February 2017

# Pharma Grade Statement
# CAB-O-SIL® M-5P and M-5DP Fumed Silicas for Pharmaceutical Applications

CAB-O-SIL®M-5P and M-5DP fumed silicas are high purity silicon dioxide products manufactured via a high temperature combustion process.

- CAB-O-SIL® M-5P and M-5DP fumed silicas meet all the requirements for *Colloidal Silicon Dioxide* as described in the US Pharmacopoeia National Formulary.
- CAB-O-SIL® M-5P and M-5DP fumed silicas meet the requirements of *Silica Colloidalis Anhydricas* as described in the European Pharmacopoeia
- CAB-O-SIL® M-5P fumed silica meets the requirements of the *Light Anhydrous Silicic Acid* as described in the Japanese Pharmacopoeia

Appendix 1 shows the list of Pharmacopoeia Monograph parameters that are tested on each lot.

## 1. US and European Pharmacopoeia Residual Solvents

Chemical Test <467> Residual Solvents contained in the current United States Pharmacopoeia 39/National Formulary 34 states: "Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification processes".

European Pharmacopoeia Chapter 5.4 on residual solvents and current EMA[1] Guideline for Residual Solvents (EMA_CHMP_ICH_82260_2006) states “Testing in drug substances, excipients, and in drug products should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product.”

Japanese Pharmacopoeia Chapter 2.46 on residual solvents states “Testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products.”

Cabot has reviewed its manufacturing processes and has concluded that no Class I, II or III solvents or other organic solvents are used or produced in the manufacture of CAB-O-SIL® M-5P and M-5DP fumed silicas.

1 European Medicine Agency

## 2. US and European Pharmacopoeia Elemental (Metal) Impurities and Metal Catalysts/Reagent Residues

The US Pharmacopoeia - USP Chapter <232> sets out elemental impurities (E.I.) limits in drug products. Those limits do not apply to excipients, except where specified in individual monographs. However, E.I. levels present in excipient must be known, controlled and documented.
Some default concentration limits of metals in finished drug products cannot be exceeded for excipients or active substances as per USP Chapter <232> - Table 2. USP Chapter <232> became official on December 2015. Please note that USP has announced January 1st, 2018 as the new date of applicability of General Chapters <232> - Elemental Impurities via General Notices provision 5.60.30 Elemental Impurities in USP Drug Products unless Chapter <232> is referenced in a particular monograph. For new drug product applications, the June 2016 FDA Guidance for Industry recommends following the ICH Q3D[2] guidelines on E.I. after June 1, 2016.

The European Pharmacopoeia - EP 5.20 Chapter and EMA guideline on the specification limits for residues of metal catalysts and metal reagents (EMA_CHMP_SWP_4446_2000) set out limits for residues of metal catalysts or metal reagents used in production of drug product and pharmaceutical substances, i.e. active substances and excipients. Those limits apply to new drug products to be marketed in Europe. The text of the ICH Q3D guideline on E.I. has been published in the EMA guideline on E.I. EMA/CHMP/ICH/353369/2013 last summer, with implementation dates of June 2016 for new marketing authorization applications and December 2017 for all existing products on the EU market. However, the publication of the ICH Q3D principles in the EU pharmacopoeia EP 5.20 Chapter (replacing the specification limits for residues of metal catalysts and metal reagents) is expected for the EP 9.3 supplement release.

Cabot Corporation has conducted its own risk assessment to identify all potential sources of E.I., determine which E.I. are likely to be present and whether or not current controls are adequate.
To the best of our knowledge, Cabot Corporation does not use any metal, metal catalyst or metal reagent in the manufacturing process of our CAB-O-SIL® M-5P and M-5DP fumed silicas. Therefore metal, metal catalyst or metal reagent residues are not expected to be present in our CAB-O-SIL® M-5P and M-5DP fumed silica products above trace concentrations (i.e., low ppm or less). In addition, a testing campaign to establish our baseline on the environmental metal contaminants has been conducted at both manufacturing sites. [The presence of24 metals were tested by Glow Discharge Mass Spectroscopy (GDMS). As a result of the testing campaign, Cabot Corporation concluded that the controls in place are adequate. Cabot will not implement lot-to-lot routine testing for those 24 metal impurities as they are not expected to be present above trace concentrations (i.e. low ppm or less). To help our customers in making their own risk assessment on E.I., we offer the following information:

[2] ICH – International Conference on Harmonization of technical requirements for pharmaceuticals for human use.
Q3D: Q corresponds to “Quality” guideline, “3” refers to “impurity” and “D” corresponds to the type of “impurity”, in this case “elemental” impurities.

