CYCLOLAB
Cyclodextrin Research & Development Laboratory Ltd.
Mail address: Budapest, P.O.Box 435, H-1525 Hungary
Location: Illatos út 7., Budapest, H-1097 Hungary
TEL: (361) 347-60-60 or -70, FAX: (361) 347-60-68
E-mail: cyclolab@cyclolab.hu
Homepage: www.cyclolab.hu
VAT No.: HU 10678970

ISO 9001

Product Quality Statements

Product: Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD, Dexolve™)
Manufacturing site: CycloLab Cyclodextrin Research and Development Ltd., Illatos út 7, Budapest, H-1097 Hungary

Product origin – raw materials used

Sulfobutyl-ether-β-cyclodextrin sodium salt (SBECD, Dexolve™) Pharma Grade - is produced at CycloLab Cyclodextrin Research and Development Ltd., Illatos út 7., Budapest, H-1097 Hungary. It is manufactured from raw material beta-cyclodextrin and 1,4-butane sultone.
Beta-cyclodextrin is manufactured from starch by Wacker Chemical Corporation in Eddyville, Iowa USA, using an enzyme of microbial origin. In the fermentation process of this enzyme besides non-animal components, a casein-hydrolysate is used. The confirmation issued by Wacker about the animal enzyme content of beta-cyclodextrin (Cavamax W7) is available upon request.
1,4-Butane sultone is manufactured by Organica Feinchemie GmbH Wolfen in Germany, using a synthetic route.

TSE/BSE information

According to the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products - Revision 3 (EMEA / 410 / 01 Rev.03 - July 2011) adopted by the European Commission on 3 May 2011, (2011/C 73/01), We certify that the above product(s) and the associated substances used during the manufacturing process are not of animal origin. Therefore, there is no objective reason to suspect the presence of the Transmissible Spongiform Encephalopathies infectious agents in the product. We commit ourselves on notify you of any change in this information.

GMP certificate/GMP compliance

We certify that our Company manufactures and sells this material as an Excipient. Our GMP Certificate is issued by the Hungarian National Institute of Pharmacy and Nutrition (Certificate number: OGYEI/57792-7/2018. Furthermore, we certify that CycloLab fulfills the ICHQ7 conditions for the manufacturing of this product.
This product meets the specifications of the following monograph(s):
United States Pharmacopeia (current version)
European Pharmacopeia (current version)

Residual solvents

Hereby we declare that during the manufacture and analysis of SBECD we follow and comply with the instructions of USP<467> and EP 5.4 general chapters for residual solvents regarding applied methods and acceptance criteria.
During the manufacturing process two volatile materials are applied: 1,4-butane sultone as starting material and ethanol (Class III solvent) as an additive. Both are tested for in all batches during the release investigations applying separate, validated GC methods. The specification limit for 1,4-butane sultone content is not more than 0.5 ppm (in accordance with the USP-NF SBECD monograph), the specification limit for ethanol content is not more than 2500 ppm (the limit of USP <467> and EP 5.4 general chapters for ethanol is not more than 5000 ppm).

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MQ12-007H

Metal catalysts and reagents, elemental impurities

The "ICH guideline Q3D on elemental impurities" presents a process to assess and control elemental impurities in the drug product. We confirm that SBECD is produced neither in the presence of metal catalysts nor using any metal reagents that could lead to metal residues.

Four potential sources of metal can be identified: water, raw materials, manufacturing equipment, and packaging materials. During the manufacturing and packaging we do not use materials containing detectable amounts of Class 1 elements. Since 2017 each batch was tested for Class 1 and potential elemental impurities by ICP/MS. Statement on the identity and specification of each metal residue present in the substance can be seen below.

