



To whom it may concern

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Quality Unit

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Doc.-No. EIP-1035 -B
Revision 14

Elemental Impurities

Ph. Eur. General Text 5.20; USP-NF General Chapter <232> and <233>; ICH Guideline Q3D(R2)

MEGGLE Product:

Lactose Monohydrate (USP-NF / Ph. Eur. / JP): InhaLac® 70, InhaLac® 120, InhaLac® 140, InhaLac® 150, InhaLac® 160, InhaLac® 230, InhaLac® 250, InhaLac® 251, InhaLac® 400, InhaLac® 500

In the production process of the above mentioned products, the elements classified in Class 1, 2A, 2B and 3 are not intentionally added in form of metal catalysts, metal reagents etc.

Permitted concentrations limits were calculated using the Permitted Daily Exposures and assuming a daily intake of the excipients of 100 mg (ICH Q3D(R2), No 7 Option 2a). Acceptance levels were defined as 30% of the permitted concentrations.

Testing was conducted for the elements categorised as Class 1, 2A and 3 relevant for inhalative route of administration according to the ICH Guideline Q3D(R2). Using bracketing principles several representative lots of the products were tested using ICP-MS method in conformance to USP-NF <233>. Testing method has been validated for the matrix of the products.

Results are mainly < LoQ and shown on the table below which is valid for all above mentioned MEGGLE products. In case of a quantifiable result, the highest value is given. All results are far below 30% of the acceptance levels for inhalative application. In consequence, additional controls are not required.

MEGGLE has implemented an ongoing monitoring program for elemental impurities in accordance to the regime of the initial study performed.

Best regards

MEGGLE GmbH & Co. KG

Dr. Stefan Dreiheller

Regulatory Affairs / Specification Management



Elemental impurities – Summary Results

Ph. Eur. General Text 5.20; USP-NF General Chapter <232> and <233>; ICH Guideline Q3D(R2)

Material Name Lactose Monohydrate
 Production Site All trade names except see below: MEGGLE GmbH & Co. KG Megglestr. 6 – 12, 83512 Wasserburg am Inn, Germany
 Subcontracted Production Site InhaLac® 400, InhaLac® 500: Micronisierungs-Kontor Oberrot GmbH, Industriestr. 17, 74420 Oberrot, Germany
 Source/Type of Excipient Animal derived (Milk of bovine origin).
 Route of administration (RoA) Inhalative

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Class	Elements	Elements to be considered		Inhalation PDE µg/day	Perm. Conc. µg/g	Accept. Level µg/g	Results* µg/g	Method	Comments	
		Added	Based on RoA							
1	Cadmium	Cd	No	Yes	2	20	6	< 0.0009	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
1	Lead	Pb	No	Yes	5	50	15	0.001	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
1	Arsenic (inorg.)	As	No	Yes	2	20	6	< 0.0081	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
1	Mercury (inorg.)	Hg	No	Yes	1	10	3	< 0.0005	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
2A	Cobalt	Co	No	Yes	3	30	9	0.0007	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
2A	Vanadium	V	No	Yes	1	10	3	< 0.0093	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
2A	Nickel	Ni	No	Yes	6	60	18	< 0.0084	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
2B	Thallium	Tl	No	No	n/a					
2B	Gold	Au	No	No	n/a					
2B	Palladium	Pd	No	No	n/a					
2B	Iridium	Ir	No	No	n/a					
2B	Osmium	Os	No	No	n/a					
2B	Rhodium	Rh	No	No	n/a					
2B	Ruthenium	Ru	No	No	n/a					
2B	Selenium	Se	No	No	n/a					
2B	Silver	Ag	No	No	n/a					
2B	Platinum	Pt	No	No	n/a					
3	Lithium	Li	No	Yes	25	250	75	< 0.0025	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Antimony	Sb	No	Yes	20	200	60	< 0.0025	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Barium	Ba	No	Yes	300	3000	900	0.051	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Molybdenum	Mo	No	Yes	10	100	30	0.020	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Copper	Cu	No	Yes	30	300	90	< 0.0030	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Tin	Sn	No	Yes	60	600	180	< 0.0035	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)
3	Chromium	Cr	No	Yes	3	30	6	< 0.0112	ICP-MS; USP 40 NF35 <233>	7 batches tested. Monitoring installed (1 / year)

* "< X": < LoQ (Limit of Quantification)