Table 1 – Metal elemental impurities levels in CAB-O-SIL® M-5P and M-5DP fumed silicas

| Metal | Limit (in ppm) |
|---|---|
| Hg | < 1 |
| As | < 3 |
| Pb | < 5 |
| Cd | < 5 |
| Ir, V, Os, Pt, Pd, Rh, Ru, Co, Ag, Ba, Li, Tl | < 10 |
| Se | < 20 |
| Cr, Cu, Mo, Ni, Sn, Au, Sb | < 50 |

## 3. Genotoxicity

Silicon Dioxide (i.e. Silica) has been tested in the ECETOC[3] program - Joint Assessment of Commodity Chemicals (JACC Report n°51 - Sept.2006) and for REACH registration purposes. Silicon dioxide has demonstrated no mutagenic activity in Salmonella typhimurium or Escherichia coli with and without metabolic activation (microorganism gene mutation test in vitro). In addition no clastogenic activity has been observed in the chromosome aberration test in Chinese hamster ovary (CHO) cells.

To the best of our knowledge, Cabot Corporation believes CAB-O-SIL® M-5P and M-5DP fumed silicas have no genotoxic activity.

[3] European Centre for Ecotoxicology and Toxicology of Chemicals

## 4. Other Information

CAB-O-SIL® M-5P and M-5DP fumed silicas are **synthetic** amorphous silica products manufactured by a chemical process that does not use human, animal or vegetal origin raw materials. In addition, our products are not manufactured using a fermentation process or a recombinant DNA technology.
In addition, to the best of our knowledge, CAB-O-SIL® M-5P and M-5DP fumed silica products do not contain

**a.** Genetically Modified Organism (GMO) products or materials, nor do they come into contact with any GMO product or material during our manufacture and handling processes;

**b.** Products of animal origin, nor do they contain any animal product associated with Transmissible Spongiform Encephalopathy (TSE), Bovine Spongiform Encephalopathy (BSE) or Creuzfeldt-Jakobs Disease (CJD). The regulated chemicals that typically are associated with the development of TSE, BSE or CJD are not involved in our production and handling processes;

**c.** Food Allergens regulated by US FDA (Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA)) and listed in Annex II of Regulation (EU) No 1169/2011 on the provision of food information to consumers (formerly in annex IIIa of the EU Directive 2000/13/EC) and amendments. Specifically, Cabot's CAB-O-SIL®M-5P and M-5DP fumed silica products do not contain allergenic proteins derived from crustacean shellfish (e.g., crab, crayfish, lobster, shrimp, etc.), fish, egg, milk, peanuts, soy, cereals containing gluten including wheat, tree nuts (e.g., almonds, Brazil nuts, cashews, hazelnuts/filberts, macadamia nuts, pecans, pine nuts, pistachios, walnuts, etc.) and also celery, mustard, sesame seeds, sulfur dioxide and sulphites, lupin and products thereof;

**d.** Corn and corn derivatives. Cabot does not use any corn and corn derivatives as raw material in our manufacturing process. Our paper bags are sealed with a mix of corn and potato starch glue, we cannot exclude a potential contact of silica material with the glue.

**e.** Mycotoxins including aflatoxin. Those substances are the main contaminants of plant origin material (e.g., grains, cereals, nuts, oilseeds, and spices) and Cabot does not use any plant origin material as raw material in our high temperature manufacturing process. Therefore such mycotoxins are not expected to be present in our CAB-O-SIL® M-5P and M-5DP fumed silica products.

**f.** Melamine. Cabot Corporation does not analyze CAB-O-SIL® M-5P and M-5DP fumed silica products for the presence of melamine. Cabot Corporation does not use melamine in the manufacturing process of our CAB-O-SIL® M-5P and M-5DP fumed silicas. Based on our knowledge of the production and handling processes, Cabot does not expect melamine to be present in CAB-O-SIL® M-5P and M-5DP fumed silica products above trace levels.

**g.** Contaminants: Fungi and mycoplasma. Cabot Corporation does not analyze CAB-O-SIL® M-5P and M-5DP fumed silica products for the presence of fungi or mycoplasma. Cabot Corporation does not use fungi or mycoplasma in the manufacturing process of our CAB-O-SIL® M-5P and M-5DP fumed silicas. Based on our knowledge of the production and handling processes, Cabot

does not expect these substances to be present in CAB-O-SIL® M-5P and M-5DP fumed silica products above trace levels.

