CYCLOLAB
CYCLODEXTRIN RESEARCH & DEVELOPMENT LABORATORY LTD.
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ISO 9001
MQ12-007H

PRODUCT QUALITY STATEMENT

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/22915-11/2022. 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 – National Formulary (current version) Betadex Sulfobutyl Ether Sodium
European Pharmacopoeia (current version) Sulfobutylbetadex sodium
DMF has been filed to FDA in 2008 (no. 21922), to Health Canada in 2009 (No. 2009-080), both maintained ever since. Cyclolab is registered as the manufacturer of SBECD in EMA's EudraGMDP database since 2014.

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Stability data, storage
We have stability data 25°C 60rH% for 60 months and 40°C 75 rH% for 6 months. The expiry date is based on the start of manufacturing. Storage condition: Preserve in well-closed containers, store at room temperature. Protect from moisture.

Packaging
The product is filled in gamma-irradiated PE bag and twist-tied and shut with a cable tie. The PE bag is placed in a triplex (PP/ALU/PET) bag with pressure relief valve and desiccant (active silica gel pad) in between the bags. The triplex bag is heat sealed and put in HDPE or fiber drum with locking clamp.

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).

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.

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Element	ICH Class	Specification* (µg/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
Lead	1	0.5	No	No	
Arsenic	1	1.5	No	No	
Mercury	1	0.3	No	No	
Cobalt	2A	0.5	No	No	Tested in each batch
Vanadium	2A	1	Yes	No	
Nickel	2A	2	Yes	No	
Thallium	2B	0.8	No	No	3 batches were tested
Gold	2B	10	No	No	
Palladium	2B	1	No	No	
Iridium	2B	1	No	No	
Osmium	2B	1	No	No	
Rhodium	2B	1	No	No	
Rhutenium	2B	1	No	No	
Selenium	2B	8	No	No	
Silver	2B	1	No	No	
Platinum	2B	1	No	No	
Lithium	3	25	No	No	
Antimony	3	9	No	No	
Barium	3	70	No	No	
Molybdenum	3	150	Yes	No	Tested in each batch
Copper	3	30	No	No	3 batches were tested
Tin	3	60	No	No	
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 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.

Nitrosamines
For the formation of nitrosamines two factors shall be present: 1.) secondary amines and 2.) nitrosating agent.

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1.) During the manufacturing process the only possible amine source could come from the anion exchange resin. Since the resin is virtually insoluble, the possibility of the formation of the amine degradation products is very low.
We measured the washing waters of the resins and traces of two amines could be detected at around 15 ppm: 2-Dimethylaminoethanol and dimethyl amine.
Also, according to the batch record the resins are washed twice before use.
2.) In our manufacturing process no nitrosating agent or any kind of oxidizing agents are used.

In summary, during the production of SBECD formation of nitrosamines cannot be possible, due to lack of the necessary parameters and reagents.
Based on our evaluation **no risk can be identified** for nitrosamine formation.

Genotoxicity, CMR classification
There is no substance present in the product classified as Carcinogenic, Mutagenic or Toxic to Reproduction (CMR) according to the EC No. 1272/2008. The SBECD may cause an allergic skin reaction, see further details in Safety Information.

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.

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

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

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

Gelatin
We declare that SBECD is manufactured without using any gelatin.

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Preservatives and dyes
We declare that SBECD is manufactured without using any preservative or dyes.

Di (2-ethylhexyl) phthalate (DEHP)
We declare that SBECD is manufactured without using any DEHP.

Allergens
Raw material of SBECD is not contain any allergen and intolerance agent. During the manufacturing the product is not encounter any of them and its production area are free of intolerance agents. For this reason, allergen and intolerance agent content of SBECD is not measured. Allergens and intolerance agent can be 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 10 mg/kg or 10 mg/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.

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.

Carbohydrates
SBECD is based on sugar, it contains carbohydrates.

List of regulated computerized system
The analytical results obtained during instrumental measurements are stored in the form of electronic data in accordance with FDA 21 CFR part 11
The regulated computerized system consists of 3 main components:

- Analytical instruments (HPLCs, GC, Capillary Electrophoresis) can be controlled from client machines with a remote desktop connection.
- AIC (Agilent Instrument Controller): the measuring programs actually run on these high-performance computers, and the client machines are connected to them
- ECM server (Enterprise Content Manager): data storage system, into which

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the generated data is automatically uploaded, it can be clearly identified who, when, from which machine, what changed compared to the original raw data (audit trail).

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: 8th of June 2023

Quality Assurance
CycloLab Ltd.