INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

NAME OF PRODUCT: **Nabilone 0.25 mg Capsules**

DRUG SUBSTANCE: **Nabilone**

Contents

Appendices:

Appendix No.	Document	No. of pages
2.1.A.5	Method Transfer Report, Nabilone 1.0 mg Capsules Identity, Assay, Related Substances, Content Uniformity and Dissolution by HPLC, MTRC_2014/002_1_0_ENG	60 pages
2.1.A.6	Addendum to Method Transfer Report – Validation of the new test solution preparation Method Validation Report, Nabilone 1.0 mg Capsules Preparation of Test solutions for Assay/Related substances and Content uniformity according CC16-006, AO-01-MVAR_02_V01	18 pages
2.1.A.7	Method Verification Report, Nabilone 1.0 mg Capsules Water content KF/ Ph.Eur. 2.5.12 method A	11 pages
2.1.A.8	Method Transfer Report, Nabilone 1.0 mg Capsules Residual solvent Ethanol	22 pages
2.1.A.9	Validation Report, Nabilone 1mg capsules Report Nr. 1	13 pages
2.1.A.10	Method Validation Report, Nabilone 0.25 mg Capsules ID, Assay and Related Substances by UV_HPLC, validation part 1	44 pages
2.1.A.11	Method Validation Report, Nabilone 0.25 mg Capsules Content uniformity by UV-HPLC, validation part 1	28 pages
2.1.A.12	Method Validation Report, Nabilone 0.25 mg Capsules Dissolution with off-line HPLC Quantification, validation part 1	32 pages
2.1.A.13	Method Validation Statement, Nabilone 0.25 mg Capsules Water content by KF	6 pages
2.1.A.14	Method Validation Statement, Nabilone 0.25 mg Capsules Ethanol content by GC	7 pages
2.1.A.15	GMP certificate of API and FP manufacturers	15 pages

2.1.S DRUG SUBSTANCE

As stated in the "*Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - CHMP/QWP/185401/2004 final*" reference for the drug substance part of the IMPD for Nabilone is made to the registered product Canemes 1 mg Capsules. The national license number of the product is 1_31358.

Therefore, the drug substance part is not provided in this version of the IMPD.

2.1.P.1 Description and Composition of the Drug Product (Nabilone, 1 mg capsules and Nabilone, 0.25 mg capsules)

Description

Nabilone is a synthetic cannabinoid derivative, which has been developed in the 1970's. Nabilone 1 mg capsules have a marketing authorisation in Austria and Germany for CINV, the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer in patients who have failed to respond adequately to conventional antiemetic treatments.
Nabilone capsules are an oral dosage form in hard gelatine capsules. Each capsule contains 0.25 mg respectively 1.0 mg Nabilone as the active pharmaceutical ingredient, in the form of a poly-vinylpyrollidone (Povidone) co-precipitate. An additional excipient of the formulation is corn starch which is used as filler. The final product is packaged into PE bottles. Each PE bottle contains 28 capsules.
Nabilone capsules are manufactured in two different strengths. Both strengths are produced out of the same granulate and are only differing by the filling weight.
For the Nabilone 1.0 mg capsules 147.1 mg of granulate is filled into yellow/white hard gelatine capsules size 2.
For Nabilone 0.25 mg capsules 36.78 mg of granulate is filled into white/white hard gelatine capsules size 4.

Composition

The Nabilone 0.25 mg and 1.0 mg capsules consist of the following compounds:

- Nabilone
- Povidone (K25)
- Corn starch, pre-gelatinised
- Ethanol (not present in the final product)

The quantitative composition per capsule and strength is presented below.

Substance	Composition (kg/Granulate)	Composition Nabilone 1 mg (mg/Capsule *)	Composition Nabilone 0.25 mg (mg/Capsule **)	Function
Nabilone	0.100	1.0	0.25	Active Ingredient
Povidone (K25)	1.000	10.0	2.50	Dispersion Matrix
Corn starch, pre-gelatinised	13.610	136.1	34.03	Filler
Ethanol ***	(2.360 – 2.560)	-	-	Granulation Solvent
Total	14.710	147.1	36.78	

* Net capsule weight is approx. 61 mg and capsules are of capsule size 2.

** Net capsule weight is approx. 38 mg and capsules are of capsule size 4.

*** Ethanol serves as a granulation solvent and is not present in the final product

Hard gelatine capsules used for Nabilone 1 mg capsules consist of a yellow cap and a white body, both opaque, with the composition and the amount of ingredients given in the figures below.

Composition of capsule cap (yellow opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Yellow iron oxide (E172)	Colorant	0.784	0.191
Titanium dioxide (E171)	Opacifier	1.120	0.273
Gelatine q.s.	Structure	98	23.935
Total		100	24.400

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.732
Gelatine q.s.	Structure	98	35.868
Total		100	36.600

Hard gelatine capsules used for Nabilone 0.25 mg capsules consist of a white cap and a white body, both opaque, with the composition and the amount of ingredients given in the figures below.

Composition of capsule cap (white opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Titanium dioxide (E171)	Opacifier	2	0.3040
Gelatine q.s.	Structure	98	14.8960
Total		100	15.2000

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.4560
Gelatine q.s.	Structure	98	22.3440
Total		100	22.8000

Container

White 50 ml Duma Twist-Off containers made of high density polyethylene (HDPE) and the tamper-evident Twist-Off caps made of polypropylene (PP) containing a desiccant are used.

Pack size: 28 capsules per container (valid for both strengths).

All components conform to the current requirements of food and medicinal products packaging.

2.1.P.2 Pharmaceutical Development (Nabilone, 1 mg and 0.25 mg Capsules)

2.1.P.2.1 Composition of the Drug Product

2.1.P.2.1.1 Drug substance

Active ingredient: Nabilone

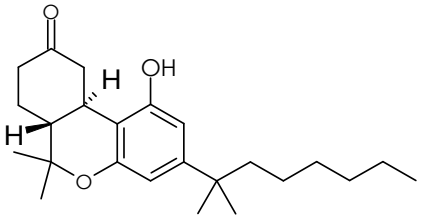
Nomenclature: Nabilone

Chemical name: trans-3-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzol[b,d]pyran-9-one

Chemical formula: $C_{24}H_{36}O_3$

Molecular weight: 372.55

Structural formula:



Solubility:

Solubility of Nabilone in several solvents at room temperature is shown below.

Solvent	Ratio Nabilone: Solvent	Solubility
Distilled water	1 : 10000	Practically insoluble
Methanol	1 : 100	Sparingly soluble
Ethanol	1 : 100	Sparingly soluble
Cyclohexane	1 : 1000	Slightly soluble
Acetonitrile	1 : 1000	Slightly soluble

Particles size distribution:

The particles size distribution is not tested during API release as during formulation the API is completely dissolved in Ethanol and an influence of the API particle size on the final product is therefore excluded.

Polymorphism:

Nabilone may occur in at least four distinct polymorphic forms depending upon the solvent and crystallization conditions. The table below summarizes these forms which have been characterized by differential thermal analysis (DTA) and X-ray diffraction powder patterns.

Polymorph	*Crystallization Solvent*	*Endothermic DTA Transition Temperature [°C]*
A	*hexane*	*162*
B	*ethanol-water [(a)]*	*155, 162*
C	*ethanol-water [(b)]*	*132, 155, 162*
D	*chloroform*	*120, 140, 162*

(a) Crystallization allowed to occur from warm ethanol-water solution.

(b) Crystallization forced by the addition of ethanol solution to water.

From the route of API synthesis only one polymorphic form is obtained, which was identified as polymorph A.

As only the amorphous form is bioavailable, the API is transferred from polymorph A to the bioavailable amorphous form during formulation of the finished product. The amorphous state is achieved by dissolving the active substance in ethanol and poly-vinylpyrollidone (Povidone) prior to the blending step. Nabilone and Povidone form a stable matrix, in which the amorphous form is obtained.

API sources:

Two API sources are available for manufacturing of Nabilone final product. Both API suppliers fulfil the API specification defined in 3.2.S.4.1. The API manufacturers are listed below:

API manufacturers	Chemisch-pharmazeutisches Labor (CPL), Rolf Sachse GmbH	Stieffring 14 13627 Berlin Germany
	LOBA FEINCHEMIE GmbH	Fehrgasse 7 A-2401 Fischamend Austria

For CPL Sachse GmbH 60 months stability data at 25°C and 6 months accelerated data at 40°C are available. A re-test period of 60 months is stated in section 3.2.S.7.

For Loba Feinchemie GmbH 36 months stability data at 25°C are available. A re-test date of 48 months is stated in section 3.2.S.7.

Both API sources were used for the manufacturing of final product validation batches as presented in section 2.1.P.3.5 and lead to batches fulfilling the final product specification.

The drug substance has proven to be compatible with the excipients listed in Section 3.2.P.1.

Nabilone 1 mg capsules are marketed in Europe in the UK since the 1970's.

Nabilone 0.25 mg capsules were developed at FP manufacturer SwissCo Services AG in 2016.

2.1.P.2.1.2 Excipients

Capsule Content

The excipients and their relative functions are the following: corn starch, partially pre-gelatinised, is used in these capsules as carrier and disintegrant. This special kind of corn starch has a better flowability and quicker time of swelling in aqueous surroundings.

Ethanol was used for the solution of Nabilone in its amorphous form. Nabilone is insoluble in water. Povidone K25 (Polyvidone, Polyvinylpyrrolidone) is used as binder and matrix to stabilise the bioavailable form of the active ingredient. Both ingredients are well known as indifferent against the most active ingredients and therefore they are often used in above mentioned functionalities in oral pharmaceutical products.

The amount of Povidone is chosen not only to be a binder, but more to fix the bioavailable form of the active ingredient in an amorphous form. Being dissolved in aqueous surrounding the active ingredient is released in its bioavailable form.

The amount of corn starch is responsible for a proper filling volume of the capsules.

Capsule Shell

Gelatine is commonly used as forming material of pharmaceutical capsules. To ensure differences between different products in visual matters, the gelatine is coloured with substances as used for colouring foods. In case of Nabilone 1 mg Titanium dioxide (E171) and Yellow iron oxide (E172) are used. For Nabilone 0.25 mg only Titanium dioxide (E171) is used to ensure differentiation between the two strengths.

Nabilone 1 mg capsules

Composition of capsule cap (yellow opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Yellow iron oxide (E172)	Colorant	0.784	0.191
Titanium dioxide (E171)	Opacifier	1.120	0.273
Gelatine q.s.	Structure	98	23.935
Total		100	24.400

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.732
Gelatine q.s.	Structure	98	35.868
Total		100	36.600

Nabilone 0.25 mg capsules

Composition of capsule cap (white opaque)

Name of excipient	Function	Amount [%]	mg/Cap
Titanium dioxide (E171)	Opacifier	2	0.3040
Gelatine q.s.	Structure	98	14.8960
Total		100	15.2000

Composition of capsule body (white opaque)

Name of excipient	Function	Amount [%]	mg/Body
Titanium dioxide (E171)	Opacifier	2	0.4560
Gelatine q.s.	Structure	98	22.3440
Total		100	22.8000

2.1.P.2.2 Drug Product

2.1.P.2.2.1 Formulation Development

The development of a formulation suitable for filling into hard gelatine capsules was carried out at lab scale at Chemisch Pharmazeutisches Labor (CpL) Sachse, Berlin using the following literature as a basis:

Solid dispersion approach for overcoming bioavailability problems due to polymorphism of Nabilone, Arvind L. Thakkar, J. Pharm. Pharmac. 29 (1977) 783-4

According above referenced literature a 1:9 dispersion of Nabilone in Polyvinylpyrrolidone (PVP), which was prepared by dissolving of Nabilone and PVP in 95% ethanol and subsequent removal of the solvent by vacuum drying, lead to a solid dispersion in non-crystalline form. The non-crystalline state was confirmed by diffuse X-ray diffraction. Based on the data it is concluded, that Nabilone is molecularly dispersed in the PVP matrix and is therefore transferred in a stable amorphous state.

A further optimisation of the solid dispersion received by Thakkar was described in the patent with the application number 80300094.2 by Eli Lilly and Company, 307, East McCarty Street, Indianapolis Indiana (US), 1980. The patent describes a process for formulating Nabilone for oral administration to mammals which comprises dissolving Nabilone and polyvinylpyrrolidone or polyethylene glycol in anhydrous ethanol and using the thus-formed viscous solution to granulate a pharmaceutically acceptable ethanol-insoluble excipient by thoroughly mixing the solution with the excipient, and then drying the thus-formed granulation. As excipients starch, lactose and cellulose are suggested. The ratio of Nabilone to PVP is given with one part of Nabilone to 2 to 20 parts of PVP.

At the beginning of the formulation development the ratio from Nabilone to PVP was defined with one part of Nabilone to 10 parts of PVP, which almost complies with the dispersion suggested by Thakkar and which is in the defined range of the patent by Eli Lilly.