**h.** Other: Intentionally added sugars (lactose, glucose, etc…), gluten, alcohol, latex, hormones, antibiotics, stabilizers, antioxidants, enzymes, colorants, pigments, flavors, biocides, preservative, Jatropha-derived glycerin and related materials.

## 5. Manufacturing Sites

CAB-O-SIL® M-5P fumed silica is manufactured in two fumed silica facilities located in Rheinfelden, Germany and in Tuscola, Illinois, United States of America. Each manufacturing site supplies their respective regional customers and distributors. Both Tuscola and Rheinfelden processes are similar and produce CAB-O-SIL® M-5P fumed silica to the same global product specification.

Our plants operate in using the highest quality standard and are ISO 9001 certified. CAB-O-SIL® M-5P fumed silica product from both facilities are produced following Cabot manufacturing processes inspired from good manufacturing practices that we believe are suitable for the production of this excipient. If a change of source would be needed, customers should consider whatever internal qualifications and/or testing they feel is appropriate for their specific application.

CAB-O-SIL® M-5DP fumed silica is manufactured only in our Rheinfelden facility.

## 6. Cations content for drug notice

We do not routinely test CAB-O-SIL® M-5P and M-5DP fumed silicas for sodium, magnesium, calcium and potassium content. To the best of our knowledge, Cabot Corporation believes that sodium, magnesium, calcium and potassium are not being used as raw materials in the manufacture of our CAB-O-SIL® M-5P and M-5DP fumed silica products; and accordingly; are not expected to be present in those products above trace concentrations (i.e., low ppm or less).

Based on GD-MS data on this product and similar products, the maximum amount of sodium, magnesium, calcium and potassium should not exceed 20ppm each. These values are given for information only and do not represent a specification of our products.

## 7. Use as an Additive in Dietary/Food Supplements

Silicon dioxide is authorized as an ingredient of dietary/food supplements per listing in Annex II.B – Minerals of the European Directive 2002/46/EC and amendments.
Per Article 4.3 of the above Directive, the purity criteria for the authorized substances that are specified in a Community Legislation related to foodstuffs shall apply.

To help our customers in meeting their legal obligations associated with dietary/food supplements production, we provide the following information:

CAB-O-SIL® M-5P and M-5DP fumed silicas are not routinely tested for E551 purity criteria of the Commission Regulation (EU) N° 231/2012 laying down specifications for food additives. However, based on our knowledge of the process and an analysis performed on a similar product, the E551 purity criteria are not expected to be exceeded for CAB-O-SIL® M-5P and M-5DP fumed silicas.

Please note that the ingredients in dietary supplements sold or manufactured in the US must comply with the requirements of the Food Safety Modernization Act (FSMA). CAB-O-SIL® M-5P and M-5DP fumed silicas are not as of now FSMA compliant.

## 8. Certificates

ISO, OHSAS, Halal, Kosher and HACCP certificates: Please refer to the following link http://www.cabotcorp.com/responsibility/product-stewardship/ for any updated information.

Buyer assumes full responsibility for testing and determination of suitability of a product for buyer's intended application or use according to the applicable pharmacopoeia requirements.

This information is being provided as of the date hereof. Please refer to Cabot's website – www.cabot-corp.com – for any updates to this information.



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Appendix 1 – Pharmacopoeia Monograph Requirements

| Endpoint | US39/NF34 | EP 9th Ed. | JP 17th Ed. |
|---|---|---|---|
| **Identification** | Test A meets<br>Test B requirement | Silicates test:<br>meets requirement | Test 1 meets<br>Test 2 requirement<br>Test 3 |
| **Assay** | 99.0–100.5% | 99.0–100.5% | > 98.0% |
| **Loss on drying** | < 2.5% | | < 7.0% |
| **Loss on ignition** | < 2.0% | < 5.0% | |
| **pH** | 3.5–5.5 | 3.5–5.5 | < 12.0% |
| | | | |
| **Arsenic** | < 8 ppm | | < 5 ppm |
| **Chlorides** | | < 250 ppm | < 0.011% |
| **Heavy Metals** | | * | < 40 ppm |
| **Aluminum** | | | meets requirement |
| **Iron** | | | < 500 ppm |
| **Calcium** | | | meets requirement |
| **JP volume test** | | | 5 g sample:<br>volume> 70ml |

*See paragraph 2 - US and European Pharmacopoeia Elemental (Metal) Impurities and Metal Catalysts/Reagent Residues for more information