Element	ICH Class	Specification* (ug/g)	Likely to be present (Yes/No)	Intentionally added (Yes/No)	Note
Cadmium	1	0.2	No	No	Each batch is tested for the Class 1 elements
Lead	1	0.5	No	No	
Arsenic	1	1.5	No	No	
Mercury	1	0.3	No	No	
Cobalt	2A	0.5	No	No	3 validation batches were tested
Vanadium	2A	1	Yes	No	tested in each batch
Nickel	2A	2	Yes	No	
Thallium	2B	0.8	No	No	3 validation batches were tested
Gold	2B	10	No	No	3 validation batches were tested
Palladium	2B	1	No	No	3 validation batches were tested
Iridium	2B	1	No	No	3 validation batches were tested
Osmium	2B	1	No	No	3 validation batches were tested
Rhodium	2B	1	No	No	not tested
Ruthenium	2B	1	No	No	3 validation batches were tested
Selenium	2B	8	No	No	3 validation batches were tested
Silver	2B	1	No	No	3 validation batches were tested
Platinum	2B	1	No	No	3 validation batches were tested
Lithium	3	25	No	No	3 validation batches were tested
Antimony	3	9	No	No	3 validation batches were tested
Barium	3	70	No	No	3 validation batches were tested
Molybdenum	3	150	Yes	No	tested in each batch
Copper	3	30	No	No	3 validation batches were tested
Tin	3	60	No	No	3 validation batches were tested
Chromium	3	110	Yes	No	tested in each batch

* Permitted concentrations of elemental impurities for parenteral use

We confirmed that the substance meets reproducibly the aforementioned specification.

Irradiation

Our products do not contain compounds treated with ionizing radiation and are not submitted to an ionizing treatment at any stage of the production. Therefore, they do not fall within the scope of Directives 1999/2/CE and 1999/3/CE concerning Foods and Food ingredients treated with ionizing

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radiation.

Viral status
CycloLab does not sell or manufacture or use any of the following active substances or product groups: penicillins, cephalosporins, other β-lactam antibiotics, cytotoxic substances, cytostatics, steroids, hormones.

CMR
There is no substance present in the product classified as Carcinogenic, Mutagenic or Toxic (except for 1,4-butane sultone residue, limited at NMT 0.5 ppm) to Reproduction (CMR) according to the Commission Directive 2004/93/EC and Directive 76/768/EEC.

Testing compliance
Methods of analysis used by our laboratories are Ph. Eur. or USP-NF or internal validated methods which have been compared (cross-validated) to the pharmacopeia monograph. A summary of analytical methods used for this product is available upon request.

Third party statement
We declare that SBECD is manufactured and released entirely by CycloLab personnel.

Sieving
We declare that SBECD is performed without sieving of the final product.

Allergens and intolerance agents

Melamine
We declare that SBECD is manufactured without using any melamine.

Latex
We declare that SBECD is manufactured without using any latex.

Gluten
We declare that SBECD is manufactured without using any gluten.

Dioxin
We declare that SBECD is manufactured without using any dioxin.

We declare that SBECD, its starting materials and its production area are free of intolerance agents such as gluten, crustaceans and products thereof, eggs and products thereof, fish and products thereof, peanuts and products thereof, soybeans and products thereof, milk and products thereof (including lactose), nuts, i.e. almonds, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia nuts and Queensland nuts and products thereof, celery and products thereof, mustard and products thereof, sesame seeds and products thereof, sulphur dioxide and sulphites at concentrations of more than 10mg/kg or 10mg/litre expressed as SO_2, lupin and products thereof, molluscs and products thereof, natural rubber latex, iodine, cinnamon, cocoa, vanilla, chicken, yeast, legumes, pulses, coriander, umbellifereae, flavour (any artificial/natural), glutamate, carrot, and fruits.

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GMO
We declare that SBECD is manufactured without using any GMO material.

Aflatoxin
We declare that SBECD is manufactured using starting materials and production area which are free of aflatoxin producing microbiological contamination.

Batch identification codes
We declare hereby that forming of batch identification codes is regulated in our SOP-006 as follows:
Batch identification code is: aaabbccdd
where
- "aaa" is the code of the product, for SBECD it is 47K.
- "bb" is the running number of the batch in the year.
- "cc" is the number of the month of the starting of the batch.
- "dd" is the last two numbers of the year.

Date: 11.02.2019.

CYCLOLAB
Cyclodextrin Kutató-Fejlesztő Kft.
1097 Bp., Illatos út 7.

Quality Assurance
CycloLab Ltd.