- 1.0 mg Nabilone
- 10 mg Kollidon® 25 (PVP)

The patent describes an ethanol quantity of 125 ml for 5 g of Nabilone. The ethanol quantity was increased to receive a more viscous solution appropriate for pumping through tubes. 150 ml for 5 g Nabilone was regarded appropriate for better flowability of granulation solution

- 30 ml Ethanol (23.6 g)

As carrier excipient corn starch, pre-gelatinised was chosen. This special kind of corn starch has a better flowability and quicker time of swelling in aqueous surroundings. The amount of corn starch was defined with 139 mg and is responsible for a proper filling volume of the size 3 capsules when using a 100-hole hand-held filler.

Size 3 capsules have a defined capsule capacity of 180 mg at a powder density of 0.6 g/ml and with a planned filling mass of 150 mg, the capsule is filled by 83% of its volume.

- 139 mg starch 1500 (partially pregelatinized maize starch)

Due to explanations provided above, the formulation of the first development batch at CPL Sachse was defined with

- 1.0 mg Nabilone
- 10 mg Kollidon® 25 (PVP)
- 139 mg starch 1500 (partially pregelatinized maize starch),

in size 3 gelatine capsule. The total filling weight of each capsule was ca. 150 mg.

During process transfer to Nycomed the formulation was changed in regard to the quantity of corn starch which was decreased to 136.1 mg.
Size 3 capsules as established by CPL Sachse were used at the beginning of the implementation at Nycomed. The filling mass of 147.1 mg could barely be filled into the capsule shell. Therefore, it was decided to increase the capsule size from size 3 to size 2 to simplify the encapsulation process. Size 2 capsules have a defined capsule capacity of 222 mg at a powder density of 0.6 g/ml and with a planned filling mass of 147.1 mg, the capsule is filled by 66% of its volume.

After successful transfer of the manufacturing process of Nabilone 1 mg capsules from Nycomed to SwissCo, the development for Nabilone 0.25 mg capsules were started there. The capsule fill material (=granulate) is identical for both product strengths. For manufacturing of Nabilone 1 mg Capsules, capsules size 2 are filled with 147.1 mg granulate and for manufacturing of Nabilone 0.25 mg Capsules, capsules size 4 are filled with 36.8 mg granulate.

2.1.P.2.2.2 Overages

Nycomed

Based on the lab scale experiments performed at CpL Sachse, an overage of 5% for the API was included to compensate for the loss of drug substance during the manufacturing process. However, based on the assay results of the process validation batches at Nycomed, the need for the overage was not confirmed. The manufacturing process and the analytical results of the validation batches demonstrated that it could be left out.

SwissCo

As the manufacturing process implemented at SwissCo is almost identical to those developed at Nycomed, no process overage for the API was deemed necessary.

2.1.P.2.2.3 Physicochemical and Biological Properties

2.1.P.2.2.3.1 Development of Dissolution Method

The parameter relevant to the performance of the drug product is the **dissolution** of the finished product.

For the product development, the dissolution of the finished product is critical. CpL Sachse performed a dissolution study considering 3 different dissolution media (described in the following section). The aim of this study was to demonstrate in vitro bioequivalence and to establish the best dissolution medium as a release specification for the finished product at the drug product manufacturer.

1.) Summary

A HPLC method for the assay of Nabilone for the use as determinative step for the dissolution testing of Nabilone capsules was validated with respect to specificity, linearity, accuracy and ruggedness.

Due to the low solubility of the active substance Nabilone in aqueous media, a modification of the dissolution medium was necessary by adding a low concentration of surfactant as suggested in Ph. Eur. 5.17.1.
0.1% Sodium Dodecyl Sulfate (SDS) was chosen to sufficiently dissolve the product.

Dissolution profiles of the test capsules in varying dissolution media were generated and compared with those of the originator product.

The test product used to perform the studies was a development batch (lot LJ 061016) prepared at CpL Sachse. Each Nabilone capsule contained:

- 1.0 mg Nabilone
- 10 mg Kollidon® 25 (PVP)
- 139 mg starch 1500 (partially pregelatinized maize starch),

in size 3 gelatine capsule. The total filling weight of each capsule was ca. 150 mg.

2.) Method description

HPLC Method for Assay

Preparation of reference solutions

Mobile Phase: 90 % (v/v) acetonitrile
10 % (v/v) 0.05 M H_3PO_4

10 mg of Nabilone working standard are dissolved in 10.0 ml Acetonitrile. 1.0 ml of this solution is diluted to 10.0 ml with mobile phase. 0.1 ml of this solution is further diluted with mobile phase to 10.0 ml.

Test solutions

Dissolution solutions are injected after filtration (HPLC membrane filter Sartorius Minisart RC 25) without further dilution. Solutions in acetate buffer were additionally centrifuged (Eppendorf centrifuge 5417c, 10000 rpm for 3 minutes).

HPLC conditions

Column	Lichrosorb 100 RP18, 250 x 4.6 mm, 5 µm, Supelco or equivalent
Mobile Phase	90 % (v/v) acetonitrile 10 % (v/v) 0.05 mol/l phosphoric acid in water for chromatography
Gradient	isocratic
Flow rate	1.0 ml/min
Detection	UV at 208 nm
Injection volume	10 µl
Temperature	25° C
Run time	10 min

Calculation

The content in [mg/ml] of Nabilone in the test solution is calculated by the formula:

$$Content[mg/ml] = A_{Nabilone}\,[AU] * RF[\frac{mg/ml}{AU}] * 10$$

$A_{Nabilone}$ = area of Nabilone in the chromatogram obtained with the test solution

RF = response factor: concentration of Nabilone in reference solution [mg/ml]/ area of Nabilone in the chromatogram obtained with the reference solution

Dissolution Conditions

The basket method (Apparatus 1) according to Ph. Eur. 2.9.3 was used.

Agitation	75 rpm
Volume	1000 ml
Temperature	37°C ± 0.5 C
Sample volume	5 ml

After each sampling the volume of the dissolution medium was added up to 1000 ml.

Calculation

Dissolution of Nabilone for each time point was calculated according to the formula:

% Dissolution at time point t = C(t) * 1000 [ml] + (ΣC (t-n) [mg/ml]*5 [ml]) *100 /1 [mg]

With

C(t) = Nabilone concentration in the dissolution medium at time point t

t-n = previous time points

Dissolution media

Aqueous media with a pH range from 1 to 6.8 were used:

1) 0.1 N HCl + 0.1 % SDS (Sodium dodecyl sulfate)
2) Acetate buffer + 0.1 % SDS
3) Phosphate buffer + 0.1 % SDS

The gastric fluid medium (0.1N HCl + 0.1 % SDS) was used for the HPLC method validation experiments.

Justification

The use of the surfactant SDS was essential. When Nabilone capsule mass was suspended in 0.1 N HCl no Nabilone could be measured in the clear medium after filtration.

To find the optimum surfactant concentration, Nabilone capsule mass containing 0.1 mg of Nabilone was each dissolved in 100 ml of 0.1 N HCl containing varying SDS concentrations from 0.01 % to 0.2 %.

After filtration through a membrane filter the peak area of Nabilone in the HPLC chromatogram obtained were recorded. The amount of dissolved Nabilone was highest with an SDS concentration of 0.1 %.

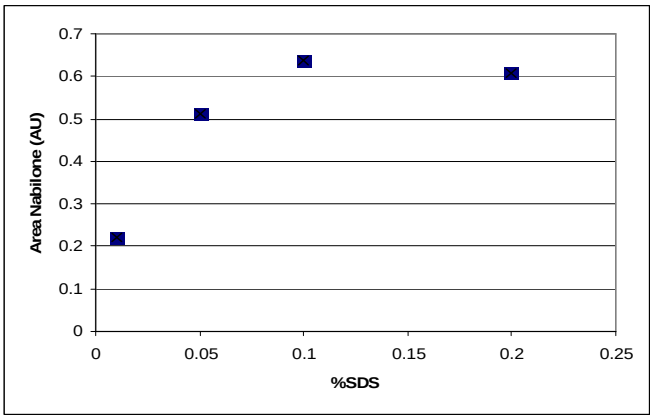


Fig.1: Peak area of Nabilone in dissolution medium containing different concentrations of SDS after filtration through a membrane filter.

3.) Comparison of dissolution media

The dissolution measurements in each dissolution medium of the Nabilone capsule batch LJ 061016 (test capsules) and batch 021 (Cambridge originator product) were made under exactly the same conditions. Samples from 12 capsules per batch and medium were withdrawn from the dissolution medium during the dissolution at 5 time points. Each sample was analyzed by HPLC chromatography for the % of Nabilone dissolved and a graph of % Nabilone dissolved against time was recorded (dissolution profile).

Investigated media:

1.) 0.1 M HCl + 0.1% SDS (MEDIA 1)
2.) Acetate buffer pH 4.5 + 0.1% SDS (MEDIA 2)
3.) Phosphate buffer pH 6.8 + 0.1% SDS (MEDIA 3)

The results are presented on the following pages.

MEDIA 1 – 0.1 N HCL + 0.1% SDS

Table 1: Dissolution of originator product (Cambridge lot 021) in 0.1 N HCl + 0.1 % SDS

Withdrawal t (min)	Dissolution R(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	65 %	7 %	10.8 %
30	77 %	6 %	7.8 %
45	82 %	5 %	6.1 %
60	84 %	4 %	4.8 %
75	85 %	4 %	4.7 %

Table 2: Dissolution of Nabilone test batch (LJ 061016) in 0.1 N HCl + 0.1 % SDS

Withdrawal t (min)	Dissolution T(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	70 %	7 %	10.0 %
30	79 %	4 %	5.1 %
45	82 %	4 %	4.9 %
60	83 %	4 %	4.8 %
75	85 %	3 %	3.5 %

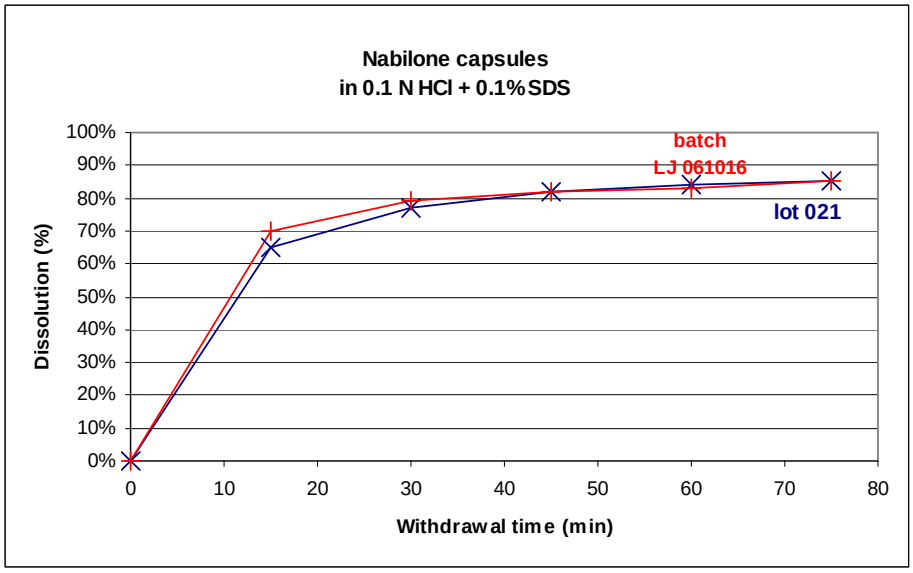


Figure 2: Comparison of profiles in 0.1 N HCl + 0.1 % SDS

Difference factor:	f1 = 2	f1 ≤ 15
Similarity factor:	f2 = 79	f2 ≥ 50

Based on the results, the dissolution profiles of the test batch (LJ 061016) and originator product (Cambridge, lot 021) in 0.1 N HCl + 0.1 % SDS are considered as similar.

