To whom it may concern

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Date of issue: 28.04.2022

Doc.-No. EIP-1035 -USA-A
Revision 3

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): GranuLac® 70 US, GranuLac® 140 US, GranuLac® 200 US

In the production process of the above mentioned product, 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 excipient of 10 g (ICH Q3D(R2), No 7 Option 1, stated in table A.2.2). Acceptance levels were defined as 30% of the permitted concentrations.

Testing was conducted on the product GranuLac® 200 produced at MEGGLE GmbH & Co. KG, Wasserburg am Inn, Germany for the elements categorised as Class 1 and 2A relevant for oral route of administration according to the ICH Guideline Q3D(R2). This product is equivalent in terms of the monograph requirements, i.e. characters, identification, tests, functionality-related characteristics under consideration of the PDG harmonization process (Stage 6). It is expected that the results of the product are at least comparable to those of the US product. Several representative lots of GranuLac® 200 were tested using ICP-MS method in conformance to USP-NF ‹233›.Testing method has been validated for the matrix of the product.

Representative results are shown on the table below which are valid for the mentioned product. All results are far below 30% of the acceptance levels for oral application. In consequence, additional controls are not required.

MEGGLE USA has implemented an ongoing monitoring program for elemental impurities in accordance to the regime of the initial study performed. The program is conducted at MEGGLE GmbH & Co. KG.

Best regards

MEGGLE USA inc.

Dr. Gabriele Müller

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 and Release Site	Agropur inc., 719 North Main Street, Le Sueur, MN 56058-1404, USA
Source/Type of Excipient	Animal derived (Milk of bovine origin)
Route of administration (RoA)	Oral

Class	Elements		Elements to be considered		Oral PDE	Perm. Conc.	Accept. Level	Representative Results *	Method	Comments
			Added	Based on RoA	µg/day	µg/g	µg/g	µg/g		
1	Cadmium	Cd	No	Yes	5	0.5	0.15	< 0.0009	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
1	Lead	Pb	No	Yes	5	0.5	0.15	< 0.0006	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
1	Arsenic (inorg,)	As	No	Yes	15	1.5	0.45	< 0.0081	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
1	Mercury (inorg.)	Hg	No	Yes	30	3	0.9	< 0.0005	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
2A	Cobalt	Co	No	Yes	50	5	1.5	0.0007	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
2A	Vanadium	V	No	Yes	100	10	3	< 0.0093	ICP-MS; USP-NF ‹233›	7 batches tested. Monitoring installed (1 / year)
2A	Nickel	Ni	No	Yes	200	20	6	< 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	No	n/a					
3	Antimony	Sb	No	No	n/a					
3	Barium	Ba	No	No	n/a					
3	Molybdenum	Mo	No	No	n/a					
3	Copper	Cu	No	No	n/a					
3	Tin	Sn	No	No	n/a					
3	Chromium	Cr	No	No	n/a					

* "< X" implies values are below **LoQ** (limit of quantification) which is X: Further remarks see page 1