European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability No. R0-CEP 2009-050-Rev 00

Name of the substance:
CHOLECALCIFEROL

Name of holder:
DSM NUTRITIONAL PRODUCTS LTD.
Wurmisweg 576
Switzerland-4303 Kaiseraugst

Site(s) of production:
DSM NUTRITIONAL PRODUCTS FRANCE SAS
1 Boulevard D' Alsace
France-68128 Village-Neuf

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production mentioned above, we certify that the quality of the substance is suitably controlled by the current version of the monograph **CHOLECALCIFEROL** no. 72 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

– Test for residual solvents by gas chromatography (Annex 1)
Methyl formate not more than 1000 ppm

In the last steps of the synthesis water is used as solvent.

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **CHOLECALCIFEROL** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

– nature of animal tissues used in manufacture: Sheep whool

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

AFAQ ISO 9001

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from **31 January 2011**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has one annex of 2 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM

Strasbourg, 31 January 2011

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

DSM Nutritional Products Ltd., as holder of the certificate of suitability

R0-CEP 2009-050-Rev 00 for CHOLECALCIFEROL

hereby authorises Curtis Health Caps Sp. z o.o. Wysogotowo, ul. Batorowska 52 62-081 Przeźmierowo
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

Protego Witamina D1000 (Y81)

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

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GC-method for the detection and quantification of residual solvents in cholecalciferol.

Determination	
Residual solvents	Methanol, methyl formate, acetone, n-Hexane, pyridine, benzene
Method principle	Gas chromatography using headspace sample preparation and FID detection based on the following parameters
Sample preparation	
Blank solution	Pipet 10.0 ml of dimethylformamide (DMA) into a serum vial and close hermetically.
Standard solutions	In a 100 ml volumetric flask containing a little quantity of DMA (FLUKA HPLC), accurately weigh 90-110 mg of acetone (PROLABO NORMAPUR) and methylformate (MERCK for synthese), 250-350 mg of methanol (PROLABO NORMAPUR), 15-30 mg of n-Hexane (FLUKA PURISS P.A.) and 190-210 mg of pyridine (MERCK P.A.). Bring up to volume with DMA.(= solution 1) Pipet 1.0 ml of solution 1 and dilute to 100.0 ml with DMA (= test solution). Pipet 10.0 ml of the test solution into a serum vial and close hermetically.
Sample Solution	Accurately weigh 0.95 - 1.05 g of product in a serum vial and dissolve with 10.0 ml of DMA. Close hermetically.
Operating procedure	Apply the 'HEADSPACE' method. Place the serum vial in an oven for one hour at 100°C. Inject 1.0 ml of the headspace vapour phase from the vial.
Equipment	
Instrument	Hewlett Packard 6890 series Plus with split/splitless injector
Detector	FID
Temperatures a) Column b) Injector c) Detector	 from 35 °C to 140 °C at 10°C/mn 140 °C 250 °C
Capillary column	length 30 m, internal diameter 0.25 mm, thickness of stationary phase 1.4 μm
Stationary phase	CP-Select 624 CB reference 7412 Chrompack (94%dimethylsiloxane and 6 % cyanopropylphenylsiloxane)
Carrier gas	Helium
Linear velocity of carrier gas	35 cm/s
Split ratio	1/5

Integration and calculations	
Retention times	Methanol approximately (≈) 2.2 min Methyl formate ≈ 2.35 min Acetone ≈ 3.1 min n-Hexane ≈ 3.8 min Pyridine ≈ 7.2 min n-Hexane Low fraction ≈ 3.4 and ≈ 3.6 n-Hexane Low fraction ≈ 4.3 and ≈ 4.9
Separation time	approx. 16 min
Standardisation	External standardisation.
Calculations	$\mu g / g = \frac{S_{Sample}}{S_{Std}} \times \frac{P_{Std} \times 10^3}{100} \times \frac{1}{100} \times 10 \times \frac{1}{P_{Sample}}$ S_{Sample} area of peak of the considered solvent from the sample solution S_{Std} area of peak of the considered solvent from the standard solution P_{Std} weighed amount of the considered solvent in standard in mg P_{Ech} weighed amount of sample in g 10 and 100 dilution factors 10^3 unit factor (mg to μg)