MEDIA 2 – Acetate buffer pH 4.5 + 0.1 % SDS

Table 3: Dissolution of originator product (Cambridge lot 021) in acetate buffer + 0.1% SDS

Withdrawal t (min)	Dissolution R(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	52 %	4 %	7.7 %
30	59 %	3 %	5.1 %
45	60 %	5 %	8.3 %
60	63 %	4 %	6.3 %
75	63 %	5 %	7.9 %

Table 4: Dissolution of Nabilone test batch (LJ 061016) in acetate buffer + 0.1 % SDS

Withdrawal t (min)	Dissolution R(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	58 %	4 %	6.9 %
30	64 %	4 %	6.3 %
45	65 %	4 %	6.2 %
60	66 %	3 %	4.5 %
75	66 %	3 %	4.5 %

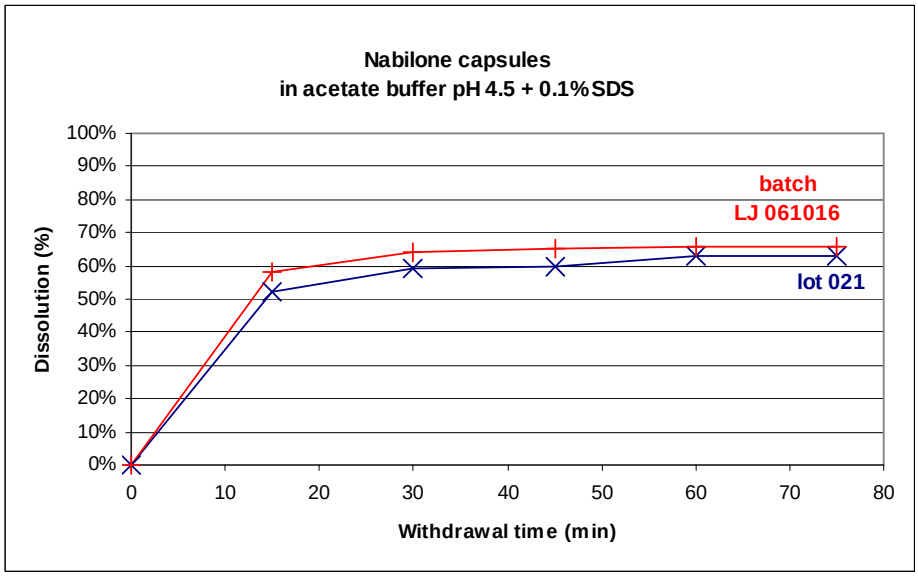


Figure 3: Comparison of profiles in acetate buffer pH 4.5 + 0.1 % SDS

Difference factor:	f1 = 7	f1 ≤ 15
Similarity factor:	f2 = 67	f2 ≥ 50

Based on the results, the dissolution profiles of the test capsules (LJ 061016) and originator product (Cambridge, lot 021) in acetate buffer pH 4.5+ 0.1 % SDS are considered as similar.

MEDIA 3 – Phosphate buffer pH 6.8 + 0.1 % SDS

Table 5: Dissolution of originator product (Cambridge # 021) in phosphate buffer+0.1% SDS

Withdrawal t (min)	Dissolution R(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	63 %	6 %	9.5 %
30	74 %	5 %	6.8 %
45	76 %	5 %	6.6 %
60	79 %	5 %	6.3 %
75	81 %	4 %	4.9 %

Table 6: Dissolution of Nabilone test batch (LJ 061016) in phosphate buffer + 0.1 % SDS

Withdrawal t (min)	Dissolution R(t) (n= 12)	Standard deviation (n=12)	Coefficient of variation (CV)
15	58 %	6 %	10.3 %
30	69 %	6 %	8.7 %
45	73 %	6 %	8.2 %
60	75 %	5 %	6.7 %
75	77 %	5 %	6.5 %

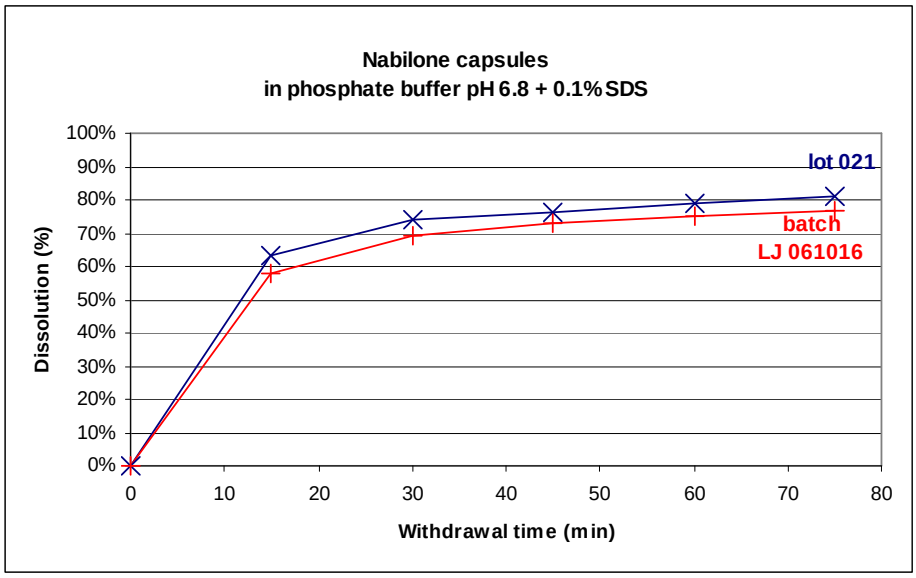


Figure 4: Comparison of profiles in phosphate buffer pH 6.8 + 0.1 % SDS

Difference factor: f1 = 6 f1 ≤ 15
Similarity factor: f2 = 68 f2 ≥ 50

Based on the results, the dissolution profiles of the test capsules (LJ 061016) and originator product (Cambridge, lot 021) in phosphate buffer pH 6.8+ 0.1 % SDS are considered as similar.

4.) Conclusion

The validation of the determinative HPLC method was conducted in terms of specificity, linearity, accuracy and ruggedness. All data confirmed that the HPLC method is suitable for the determination of the content of Nabilone released from Nabilone capsules.

The Nabilone capsule batch LJ 061016 show similar dissolution profiles in all 3 media tested.

Due to the highest dissolution rate in 0.1 N HCl containing 0.1% SDS medium this dissolution medium was selected for use in the control of the finished product.

2.1.P.2.2.3.2 Comparative Dissolution Profile After Minor Change in Process

The manufacturing process was transferred from Nycomed GmbH to SwissCo Services AG. Please refer to Section 2.1.P.2.3 for a summary of the tech transfer activities.

As investigated at Nycomed, a process overage was not required in the manufacturing process implemented at SwissCo Services AG. However, a greater quantity of ethanol during granulation was required in order to obtain a less viscous granulation solution to prevent clogging of the spraying nozzle. As the solvent is removed during the drying process, this has no impact on the final composition of the drug product.

Dissolution profile data of the two validation batches manufactured at SwissCo Services AG and comparative data of two batches from previous final product manufacturer Haupt Pharma Wolfratshausen was generated in order to demonstrate that changes made to the manufacturing process has no impact on the bioavailability of the finished product.

The comparative dissolution profiles were generated using the method described in Section 2.1.P.5.2. The results are presented in the Table 7 and graph below (each value is the mean of 12 values – one per vessel).

Table 7: Overview of the Results for the Dissolution Comparative Study

	Haupt Pharma Wolfratshausen		**SwissCo Services AG**	
Time [min]	**Batch A799A**	**Batch D443A**	**Batch 09030016**	**Batch 09010036**
0	0	0	0	0
15	85	85	75	77
30	92	92	85	87
45	95	95	88	91
60	95	96	90	92
75	95	97	91	93

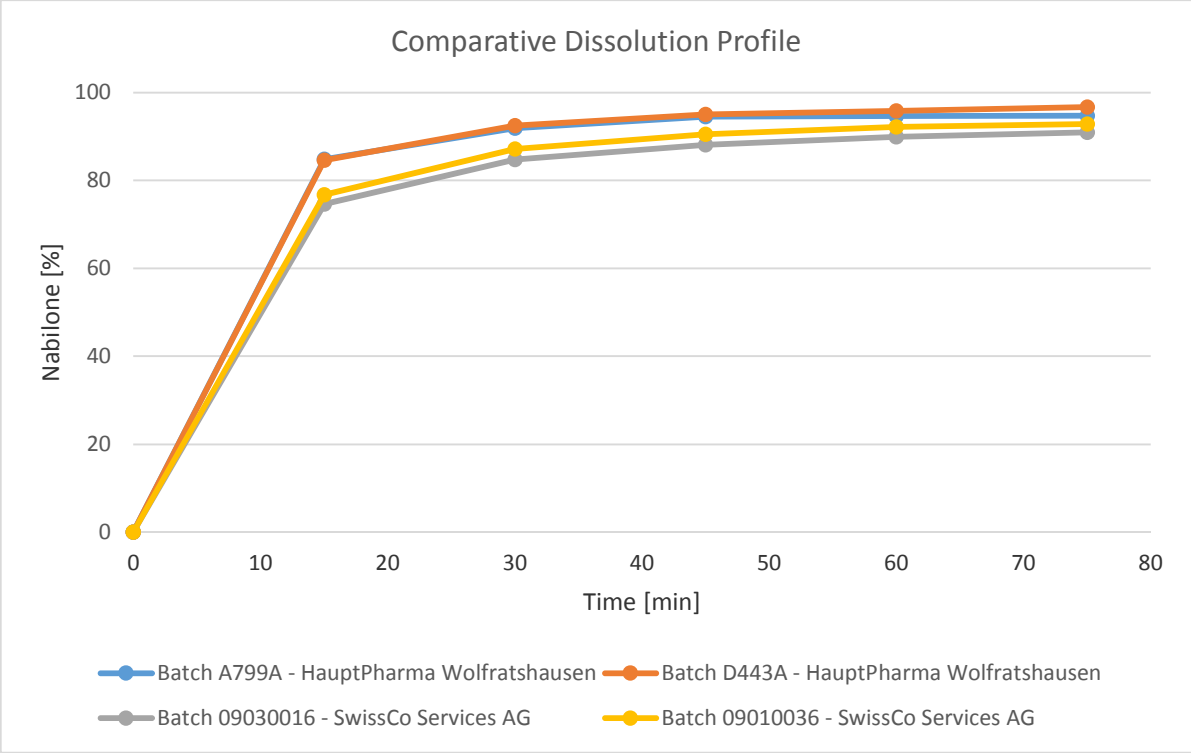


Figure 5: Comparative Dissolution Profile of SwissCo vs Haupt Pharma Batches

A comparison with batches manufactured at Nycomed was not possible as no batches were manufactured since the validation batches (2008) and thus no samples were available. In addition, while both batches manufactured at SwissCo Services AG were manufactured without process overage for the drug substance, only batch 09010036 has been manufactured using a granulation solution containing a greater quantity of Ethanol.

The dissolution data generated are comparable for all batches: more than 85% is dissolved within 15 – 30 minutes, thereby confirming that the changes made to the manufacturing process have no impact on the bioavailability of the finished product.

2.1.P.2.2.3.3 Dissolution testing for Nabilone 0.25 mg capsules

During development of the 0.25 mg strength, size 4 capsules were manually filled with 36.8 mg Nabilone. These test capsules were used for dissolution testing (n=6). Two runs were performed and compared to the results received for Nabilone 1 mg capsules during process validation.

1st run

Samples	%Nabilone/capsule	%Nabilone/capsule MEAN
1	89.4	93
2	91.3	
3	89.8	
4	94.9	
5	96.2	
6	95.5	

2nd run

Samples	%Nabilone/capsule	%Nabilone/capsule MEAN
1	89.1	93
2	86.1	
3	94.2	
4	95.6	
5	94.7	
6	99.6	

Comparison between 1 mg and 0.25 mg capsules

0.25 mg capsules		1 mg capsules	
Run	Dissolution [%] after 60 min	Batch	Dissolution [%] after 60 min
1st run	93	1st validation batch	85
2nd run	93	2nd validation batch	91
MEAN	93	MEAN	88

The release of the API into the dissolution media is within the final product specification of NLT 70% (Q) for both strengths after 60 min. No relevant difference in dissolution between the two strengths could be observed.

The dissolution method for 0.25 mg capsules was validated with the conditions described below which are identical to the conditions used for 1 mg capsules. Details are shown in 2.1.P.5.3.

Apparatus	Basket apparatus
Stirring rate	75 rpm/min
Medium	0.1 M hydrochloric acid containing 0.1% sodium dodecyl sulphate
Temperature	37°C
Volume	1000 ml
Sample drawing	After 60 min / 1.5 ml

2.1.P.2.3 Manufacturing Process Development

Lab scale process development was performed at Chemisch-pharmazeutisches Labor Rolf Sachse GmbH (CpL Sachse), Germany. The scale-up and resulting commercial manufacturing process was done at Nycomed (now Takeda), Germany using a single pot granulation process. Three validation batches were manufactured at Nycomed.

Later, the product was transferred to Haupt Pharma Wolfratshausen. The manufacturing process at Haupt differed from the Nycomed process in regard to equipment and splitting into sublots.

Finally, the process was implemented at SwissCo. The manufacture at SwissCo will be carried out according to the initial single pot granulation process developed by Nycomed.

2.1.P.2.3.1 Lab Scale Process Development at CpL Sachse

The following procedure was applied:

Povidone (K25) was added to Ethanol in portions via a glass funnel upon stirring. The funnel was rinsed and stirring continued until complete dissolution of Povidone (clear yellow solution, viscous).

Nabilone was added in portions and solution was sonicated to support dissolution.

The solution was filtered (clear, yellow solution). Filter was rinsed with Ethanol.

The solution of Nabilone and Povidone in Ethanol was added to a part of the corn starch in a stainless steel vessel in portions upon gentle stirring. As a result a viscous, almost white suspension is obtained.

The suspension is applied as a thin layer and dried in a drying hurdle at room temperature (best upon applying vacuum) overnight resulting in a white slightly humid solid. This solid was grinded in a mortar and dried in the drying hurdle until uniformity of weight.

The solid was then grinded again in a mortar. Remaining starch was added and gently mixed. The thus resulting capsule mass was filled and stored in brown glass bottles.

