



Elemental Impurities

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

MEGGLE Products:

Lactose Monohydrate: InhaLac® 70, InhaLac® 120, InhaLac® 140, InhaLac® 145, InhaLac® 150, InhaLac® 160, InhaLac® 180, InhaLac® 230, InhaLac® 251, InhaLac® 300, InhaLac® 400, InhaLac® 500

In the production process of the above mentioned MEGGLE 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 product 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 below 30 % of the acceptance levels for oral 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.

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Elemental impurities – Summary Results
ICH Guideline Q3D (R2);
Ph. Eur. General Text 5.20;
USP-NF General Chapter (232) and (233)

Material Name: Lactose Monohydrate; trade names see above
Production and Release Site: MEGGLE GmbH & Co. KG, Megglestr. 6-12, 83512 Wasserburg am Inn, Germany
for Inh 400 and 500: Subcontr. Production Site: Micronisierungs-Kontor Oberrot GmbH, Industriestr. 17, 74420 Oberrot, Germany
Source/Type of Excipient: Animal origin. Milk from *Bos taurus*.
Route of administration (RoA): Inhalative

Class	Elements		Elements to be considered		Inhalative 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	3	30	9	< 0.0009	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
1	Lead	Pb	No	Yes	5	50	15	0.001	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
1	Arsenic (inorg.)	As	No	Yes	2	20	6	< 0.0081	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
1	Mercury (inorg.)	Hg	No	Yes	1	10	3	< 0.0005	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
2A	Cobalt	Co	No	Yes	3	30	9	0.0007	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
2A	Vanadium	V	No	Yes	1	10	3	< 0.0093	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
2A	Nickel	Ni	No	Yes	6	60	18	< 0.0084	ICP-MS; USP-NF (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-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Antimony	Sb	No	Yes	20	200	60	< 0.0025	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Barium	Ba	No	Yes	300	3000	900	0.051	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Molybdenum	Mo	No	Yes	10	100	30	0.020	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Copper	Cu	No	Yes	30	300	90	< 0.0030	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Tin	Sn	No	Yes	60	600	180	< 0.0035	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)
3	Chromium	Cr	No	Yes	3	30	9	< 0.0112	ICP-MS; USP-NF (233)	7 batches tested. Monitoring installed (1 / year)

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

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