August 2015

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

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

- CAB-O-SIL® M-5P and M-5DP Fumed Silica 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 Silica 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

## 1. US and European Pharmacopoeia Residual Solvents

Chemical Test <467> Residual Solvents contained in the current United States Pharmacopoeia 38/National Formulary 33 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 May 2014 EMA 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.”

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 Silica.

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

The US Pharmacopoeia - USP Chapter <232> sets out elemental impurities limits in drug products. Those metals limits always refer to drug finished products, although some default concentration limits of metals in drug finished product cannot be exceeded for excipients or active substances as per USP Chapter <232> - Table 2. USP Chapter <232> becomes 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.

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 ICH Q3D guideline on elemental impurities will replace current EMA guideline on the specification limits for residues of metal catalysts and metal reagents in EU pharmacopoeia EP 5.20 Chapter with implementation dates of June 2016 for new marketing authorisation applications and December 2017 for all existing products on the EU market.

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 Silica. 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, environmental metal impurities are not routinely tested but, to the best of our knowledge; those metal impurities are not expected to be present above trace concentrations (i.e. low ppm or less).

## 3. Genotoxicity

Silicon Dioxide/Silica has been tested in the ECETOC program - Joint Assessment of Commodity Chemicals (JACC Report n°51 - Sept.2006) and for REACH registration purposes. Silicon dioxide/Silica 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 Silica has no genotoxic activity as such.

## 4. 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 your customer 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 Silica are not routinely tested for E551 purity criteria of the Commission Regulation (EU) N° 231/2012 laying down specifications for food additive. 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 silica.

## 5. Other Information

CAB-O-SIL® M-5P and M-5DP Fumed Silica are synthetic amorphous silica products manufactured by a chemical process that does not use human, animal or vegetal origin raw materials.
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.** Product of animal origin, nor do they contain any animal product associated with Bovine Spongiform Encephalopathy (BSE) or Creuzfeldt-Jakobs Disease (CJD). The regulated chemicals that typically are associated with the development of 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 IIIa of the EU Directive 2000/13/EC and amends. 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.** 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.

**e.** 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 Silica. 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.

**f.** 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 Silica. 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.

**g.** Other: Intentionally added hormones, antibiotics, stabilizers, antioxidants, enzymes, colorants.

## 6. Certificates

Halal, Kosher and HACCP certificate: 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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