Capsule mass was manually filled into capsules size 3 for development batches.

2.1.P.2.3.2 Scale-up & Tech Transfer CpL Sachse – Nycomed (now Takeda)

The process development for the finished product Canemes 1.0 mg was performed at CpL Sachse and further transferred to Nycomed GmbH, Germany. The scale up activities included several trials, followed by three consecutive validation batches.

The manufacturing process consists of the following manufacturing steps:

- Preparation of the spraying solution containing the API in an ethanolic PVP (Povidone) solution
- Granulation of Corn Starch with this spraying solution

- Screening of this granulate
- Preparation of the capsules filling mixture
- Filling of hard gelatine capsules (size 2)
- Packaging

For the preliminary trials at Nycomed placebo as well as surrogate material were evaluated, if the utilized equipment (see equipment list below), the selected parameters and the settings for the manufacturing process were able to lead to a product meeting predefined quality attributes.

Several trials were produced to assess the manufacturability of the anticipated product using the provided equipment. The parameters and settings of these trials are summarised below.

Based on the obtained results, the process was robust and reproducible to proceed to the process validation batches.

2.1.P.2.3.2.1 Equipment

The following pieces of equipment were used at Nycomed.

- High shear mixer-granulator-dryer type P/VAC 50, company Diosna or equivalent
- Tumble blender LM 40, 40 l container, company Bohle or equivalent
- Capsule filling machine GKF 2000, company BOSCH or equivalent
- Capsule filling machine KFM III-C, company Harro Höfliger or equivalent
- Capsule filling machine Modu C, company Harro Höfliger or equivalent
- Precisa 100% control unit for the capsules, company IMA or equivalent

All required qualification work was completed successfully prior to the utilisation.

2.1.P.2.3.2.2 Manufacturing of the pre-trial batches

Within preliminary trials, 10 scale-up batches were manufactured to assess the anticipated manufacturing process using the equipment listed in the section above. The challenge of the scale-up was to quantitatively transfer of the ethanolic API-PVP solution in the granulator bowl and to achieve a homogeneous distribution of the API in the capsule filling mixture.

For the capsule filling of the pre-trial batches, the capsule filling machine GKF 2000 of the company BOSCH was used. As the obtained yields using this full scale equipment were not acceptable with regards to losses due to the small batch size, it was decided to use the capsule filling machines of Harro Höfliger for the capsule filling process of the validation batches. Acceptable yields were obtained within filling trials prior to this.

One of the trial batches was manufactured using placebo (Starch 1500) and 9 batches were manufactured using Theophylline as a surrogate-API, as this is an established API at the Nycomed GmbH site, including cleaning validation data. Though, this API was not entirely soluble in the ethanolic PVP-solution, and therefore the filtration step of the granulation medium was removed for these trials.

The following parameters and settings were investigated:

- Amount (kg) of starch 1500
- Amount (kg) of Ethanol
- Stirring conditions for the preparation of the granulation medium
- Necessity of API-production overage
- Nozzle type
- Spray rate
- Vacuum to be applied
- Settings for impeller as well as chopper speed
- Necessity and duration of intermediate drying step
- Screen sizes for the screening of the granulate
- Blending conditions for the preparation of the capsule filling mixture
- Yields

Table 1: Summary of data for trial batches 000003, 000004, 000005, 000006, 000007

Pre-trial batches		Batch	Batch	Batch	Batch	Batch
Parameters/ Settings	**Specification/ Target**	**000003**	**000004**	**000005**	**000006**	**000007**
Input						
Theophylline	t.b.d.	105% = 107,2 g Theophyllin	100% = 102,1 g Theophyllin	100% = 102,1 g Theophyllin	100% = 102,1 g Theophyllin	100% = 102,1 g Theophyllin
Starch 1500	t.b.d.	13,0000 kg Starch	13,0000 kg Starch	13,0000 kg Starch	13,0000 kg Starch	14,1780 kg Starch
Ethanol	t.b.d.	2,4173 kg	2,4173 kg	2,4173 kg	2,4173 kg	4,0800 kg
Ultra Turrax	t.b.d.	2 minutes	2 minutes	2 minutes	2 minutes	2 minutes
Machine	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50
Spraying						
Nozzle	t.b.d.	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,2 (with compressed nitrogen)
Sprayrate	t.b.d.	200 g/ min	200 g/ min	200 g/ min	200 g/ min	300 g/ min
Impeller	t.b.d.	100 rpm	100 rpm	100 rpm	100 rpm	100 rpm
Chopper	t.b.d.	1500 rpm	1500 rpm	1500 rpm	1500 rpm	500 rpm
Intermediate-drying	t.b.d.	Yes	No	Yes	Yes	Yes
Duration	t.b.d.	20 Minutes	n.a.	20 Minutes	20 Minutes	2 x 20 Minutes
Drying						
Temp.-control system	t.b.d.	40°C	40°C	40°C	40°C	30 - 40°C
Vacuum	t.b.d.	1080 rpm	1080 rpm	1080 rpm	1080 rpm	1080 rpm
Impeller	t.b.d.	10 rpm	10 - 40 rpm, material on the walls of the bowl	10 rpm	10 rpm	blocked
Screensize	t.b.d.	2,0 and 1,0 mm	2,0 and 1,0 mm	2,0 and 1,0 mm	2,0 and 1,0 mm	3,15 mm
Partical size	t.b.d.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.
Yield Capsulefilling mix.	t.b.d.	96,90%	94,60%	94,90%	93,70%	n.a.
Blend uniformity Capsulefilling mixture	single value +/- 10% of mean; standard deviation <5,0%	95,0 - 107,1 % (5% overage)	no analytical inspection	94,2% - 105,0%	97,5% - 102,4%	no analytical inspection
Watercontent (KF)	t.b.d.	no analytical inspection	no analytical inspection	no analytical inspection	no analytical inspection	no analytical inspection
LOD	t.b.d.	8,02%	8,32%	7,41%	7,43%	8,36%
Residual solvent	ICH Guideline Q3C (0,5%)	0,46% Ethanol	no analytical inspection	0,25% Ethanol	0,27% Ethanol	no analytical inspection
Capsule filling						
Machine	t.b.d.	n.a.	Bosch GKF 2000	Bosch GKF 2000	Bosch GKF 2000	Bosch GKF 2000
Capsule size	t.b.d.	n.a.	3	3	3	2
Powder station	t.b.d.	n.a.	Yes	Yes	Yes	No
Pellet station	t.b.d.	n.a.	No	No	No	Yes => Microtablets
Capsule quantity complete	t.b.d.	n.a.	n.a.	70.498	76.877	6.880
Capsule quantitiy in spec.	t.b.d.	n.a.	n.a.	63.642	68.926	1528 => stopped process
Average [mg] (IMA Precisa)	t.b.d.	n.a.	n.a.	196,0	199,5	217,5
Coefficient of variation [%] (IMA Precisa)	t.b.d.	n.a.	n.a.	1,97	1,65	1,72
Yield Capsule filling	t.b.d.	n.a.	n.a.	65,8%	72,1%	n.a.
Uniformity of dosage Units	Ph.Eur. 2.9.40	no analytical inspection	Beginning: 90,57 - 95,47% AV=9,0 Middle 88,91 - 95,19% AV=11,3 End: 91,84 - 94,88% AV=8,4	20.000: 91,46 - 103,09% AV=10,4 40.000: 93,28 - 110,91% AV=13,1	beginning: 87,88 - 101,39% AV=14,8 20.000: 93,78 - 103,53% AV=7,4 40.000: 94,71 - 106,31% AV=8,9 60.000: 94,71 -106,31% AV= 7,1	no analytical inspection

Table 2: Summary of data for trial batches 000009, 000011, 000012, 000015, 000016

			Pre-validation batches			
		Batch	Batch	Batch	Batch	Batch
Trial/ Batch	Specification/Target	000009	000011	000012	000015	000016
Input						
Theophylline	t.b.d.	0% = 0,0 g	100% = 102,1 g Theophylline	100% = 102,1 g Theophylline	100% = 102,1 g Theophylline	100% = 102,1 g Theophylline
Starch 1500	t.b.d.	14,1782 kg Starch 1500	14,1780 kg Starch 1500	14,1780 kg Starch 1500	14,1780 kg Starch 1500	14,1780 kg Starch 1500
Ethanol	t.b.d.	2,4173 kg	2,4173 kg	2,4173 kg	2,0173 kg	2,0173 kg
Ultra Turrax	t.b.d.	2 minutes	2 minutes	2 minutes	2 minutes	2 minutes
Machine	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50	Diosna VAC 50
Spraying						
Nozzle	t.b.d.	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)	1,6/ 30° (without compressed nitrogen)
Sprayrate	t.b.d.	measuring cup	200 g/ min	200 g/ min	Diosna VAC 50	Diosna VAC 50
Impeller	t.b.d.	100 rpm	100 rpm	100 rpm	100 rpm	100 rpm
Chopper	t.b.d.	500 rpm	500 rpm	500 rpm	500 rpm	500 rpm
Intermediate-drying	t.b.d.	No	Yes	Yes	Yes	Yes
Duration	t.b.d.		6 minutes	6 minutes	6 minutes	6 minutes
Drying						
Temp.-control system	t.b.d.	45 - 50°C	40°C	40°C	40°C	40°C
Vacuum	t.b.d.	3000 rpm (max.)	3000 rpm (max.)	3000 rpm (max.)	3000 rpm (max.)	3000 rpm (max.)
Impeller	t.b.d.	5 rpm	10 rpm	10 rpm	20 rpm	5 rpm
Screensize	t.b.d.	3,15 mm	2,0 mm	2,0 mm	2,0 mm	2,0 mm
Partical size	t.b.d.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.	refer to section 2.1.2.
Yield Capsulefilling mix.	t.b.d.	75,70%	94,80%	95,50%	n.a.	n.a.
Blend uniformity Capsulefilling mixture	single value +/- 10% of mean; standard deviation <5,0%	no analytical inspection	95,6% - 105,1%	no analytical inspection	no analytical inspection	no analytical inspection
Watercontent (KF)	t.b.d.	no analytical inspection	no analytical inspection	no analytical inspection	6,0%	n.a.
LOD	t.b.d.	8,08%	6,42%	5,16%	6,44%	5,87%
Residual solvent	ICH Guideline Q3C (0,5%)	no analytical inspection	0,50% Ethanol	0,20% Ethanol	0,50% Ethanol	0,27% Ethanol
Capsule filling						
Machine	t.b.d.	n.a.	Bosch GKF 2000	Bosch GKF 2000	Harro Höfliger KPSFMA2 - Only Setup -	n.a.
Capsule size	t.b.d.	n.a.	3	3	2	n.a.
Powder station	t.b.d.	n.a.	Yes	Yes	Yes	n.a.
Pellet station	t.b.d.	n.a.	No	No	No	n.a.
Capsule quantitiy complete	t.b.d.	n.a.	87.952	81.901	n.a.	n.a.
Capsule quantity in spec.	t.b.d.	n.a.	67.985	67.949	n.a.	n.a.
Average [mg] (IMA Precisa)	t.b.d.	n.a.	198,8	197,4	n.a.	n.a.
Coefficient of variation [%] (IMA Precisa)	t.b.d.	n.a.	2,04	2,03	n.a.	n.a.
Yield Capsule filling	t.b.d.	n.a.	70,3%	69,8%	n.a.	n.a.
Uniformity of dosage Units	Ph.Eur. 2.9.40	no analytical inspection	beginning: 94,36 - 104,63% AV=8,8 60.000: 90,82 -97,71% AV= 9,6	beginning: 94,15 - 104,91% AV=9,8 60.000: 93,24 -114,05% AV= 13,8	beginning: 93,85 - 106,79% AV=11,3 10.000: 93,15 -106,34% AV= 9,2	no analytical inspection

During the set-up of the process, it was observed that using ethanolic-PVP solution as a granulation liquid and starch 1500 leads to a fine granulate. Nevertheless, it was attempted to adhere granulate with an acceptable particle size distribution leading to good flow properties for the consecutive capsule filling process. For this reason, different investigations and optimisations took place:

- The amount of starch 1500 was increased to 14.178 kg (full amount for a batch is 15 kg) to reduce over wetting and adherence of material on the inner walls of the granulator bowl.
- As it was observed - even reduced - that the granulate still tends to stick to the inner walls of the granulator bowl, an intermediate drying step was implemented and the material adhering on the walls was scraped off before the granulation was continued with the second phase. A duration for the intermediate drying of 6 min was discovered as being appropriate.
- The granulate is screened after the discharging from the granulator. During the pre-trials different screen sizes and combinations were used and the particle size distribution was determined via a sieve shaker. As there were no major differences observed with regards to the particle size due to the fact that a fine granulate can be manufactured with the transferred process, a screen size of 2.0 mm was assessed as being appropriate to destroy the few agglomerates after discharging.

