Elemental Impurities

Microcrystalline Cellulose

Product group: MCC

Brand name: Pharmacel®, Pharmacel® sMCC 90

Product description: Microcrystalline Cellulose Silicified Microcrystalline Cellulose

Dear Customer,

In framework of the ICH Q3D (R2) guideline, DFE Pharma tested batches of Microcrystalline Cellulose and Silicified Microcrystalline Cellulose products, originating from the production sites located in Cuddalore and Nagpur, India.
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).

DFE Pharma GmbH & Co. KG
Klever Strasse 187, 47574 Goch, Germany, P.O. Box 20 21 20, 47568 Goch, Germany, T. +49 2823 9288 770, F. +49 2823 9288 7799

In the tables below the data of Pharmacel® and Pharmacel® sMCC 90 is presented. These products serve as model products for all Pharmacel® products produced in Cuddalore and Nagpur, India.

Neither the elements listed in Table 1, nor other elements classified as class 2B, are intentionally added during the production process.

Table 2: Results of elemental impurities in MCC produced in Cuddalore, India

Product and batch			Pharmacel® 101 10B7FLG (ppm)	Pharmacel® 101 101091 (ppm)	Pharmacel® 101 10D6136 (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	<0.004	<0.004	<0.004
Antimony	120	0.005	<0.005	<0.005	<0.005
Barium	140	0.005	0.011	0.011	0.005
Molybdenum	300	0.020	<0.02	<0.02	<0.02
Copper	300	0.010	<0.010	<0.010	<0.010
Tin	600	0.25	<0.010*	<0.010*	<0.25
Chromium	1100	0.030	0.042	0.042	0.042
Aluminium	None	0.200	0.76	0.76	1.1
Strontium	None	0.005	0.007	0.007	0.006

*At time of measurement the reporting limit was different

Table 3: Results of elemental impurities in MCC produced in Nagpur, India

Product and batch			Pharmacel® 101 10B3W1K (ppm)	Pharmacel® 101 301096 (ppm)	Pharmacel® 101 10DXSD3 (ppm)
Metal	**Limit (ppm)**	**Report limit (ppm)**			
Cadmium	0.5	0.005	<0.005	<0.005	<0.005
Lead	0.5	0.01	0.023	<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	0.003	0.003	0.008
Nickel	20	0.030	0.085	<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	1.200	1.400	0.900
Molybdenum	300	0.020	<0.02	<0.02	<0.02
Copper	300	0.010	0.130	<0.010	0.018
Tin	600	0.25	<0.010*	<0.010*	<0.25
Chromium	1100	0.030	0.075	0.031	0.031
Aluminium	None	0.200	1.9	0.97	1.7
Strontium	None	0.005	0.055	0.17	0.16

*At time of measurement the reporting limit was different

Elemental Impurities
Microcrystalline Cellulose

Product group: MCC

Brand name: Pharmacel®
Pharmacel® sMCC 90

Product description: Microcrystalline Cellulose
Silicified Microcrystalline Cellulose

Table 4: Results of elemental impurities in sMCC90 produced in Nagpur, India

Product and batch			Pharmacel® sMCC 90 109SM42 (ppm)	Pharmacel® sMCC 90 10D1469 (ppm)	Pharmacel® sMCC 90 10DRHoC (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	<0.010*	<0.005	<0.005
Mercury	3	0.006	<0.006	<0.006	<0.006
Cobalt	5	0.005	<0.005	0.024	<0.005
Vanadium	10	0.002	0.004	<0.002	0.002
Nickel	20	0.030	0.160	0.033	0.062
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	1.500	1.200	1.400
Molybdenum	300	0.020	0.029	<0.02	<0.02
Copper	300	0.010	0.019	0.017	0.011
Tin	600	0.25	<0.010*	<0.010*	<0.25
Chromium	1100	0.030	0.25	0.042	0.072
Aluminium	None	0.200	1.4	1.0	1.1
Strontium	None	0.005	0.083	0.054	0.084

*At time of measurement the reporting limit was different

DFE Pharma GmbH & Co. KG
Klever Strasse 187, 47574 Goch, Germany, P.O. Box 20 21 20, 47568 Goch, Germany, T. +49 2823 9288 770, F. +49 2823 9288 7799

Elemental Impurities
Microcrystalline Cellulose

Product group:	MCC
Brand name:	Pharmacel® Pharmacel® sMCC 90
Product description:	Microcrystalline Cellulose Silicified Microcrystalline Cellulose
Document No.:	PD-0619

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
Klever Strasse 187, 47574 Goch, Germany, P.O. Box 20 21 20, 47568 Goch, Germany, T. +49 2823 9288 770, F. +49 2823 9288 7799