm)
Metal	Limit (ppm)	Report limit (ppm)			
Cadmium	0.5	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	<0.01	<0.01	<0.01
Arsenic	1.5	0.005	<0.005	<0.005	<0.005
Mercury	3	0.006	<0.006	<0.006	<0.006
Cobalt	5	0.005	<0.005	<0.005	<0.005
Vanadium	10	0.002	<0.002	<0.002	<0.002
Nickel	20	0.030	<0.03	<0.03	<0.03
Selenium	15	0.004	<0.004	<0.004	<0.004
Lithium	55	0.004	0.007	<0.004	<0.004
Antimony	120	0.005	<0.005	<0.005	<0.005
Barium	140	0.005	0.012	0.009	0.011
Molybdenum	300	0.020	0.038	0.042	0.042
Copper	300	0.010	<0.010	<0.010	<0.010
Tin	600	0.25	<0.01*	<0.25	<0.25
Chromium	1100	0.030	<0.03	<0.03	<0.03
Aluminium	None	0.200	0.44	0.54	0.49
Strontium	None	0.005	0.026	0.025	0.015

*At time of measurement the reporting limit was different

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In Table 4 and 5 the data of Lactochem® fine powder and Lactochem crystals is presented. These products serve a model products for all Lactochem® and Lactopress® products produced in Borculo, The Netherland.

Table 4: Results of elemental impurities in lactose produced in Borculo, The Netherlands

Product and Batch			LC fine powder 109STFP (ppm)	LC fine powder 10BH195 (ppm)	LC fine powder 10FK9DB (ppm)
Metal	**Limit (ppm)**	**Report limit (ppm)**			
Cadmium	0.5	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	<0.01	<0.01	<0.01
Arsenic	1.5	0.005	<0.005	<0.005	<0.005
Mercury	3	0.006	<0.006	<0.006	<0.006
Cobalt	5	0.005	<0.005	<0.005	<0.005
Vanadium	10	0.002	0.005	0.002	0.003
Nickel	20	0.030	<0.03	<0.03	<0.03
Selenium	15	0.004	<0.004	<0.004	<0.004
Lithium	55	0.004	<0.004	<0.004	<0.004
Antimony	120	0.005	<0.005	<0.005	<0.005
Barium	140	0.005	0.006	<0.005	<0.005
Molybdenum	300	0.020	0.043	0.048	0.057
Copper	300	0.010	<0.010	<0.010	<0.010
Tin	600	0.25	<0.01*	<0.25	<0.25
Chromium	1100	0.030	<0.03	<0.03	<0.03
Aluminium	None	0.200	0.74	0.69	0.47
Strontium	None	0.005	0.020	0.020	0.021

*At time of measurement the reporting limit was different

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Table 5: Results of elemental impurities in lactose produced in Borculo, The Netherlands

Product and Batch			LC crystals 109H1V8 (ppm)	LC crystals 10C2NNB (ppm)	LC crystals 10GL2F8 (ppm)
Metal	**Limit (ppm)**	**Report limit (ppm)**			
Cadmium	0.5	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	<0.01	<0.01	<0.01
Arsenic	1.5	0.005	<0.005	<0.005	<0.005
Mercury	3	0.006	<0.006	<0.006	<0.006
Cobalt	5	0.005	<0.005	<0.005	<0.005
Vanadium	10	0.002	0.005	0.005	0.003
Nickel	20	0.030	<0.03	<0.03	<0.03
Selenium	15	0.004	<0.004	<0.004	<0.004
Lithium	55	0.004	<0.004	<0.004	<0.004
Antimony	120	0.005	<0.005	<0.005	<0.005
Barium	140	0.005	0.009	0.006	0.008
Molybdenum	300	0.020	0.054	0.046	0.048
Copper	300	0.010	<0.010	<0.010	<0.010
Tin	600	0.25	<0.01*	<0.25	<0.25
Chromium	1100	0.030	<0.03	<0.03	<0.03
Aluminium	None	0.200	0.73	0.82	0.48
Strontium	None	0.005	0.027	0.020	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.

DFE Pharma GmbH & Co. KG

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