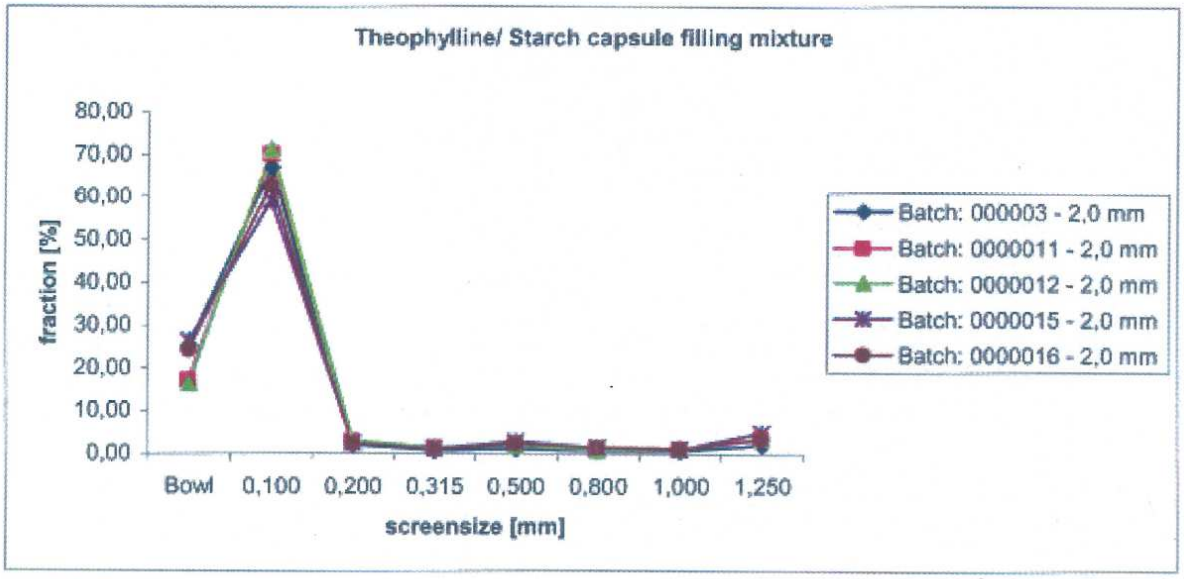


Figure 1: Particle size distribution of screened Theophylline/Starch 1500 granulate, screen size 2.0 mm

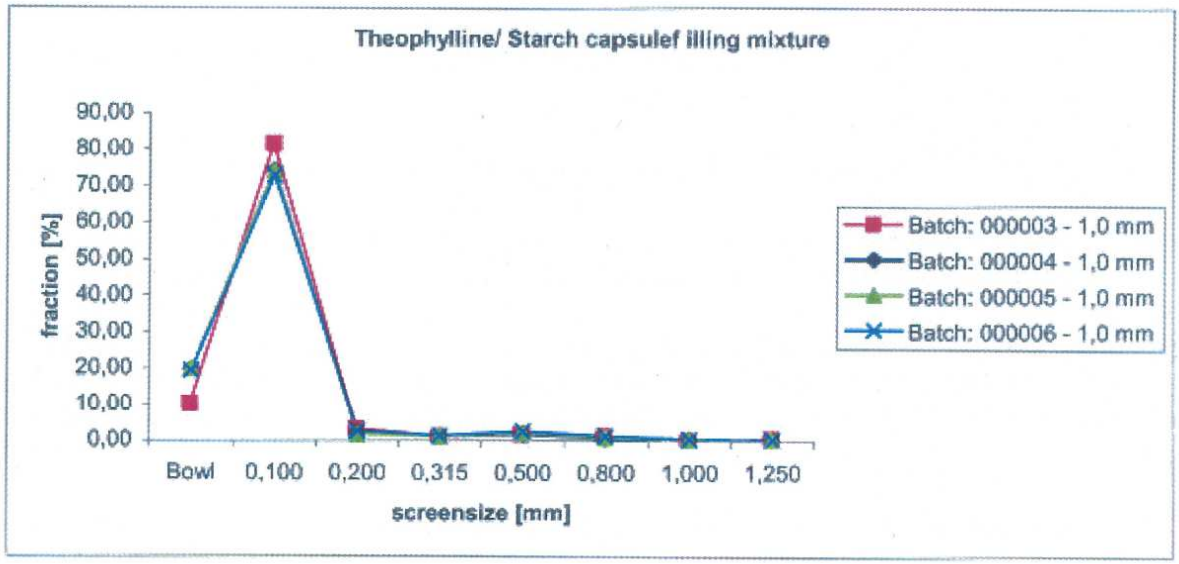


Figure 2: Particle size distribution of screened Theophylline/Starch 1500 granulate, screen size 1.0 mm

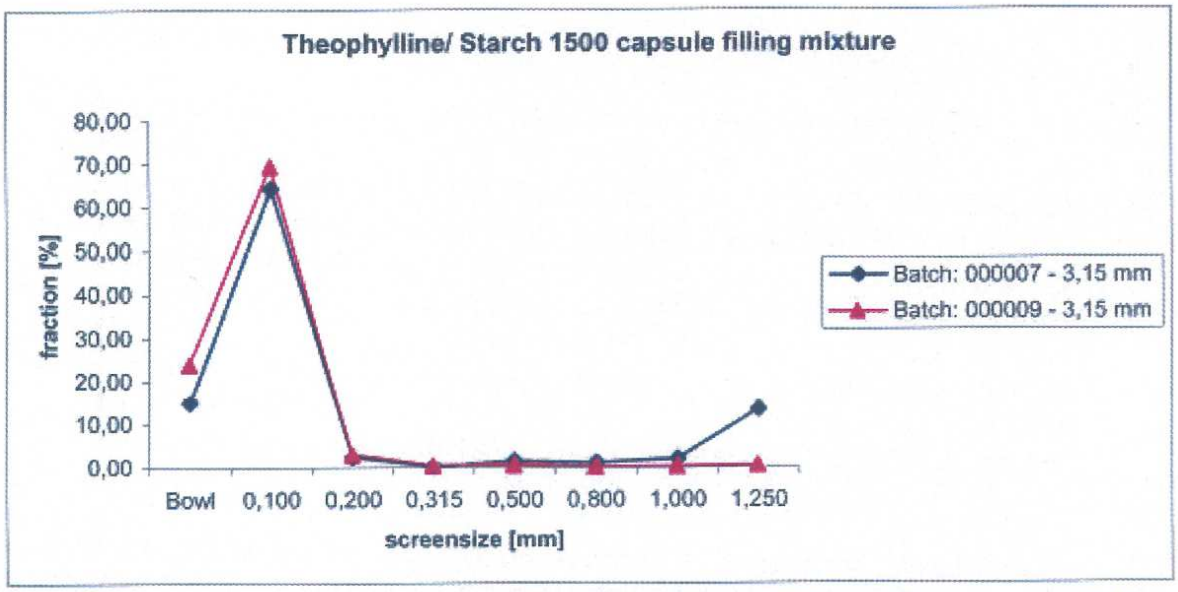


Figure 3: Particle size distribution of screened Theophylline/Starch 1500 granulate, screen size 3.15 mm

The pre-trial batches, which could be manufactured successfully resulting in consolidated findings for the upcoming process validation batches, were tested for:

- Blend uniformity of the capsule filling mixture
- Uniformity of single dosage units (beginning- middle- end of the capsule filling process)
- LOD and /or water content (Karl Fischer) of the capsule filling mixture
- Residual solvents

Please refer to Table 1 and 2 for the results pertaining to water content, LOD and residual ethanol.

The blend uniformity results are summarised in the Table 3 below. The content uniformity results are presented in Tables 4 to 9.

Table 3: Results for Blend Uniformity

Unit: mg theophylline/ 1000 mg mixture		**000003**	**000005**	**000006**	**000011**
A1	**1**	6.7320	6.9473	6.9099	6.6651
	2	7.0016	7.0093	6.8766	6.3569
A2	**1**	7.0472	6.5527	6.9493	6.2411
	2	7.0698	6.9775	6.7814	6.2579
A3	**1**	7.2982	7.1571	6.7514	6.3836
	2	6.7458	7.2988	6.6821	6.1693
A4	**1**	7.2232	6.6238	6.7117	6.5206
	2	7.1618	7.1728	6.9639	6.5053
A5	**1**	7.5829	6.9849	6.9940	6.7829
	2	6.9712	6.8219	6.6604	6.6404
Mean		7.0834	6.9546	6.8281	6.4523
%RSD		3.6%	3.4%	1.8%	3.2%

Table 4: Results for Content Uniformity – Batch 000004

Sampling / Capsule	Beginning			Middle			End		
	Fill Weight [mg]	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**
1	149.6	0.9165	91.65	144.8	0.9224	92.24	149.0	0.9488	94.88
2	143.8	0.9057	90.57	151.2	0.9191	91.91	147.9	0.9275	92.75
3	147.7	0.9468	94.68	147.2	0.9233	92.33	148.5	0.9430	94.30
4	147.7	0.9248	92.48	147.9	0.9059	90.59	150.5	0.9216	92.16
5	149.0	0.9311	93.11	149.1	0.9042	90.42	147.8	0.9169	91.69
6	150.2	0.9346	93.46	148.1	0.9091	90.91	146.3	0.9184	91.84
7	148.0	0.9248	92.48	151.9	0.9519	95.19	148.9	0.9216	92.16
8	151.8	0.9547	95.47	145.2	0.9148	91.48	148.1	0.9186	91.86
9	149.6	0.9534	95.34	149.0	0.9485	94.85	148.6	0.9394	93.94
10	150.4	0.9382	93.82	143.6	0.8891	88.91	150.2	0.9394	93.94
Mean	148.8	0.9331	93.31	147.8	0.9188	91.88	148.6	0.9295	92.95
Min – Max	143.8 – 151.8	0.9057 – 0.9547	90.57 – 95.47	143.6 – 151.9	0.8891 – 0.9519	88.91 – 95.19	146.3 – 150.5	0.9187 – 0.9488	91.84 – 94.88
%RSD	1.5	1.7	1.7	1.8	2.1	2.1	0.8	1.3	1.3
AV	N/A	N/A	9.0	N/A	N/A	11.3	N/A	N/A	8.4

Table 5: Results for Content Uniformity – Batch 000005

Sampling / Capsule	20 min			40 min		
	Fill Weight [mg]	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**
1	151.2	0.9696	96.96	149.3	0.9585	95.85
2	149.1	0.9323	93.23	150.4	0.9759	97.59
3	153.4	1.0278	102.78	149.6	0.9328	93.28
4	147.6	0.9528	95.28	144.4	0.9690	96.90
5	146.8	1.0246	102.46	147.5	1.0092	100.92
6	149.1	0.9682	96.82	150.0	1.0667	106.67
7	147.8	0.9995	99.95	153.1	1.0442	104.42
8	151.3	1.0309	103.09	152.8	1.0330	103.30
9	146.0	0.9146	91.46	150.7	1.0341	103.41
10	150.8	0.9701	97.01	149.5	1.1091	110.91
Mean	N/A	0.9790	97.90	N/A	1.0133	101.33
Min – Max	N/A	0.9146 – 1.0309	91.46 – 103.09	N/A	0.9328 – 1.11091	93.28 – 110.91
%RSD	N/A	4.2	4.2	N/A	5.4	5.4
AV	N/A	N/A	10.4	N/A	N/A	13.1

Table 6: Results for Content Uniformity – Batch 000006

Sampling / Capsule	Beginning			20 min			40 min			60 min		
	Fill Weight [mg]	**Assay [mg/caps]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/caps]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/caps]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/caps]**	**Assay [%]**
1	148.3	0.9326	93.26	150.5	1.0081	100.81	150.7	1.0283	102.83	147.6	0.9667	96.67
2	149.4	0.9425	94.25	147.6	1.0134	101.34	156.4	1.0569	105.69	144.3	0.9310	93.10
3	152.9	0.9405	94.05	147.8	0.9378	93.78	154.6	1.0631	106.31	148.1	1.0049	100.49
4	144.5	0.9117	91.17	153.3	0.9782	97.82	148.6	0.9656	96.56	149.4	0.9779	97.79
5	155.3	1.0018	100.18	150.4	0.9809	98.09	152.9	1.0024	100.24	147.5	1.0002	100.02
6	152.6	0.9974	99.74	153.6	1.0079	100.79	144.7	1.0136	101.36	148.6	0.9652	96.52
7	148.5	1.0139	101.39	156.1	1.0353	103.53	154.6	1.0202	102.02	150.8	1.0168	101.68
8	145.3	0.9045	90.45	147.1	0.9416	94.16	153.1	1.0168	101.68	143.7	0.9520	95.20
9	143.2	0.9275	92.75	148.1	0.9939	99.39	147.7	0.9491	94.91	150.0	1.0145	101.45
10	143.0	0.8788	87.88	153.6	1.0006	100.06	145.1	0.9754	97.54	150.4	0.9996	99.96
Mean	N/A	0.9451	94.51	N/A	0.9898	98.98	N/A	1.0091	100.91	N/A	0.9829	98.29
Min	N/A	0.8788	87.88	N/A	0.9378	93.78	N/A	0.9471	94.71	N/A	0.9310	94.71
Max	N/A	1.0139	101.39	N/A	1.0353	103.53	N/A	1.0631	106.31	N/A	1.0168	106.31
%RSD	N/A	4.8	4.8	N/A	3.1	3.1	N/A	3.7	3.7	N/A	2.9	2.9
AV	N/A	N/A	14.8	N/A	N/A	7.4	N/A	N/A	8.9	N/A	N/A	7.1

Table 7: Results for Content Uniformity – Batch 000011

Sampling / Capsule	Beginning			60 min		
	Fill Weight [mg]	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**
1	145.4	0.9436	94.36	143.8	0.9670	96.70
2	145.7	0.9636	96.36	145.2	0.9392	93.92
3	147.4	0.9657	96.57	142.3	0.9421	94.21
4	146.6	0.9924	99.24	152.0	0.9540	95.40
5	152.3	0.9810	98.10	143.7	0.9771	97.71
6	147.7	0.9598	95.98	143.3	0.9082	90.82
7	147.8	1.0389	103.89	143.8	0.9767	97.67
8	154.5	1.0463	104.63	149.3	0.9540	95.40
9	154.1	1.0207	102.07	144.4	0.9322	93.22
10	146.2	0.9526	95.26	144.6	0.9144	91.44
Mean	N/A	0.9865	98.65	N/A	0.9465	94.65
Min – Max	N/A	0.9436 – 1.0463	94.36 – 104.63	N/A	0.9082 – 0.9771	90.82 – 97.71
%RSD	N/A	3.7	3.7	N/A	2.5	2.5
AV	N/A	N/A	8.8	N/A	N/A	9.6

Table 8: Results for Content Uniformity – Batch 000012

Sampling / Capsule	Beginning			60 min		
	Fill Weight [mg]	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**
1	146.4	1.0240	102.40	146.8	1.0431	104.31
2	149.7	0.9555	95.55	144.6	1.0151	101.51
3	150.6	1.0156	101.56	139.8	1.0162	101.62
4	147.2	0.9553	95.53	148.6	0.9810	98.10
5	152.2	1.0111	101.11	142.4	1.1405	114.05
6	151.1	0.9445	94.45	145.6	1.0007	100.07
7	150.3	0.9875	98.75	146.7	0.9859	98.59
8	151.2	1.0491	104.91	143.2	0.9324	93.24
9	147.7	1.0408	104.08	148.7	0.9799	97.99
10	147.1	0.9415	94.15	147.6	0.9532	95.32
Mean	N/A	0.9925	99.25	N/A	1.0048	100.48
Min – Max	N/A	0.9415 – 1.0491	94.15 – 104.91	N/A	0.9324 – 1.1405	93.24 – 114.05
%RSD	N/A	4.1	4.1	N/A	5.7	5.7
AV	N/A	N/A	9.8	N/A	N/A	13.8

Table 9: Results for Content Uniformity – Batch 000015

Sampling / Capsule	Beginning			10 min		
	Fill Weight [mg]	**Assay [mg/capsule]**	**Assay [%]**	**Fill Weight [mg]**	**Assay [mg/capsule]**	**Assay [%]**
1	146.0	1.0029	100.29	156.5	0.9616	96.16
2	156.0	1.0341	103.41	154.0	0.9730	97.30
3	143.2	0.9391	93.91	155.4	0.9694	96.94
4	157.1	0.9907	99.07	159.3	1.0263	102.63
5	151.2	0.9385	93.85	159.5	1.0166	101.56
6	159.5	1.0548	105.48	157.3	1.0634	106.34
7	158.4	1.0145	101.45	150.4	0.9315	93.15
8	153.5	0.9433	94.33	154.7	0.9916	99.16
9	155.4	1.0183	101.83	150.9	0.9781	97.81
10	161.4	1.0679	106.79	152.4	0.9627	96.27
Mean	154.2	1.0004	100.04	155.0	0.9874	98.74
Min – Max	143.2 – 161.4	0.9385 – 1.0679	93.85 – 106.79	150.4 – 159.5	0.9315 – 1.0634	93.15 – 106.34
%RSD	3.8	4.7	4.7	2.1	3.9	3.9
AV	N/A	N/A	11.3	N/A	N/A	9.2

2.1.P.2.3.2.3 Bulk manufacturing of the process validation batches

The process validation of the manufacturing process of the Canemes 1.0 mg capsules was performed with three consecutive batches and was successfully completed without any deviations at Nycomed GmbH, Germany.

The parameters and settings for the manufacturing of the validation batches basically derived from the manufacturing processes of the pre-trial batches (batches 000011 and 000012) which showed good manufacturability and led to analytical results within specification for all process steps.

According to the manufacturing instructions provided by CPL Sachse, a filtration step for the ethanolic PVP-API solution was kept during the spraying (Filter: Pall, Membrane Disc Filter, 5 µm, Nylon N66 or equivalent) of the granulation medium. The vessel, the stirrer, the tube and the filter were rinsed with ethanol afterwards, no residues could be detected.

Based on the lab scale experiments performed at CpL Sachse, an overage of 5% for the API was included to compensate for the loss of drug substance during the manufacturing process. However, based on the assay results of the process validation batches, the need for the overage was not confirmed. The manufacturing process and the analytical results of the validation batches demonstrated that it could be left out.

It was shown during the manufacturing of three consecutive validation batches, that the manufacturing process described in the Master Batch Records (MBR) is capable of consistently meeting predefined specifications listed in the validation protocol.

2.1.P.2.3.3 Tech Transfer Nycomed – SwissCo

Two technical batches of the blend were manufactured as part of first experiments for process investigations. Loperamide hydrochloride was used as a surrogate API to Nabilone. The granulation process was performed in the single pot granulator; different process settings were investigated. Visual inspection was performed and product characteristics such as particle size distribution, bulk and tapped density, and loss of drying were measured. Within defined positions of the granule container, samples of the granulate were taken to investigate blend uniformity. In a second step, both batches were encapsulated with an encapsulation machine. Samples for content uniformity investigations were taken at the beginning, in the middle and the end of the encapsulation process.

2.1.P.2.3.3.1 Batch Formula

The batch formula of the technical batches is provided in the Table 10 below.

Table 10: Batch Formula of the Technical Batches

Ingredient	Amount		Function
	Per batch [kg]	Per capsule [mg]	
Loperamide HCl	0.100	1.0	Surrogate API
Povidone (K25)	1.00	10.0	Binder
Corn starch, pregelatinised	13.61	136.1	Filler
Ethanol anhydrous [1]	2.36	--	Granulation solvent
Total	14.71	147.0	---

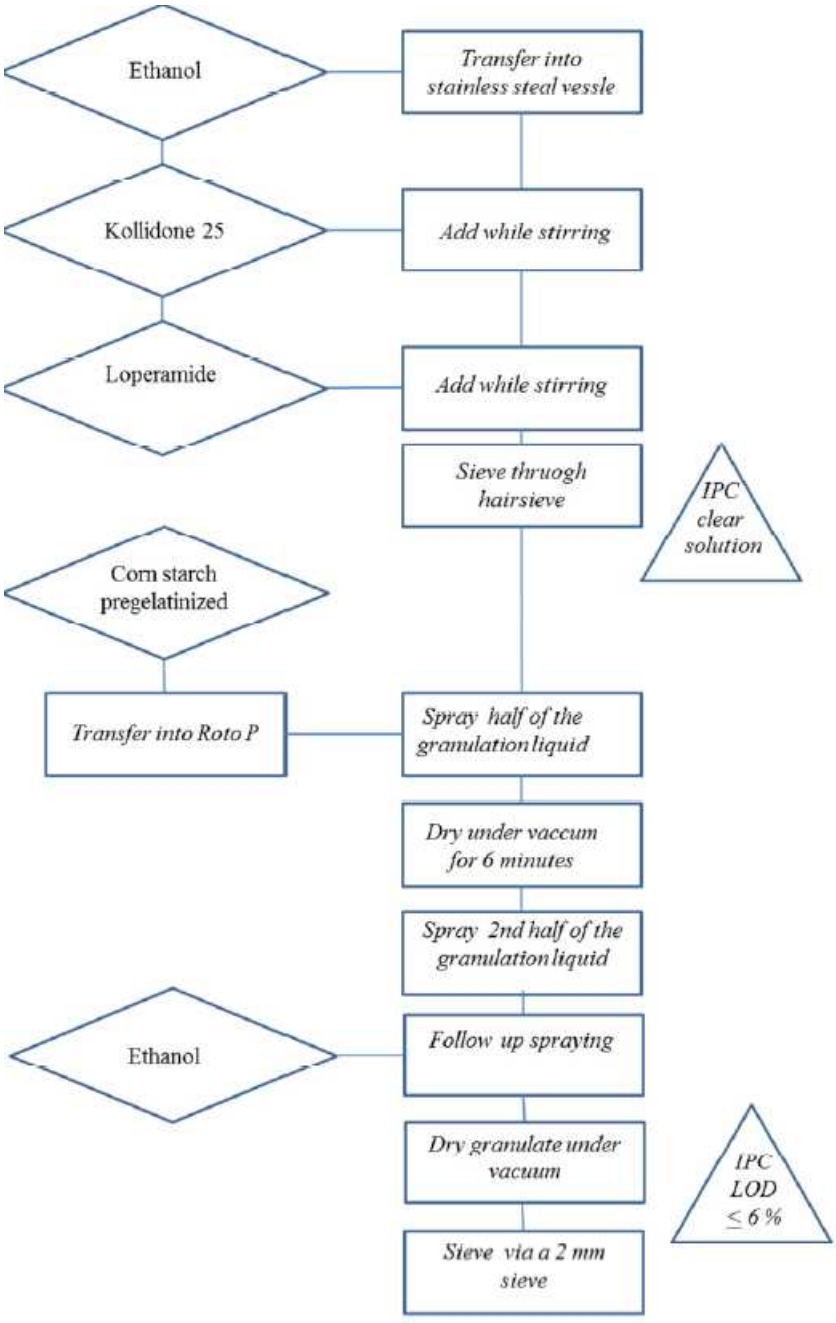
[1] Ethanol serves as a granulation solvent and is not present in the final product

2.1.P.2.3.3.2 Equipment

The granulation step was carried out in a single pot granulator Roto P 50 from Zanchetta. The encapsulation was performed with a Zanasi 5000R encapsulation machine. Although both batches are technical batches, all the pieces of equipment used for the trials are also used to manufacture commercial batches and are therefore appropriately qualified and complies with GMP requirements.

2.1.P.2.3.3.3 Manufacture of the First Technical Batch # AO01001G

Flow Chart Batch # AO01001G



Visual Inspection

The granulate was microscopically inspected and compared to the granulate taken from a Canemes® capsule. Figure 4 shows granules after Roto processing of batch AO01001G; granulate from the Canemes capsule (Batch A799A) is depicted in Figures 5 and 6.

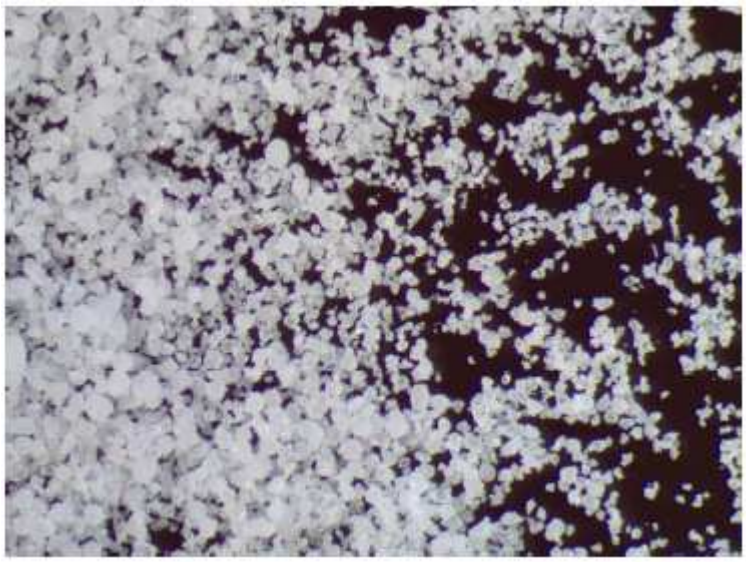


Figure 4: Granulate of Batch AO01001G

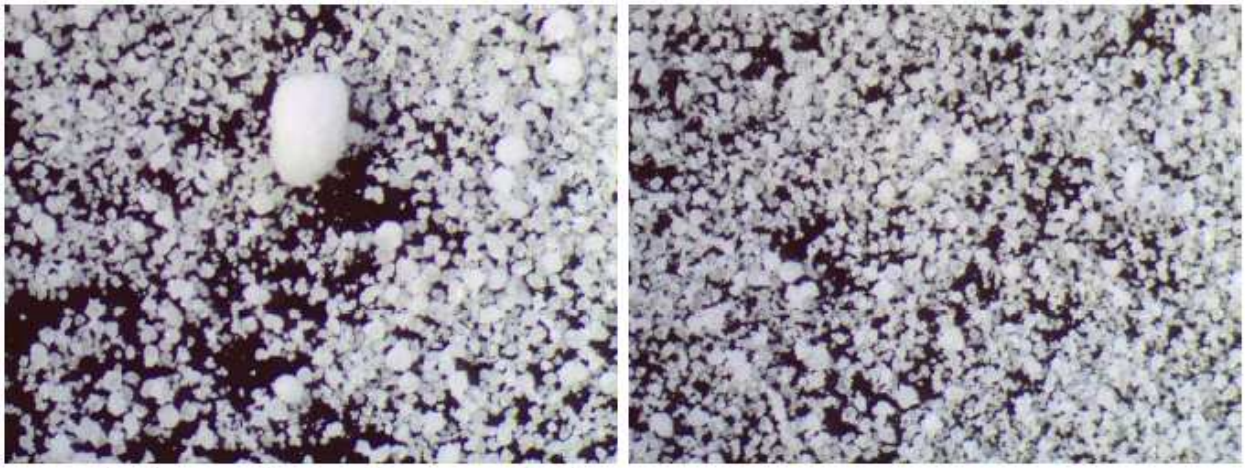


Figure 5 & 6: Granulate of Canemes Batch A799A

Visually, the granules of batch AO01001G and of the originator batch A799A look similar. The particle sizes seem comparable, though some bigger sized particles/agglomerates can be seen in the Canemes granulate.

Particle Size Distribution

The particle size distribution of the granulate AO01001G was determined by sieve analysis and the results are presented in Table 11.

Table 11: Particle Size Distribution Granulate AO01001G

Sieve Cut [µm]	Amount retained [%]
< 63	4.2
63 – 125	38.6
125 – 250	40.4
250 – 500	2.0
500 – 710	3.2
710 – 1000	5.3
> 1000	6.3

For comparison purposes, the particle size distribution obtained for the Nycomed process validation batches is provided in the Table 12 below.

Table 12: Particle Size Distribution Nycomed Process Validation Batches

Sieve Cut [µm]	Amount retained [%]
< 100	8 – 27
100 – 200	55 – 77
200 – 315	3 – 4
315 – 500	1 – 2
500 – 800	1 – 3
800 – 1000	1 – 2
1000 – 1250	1 – 2
> 1000	2 – 4

The data shows that the granulates obtained by both processes exhibit similar particle size distribution with a main particle size fraction in the range of 100 – 250 µm.

Bulk and Tapped Density

The bulk and tapped density of technical batch AO01001G was measured and compared to data of the Nycomed Process Validation batches. The results are provided in Table 13 and show that the data generated are comparable.

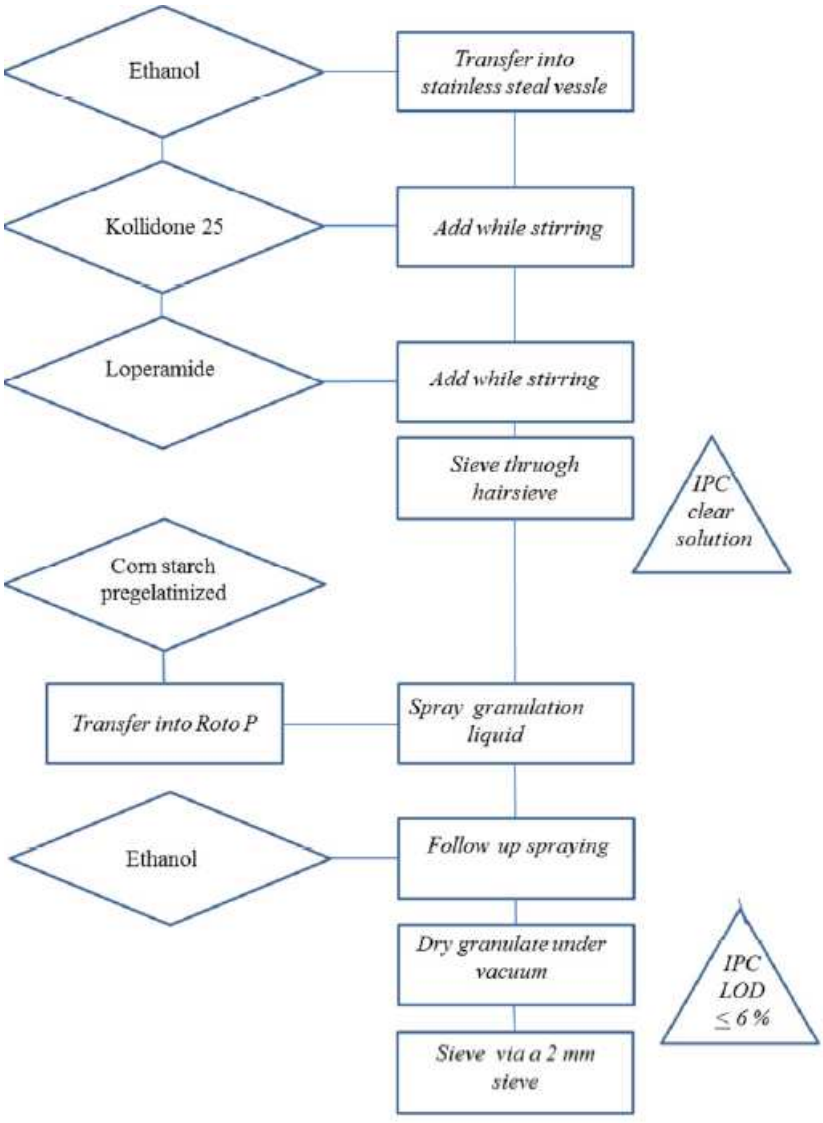
Table 13: Bulk and Tapped Density of B/N AO01001G vs Nycomed PV Batches

	AO01001G	Nycomed 380010	Nycomed 480020	Nycomed 480030
Bulk Density [g/mL]	0.63	0.61	0.64	0.64
Tapped Density [g/mL]	0.79	0.71	0.74	0.75

2.1.P.2.3.3.4 Manufacture of the Second Technical Batch # AO01002G

It was decided to process the second batch without intermediate drying during granulation to shorten and simplify the manufacture. In order to avoid potential sticking of the material on the walls of the granulation bowl, the granulator was alternately tilted at an angle of 85° on each side during the drying phase. The rest of the manufacture process remained unchanged.

Flow Chart Batch # AO01002G



Observations

During the spraying phase and in particular during the drying phase the product was strongly sticking to the walls of the Roto P and forming dry crusts. Tilting the granulation bowl during the drying stage could not prevent this phenomenon from happening. The removal of a relatively high quantity of ethanol from the granulate results in the product sticking to the walls. Skipping the intermediate drying step has thus a detrimental impact on the

manufacturing process. Therefore, the intermediate drying step should not be removed and should be maintained in the commercial manufacturing process.

Visual Inspection

The results from the light microscopy (Figures 7 and 8) reveal that the granulates of batch AO01002G is generally finer but also contains larger particles as the granulates of batch AO01001G (Figure 4) and the originator batch A799A (Figures 5 and 6).

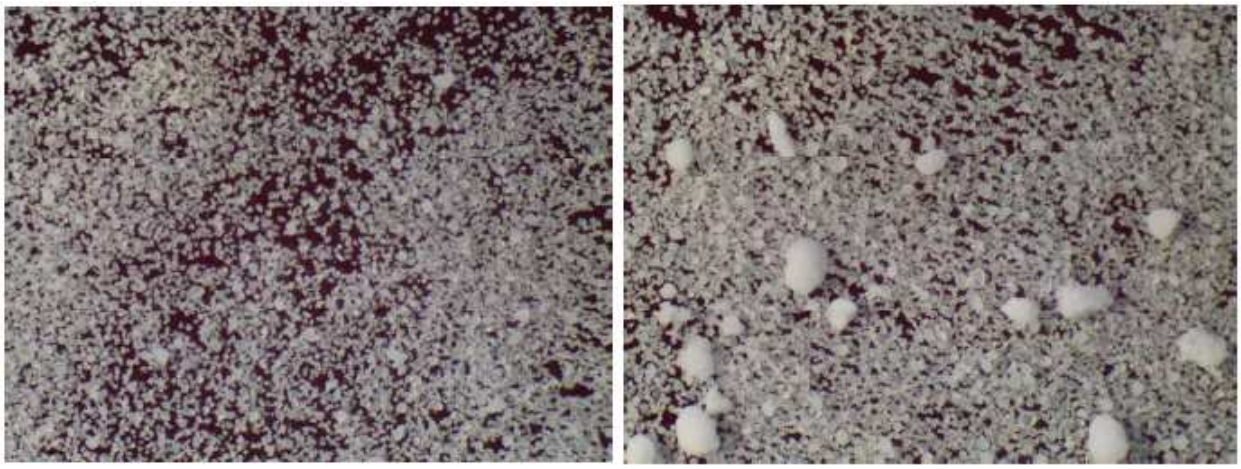


Figure 7 & 8: Granulate of Batch AO01001G

Particle Size Distribution

The particle size distribution of the granulate AO01002G was determined by sieve analysis and the results compared to those of granulate AO1001G. The results are provided in Table 14.

Table 14: Particle Size Distribution Granulate AO01002G vs. AO01001G

Sieve Cut [µm]	Amount retained [%] AO01002G	Amount retained [%] AO01001G
< 63	3.7	4.2
63 – 125	35.7	38.6
125 – 250	39.8	40.4
250 – 500	1.7	2.0
500 – 710	3.9	3.2
710 – 1000	9.9	5.3
> 1000	5.3	6.3

The sieve analysis data of both batches showed that the particle size fractions of the sieve cuts between of < 63 µm, 63 – 125 µm and 125 µm are comparable and represent the major fractions of the granules. The results further indicate that batch AO01002G exhibits more agglomerated material within the upper sieve fractions, i.e. 500 – 710 µm and 710 – 1000 µm, compared to batch AO01001G.

Bulk and Tapped Density

The bulk and tapped density of technical batch AO01002G was measured and compared to those of batch AO01001G. The results are provided in Table 15 below and show that the data generated are comparable.

Table 15: Bulk and Tapped Density of B/N AO01002G vs AO01001G

	AO01002G	**AO01001G**
Bulk Density [g/mL]	0.63	0.63
Tapped Density [g/mL]	0.79	0.79

2.1.P.2.3.3.5 Blend Uniformity Analysis

Blend uniformity studies were performed on both technical batches.

The samples were pulled from the bulk container in three locations: top (3 samples), middle (4 samples) and bottom (3 samples).

Table 16: Blend Uniformity & Assay Results

Blend Uniformity (n=10)	**AO01001G**	**AO01002G**
Mean Assay [%]	102.8	103.2
RSD [%]	1.4	2.3
Min [%]	100.5	98.5
Max [%]	105.4	105.9
Assay [%]	99.0	95.0

Both batches comply with Ph. Eur 2.9.6 (blend uniformity). However, with a RSD of 2.3% the blend uniformity of 103.2% for batch AO01002G is higher in comparison to 102.8% of the batch AO01001G with a RSD value of 1.4% only.

2.1.P.2.3.3.6 Content Uniformity Analysis

Both batches were encapsulated on a Zanasi 5000R encapsulation machine. A capsule size 4 was selected for these initial trials (note: Nabilone 1 mg capsules are size 2). During the encapsulation process, samples for content uniformity were taken at the beginning, the middle and the end of the process.

The assay and content uniformity was measured using two different methods:

1. Whole capsules
2. Content of the capsules
    a. CU: content of the capsules (i.e. powder only) as directed in the method for the determination of Nabilone 1 mg CU
    b. Assay: content of the capsule (powder) + shell rinse

The aim was to evaluate potential loss of material remaining on the shell.

The results of the assay and content uniformity are provided in Table 17.

Table 17: Assay and Content Uniformity Results

Note: 10 capsules are analysed for both assay and CU		**AO01003E (granulate AO01001G)**	**AO01004E (granulate AO01002G)**
Assay (whole capsules)	Assay [%]	100.70	102.75
Content Uniformity (whole capsules)	Mean [%]	100.74	102.53
	SD [%]	4.75	4.35
	RSD [%]	4.72	4.24
	AV [%]	11.4	11.46
Assay (powder and shell)	Assay [%]	99.66	100.75
Content Uniformity (powder only)	Mean [%]	97.87	98.28
	SD [%]	5.61	2.37
	RSD [%]	5.74	2.41
	AV [%]	14.1	5.9

The results of the content uniformity measurements within both batches indicate that encapsulation process parameters might be improved. Lower RSD values (similar to the RSD values from the blend uniformity) should be obtained with an optimized encapsulation process.

It was furthermore observed that the analytical method in place for Nabilone leads to lower mean assay values in contrast to method Ph. Eur. 2.9.40. In the latter case the entire capsule is being analyzed.

2.1.P.2.3.3.7 Conclusion

Based on the manufacture of the 2 technical batches using loperamide hydrochloride as surrogate API the following conclusions can be drawn:

- The single pot granulation process resulted in a product with appropriate blend uniformity and physical characteristics when compared to the “reference product” manufactured at Nycomed
- The intermediate drying step cannot be skipped
- The initial encapsulation trials resulted in capsules with appropriate content uniformity.
- It should be considered implementing an additional rinsing step of the capsules in the CU and/or assay method for Nabilone drug product

The process validation protocol together with the scheduled sampling planned is presented in Section 2.1.P.3.5. Preliminary observations are also summarized in Section 2.1.P.3.5. The release data of the first two validation batches are presented in Section 2.1.P.5.4.

2.1.P.2.3.4 Development of 0.25 mg capsules

After successful transfer of the 1 mg capsules to SwissCo in 2016, the development of a new strength was started. It was defined to maintain the formulation and its manufacturing process as established for the 1 mg dosage strength and to only reduce the fill mass to one fourth of the 1 mg dosage strength to 36.78 mg. Feasibility studies were started.

Feasibility studies

Within a campaign of a technical trial on the 1 mg strength, one technical batch (blend) was processed for subsequent processing into 1 mg and 0.25 mg hard gelatin capsules. Loperamide hydrochloride was used as a surrogate API to nabilone. The granulation process was performed in the single pot granulator Roto P50, the process settings were kept as for the previously manufactured 1 mg dosage forms. Visual inspection was performed and product characteristics such as particle size distribution, bulk and tapped density, and loss of drying were measured. The batch was divided as follows:

- One third of the blend for 1 mg feasibility runs (Blend batch 1403-16001, including encapsulation; data are not discussed here)
- One third of the blend for encapsulation into 0.25 mg hard gelatin capsules of capsule size 4 (Batch 1403-16001, encapsulation batch 1403Bl-0 1-01)
- One third of the blend for encapsulation into 0.25 mg hard gelatin capsules of capsule size 5 (Batch 1403-16001, encapsulation batch 1403B2-0 1-01)

Both 0.25 mg sub-batches were encapsulated with a Zanansi AZS encapsulation machine. Samples for weight uniformity were taken during the encapsulation process of both sub batches. The samples of the sub-batch with the more stable weight results, (sub-batch 1403Bl-01-01), was further analyzed for content uniformity and for assay.

a.) Materials

The materials used are listed in the table below:

Table: Materials used for process investigations

Ingredient	Quality	Function	Amount per capsule [mg] for the 0.25 mg dosage strength	Amount per batch [kg]
Loperamide hydrochloride	Ph. Eur.	Surrogate API	0.25	0.08
Ethanol 99.8%	Ph. Eur.	Granulation liquid	-	1.89
Corn starch pregelatinized	Ph. Eur.	Filler	34.025	10.89
Polyvinylpyrrolidone K25 (Kollidon 25)	Ph. Eur.	Binder	2.5	0.39
Hard gelatin capsules, size 4 and 5	Ph. Eur.	Capsule shell	-	-
TOTAL WEIGHT			36.78	11.36 (13.25 incl. ethanol)

b.) Equipment

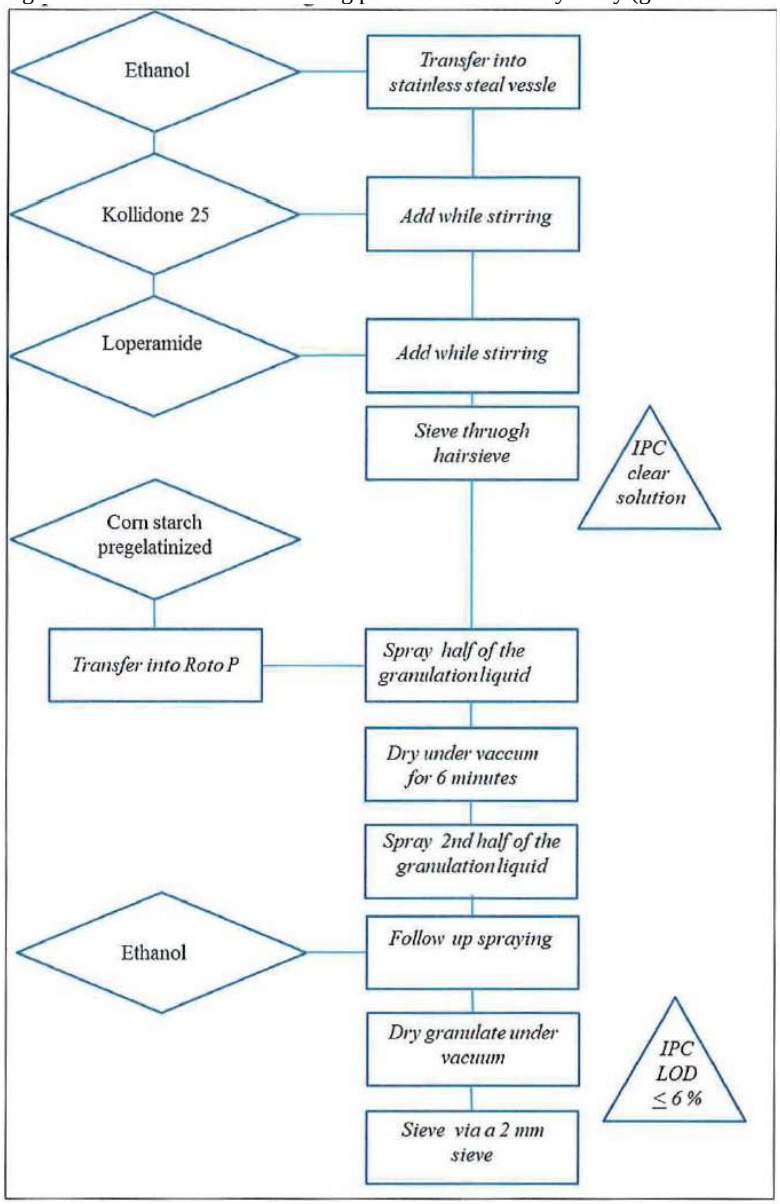
The granulation step was carried out in a single pot granulator Rota P 50 from Zanchetta. The encapsulation was performed with a Zanasi AZS encapsulation machine. The batches were defined as technical batches, though all equipment used complies with GMP requirements.

c.) Blending (batch 1403-16001)

(1) Manufacture of the blend

The batch was process as shown in the figure below:

Figure: Flow chart of manufacturing process for feasibility study (granulation stage)



For spraying of the granulation liquid a nozzle with an aperture width of 1.0 mm was used. The spray pressure was kept constant at 2 bar. The process parameters are listed in the table below

Table: Process parameters of technical batch 1403-16001

T [min]	Process	Mixer [UpM]	Chopper status	Spray rate [g/min]	Vacuum [bar]	Product Temp. [°C]	LOD [%]
0-3	Spraying	98	On	175	-	22	-
3-9	Spraying	100	On	190	-	22	-
9-15	Drying	104	Off	-	0.9	21	-
15-24	Spraying	102	On	180-195	-	21	-
25-27	Follow-up spraying	102	On	195 (total 390 g)	-	22	-
27-47	Drying	40 (20 sec interval)	Off	-	0.9	28	-
47-77	Drying	42 (20 sec interval)	Off	-	0.9	30	4.96
77-85	Cooling	28	Off	-	0.9	28	-

(1.1. Particle size distribution

Table below shows the particle size distribution of the granulate 1403-6001 determined by sieve analysis.

Table: Particle size distribution granulate 1403-16001

Sieve cut [µm]	Amount retained [%]
< 63	5.1
63 – 125	48.7
125 – 250	32.5
250 – 500	1.6
500 – 710	3.1
710 – 1000	4.3
> 1000	4.7

In comparison with data from earlier trials, the granules of the current batch shows similar particle size distribution with a main particle size fraction of in the range of 63- 250 µm.

(1.2. Bulk and tapped density

Bulk and tapped density of the batch 1403-6001 was measured. Data (in comparison to previous data and to Nycomed process validation data) is compiled in the table below. The bulk and the tapped density of the current batch is comparable to the previous batches and to the Nycomed data.

Table: bulk and tapped density of batch 1403-6001 in comparison to previous data

	AO01001G	AO01002G	Nycomed 480010	Nycomed 480020	Nycomed 480030	1403-6001 (current batch)
Bulk density [g/ml]	0.63	0.63	0.61	0.64	0.64	0.65
Tapped density [g/ml]	0.79	0.79	0.71	0.74	0.75	0.77

d.) Encapsulation process

Both sub batches foreseen for the 0.25 mg trials (capsule size 4: Batch 1403B1-0l-01 and capsule size 5: Batch 1403B2-0l-01) were encapsulated on a Zanasi AZ 5 encapsulation machine. During encapsulation samples for determination of the filling weight were taken throughout the entire process.

(1.) Batch 1403B1-01-01 (capsule size 4)

(1.1. Fill weigh batch 1403B1-01-01 (capsule size 4)

Encapsulation was executed for a period of approx. 100 minutes. The speed of the machine was initially set at approx. 3'120 cps/hours and after 1 h increased to approx. 3'600 cps/hours. The mean weight of the empty capsule was determined as 38.1 mg with n=50 capsule shells. The fill weight was defined as 36.78 mg (34.94-38.62 mg) which corresponds to the target weight of 36.78 mg +/- 5%. Following, a mean gross weight of the capsules of 73.01- 76.75 mg /capsule (corresponding to +/- 2.5 %) was defined. Table below shows the capsule's gross weight (mean, min, max, Srel) with n= 20 for time points throughout the process.

Encapsulation time	Mean [mg]	Minimum [mg]	Maximum [mg]	RSD [%]
T 0	74.1	70.0	77.0	2.93
T = 20 min	74.6	70.0	81.0	2.97
T = 40 min	75.8	72.0	78.0	2.25
T = 60 min	75.8	72.0	79.0	2.87
T = 80 min	75.0	70.0	79.0	3.35
T = 100 min	75.2	71.0	77.0	1.96

All mean values comply with the specification of 73.01 - 76.75 mg.

(1.2. Content uniformity and assay 1403B1-01-01 (capsule size 4)

The content uniformity was measured according to the method for the Nabilone 1.0 mg. To evaluate a possible loss of material by only measuring the capsule content (nabilone method), the powder plus the remaining content on the shell (obtained by rinsing) was determined. The results of the measurements are shown in table overleaf.

Table: Results of the CU measurement of batch 1403B1-01-01 (composite sample)

Assay mean (2 sample preparations, each preparation 2 HPLC injections)	[%]	98.8
CU 10 capsules (capsule content) according Ph.Eur. 2.9.40	Mean [%]	98.92
	SD [%]	5.37
	RSD [%]	5.34
	AV [%]	12.98

The capsules comply with the content uniformity acc. Ph. Eur. 2.9.40.; furthermore assay and mean value of the content uniformity are matching.

(2.) Batch 1403B2-01-01 (capsule size 5)

(2.1 Fill weigh batch 1403B2-01-01 (capsule size 5)

The filling of capsules size 5 on the Zanasi AZ5 showed to be more demanding than the filling of capsules of size 4. The machine was run at a speed of approx. 2'800 cps/hours. As before, the empty capsule's mean weight of n= 50 capsule shells was determined (25.44 mg). The fill weight was kept constant (36.78 mg (34.94 - 38.62 mg). This results in a gross weight of the capsules of 60.66 - 63.78 mg. Table below shows the fill weights of the capsules of size 5. Since the process did not run smoothly and frequent adjustments of the machine had to be made throughout the process, only a short run of 15 min was performed.

Encapsulation time	Mean [mg]	Minimum [mg]	Maximum [mg]	RSD [%]
T 0	62.8	59.0	67.0	3.86
T = 15 min	61.7	58.0	65.0	2.88

The filling process was much more difficult than for the capsules of size 5, especially in regards of obtaining the correct fill mass. The mean values were found acceptable, yet it was almost impossible to maintain a constant fill mass during encapsulation. Therefore, the run was stopped and it is proposed to consider capsules of size 4 as appropriate encapsulation material. For this reason, assay and CU determinations on this encapsulation batch were not performed.

e.) Conclusions

The following key information / conclusions can be made based on the first 0.25 mg nabilone feasibility study with loperamide hydrochloride as surrogate API:

- The reduction of the fill mass of the 1 mg nabilone capsule blend by 75% to 36.75 mg and its subsequent processing into 0.25 mg nabilone capsule product is feasible.
- 0.25 mg nabilone blend was successfully encapsulated into size 4 hard gelatin capsules with the Zanasi AZ5 encapsulation machine.
- Weight, assay and content uniformity determinations on the dosage form reveal an acceptable product.
- Since processing the blend into capsules of size 5 was not robust/feasible, it was defined to continue the development program for the 0.25 mg strength using size 4 hard gelatin capsules.

After feasibility study process validation for 0.25 mg strength of Nabilone was started. Details are provided in section 2.1.P.3.

2.1.P.2.4 Container Closure System

The intended commercial packaging that was also used for the stability studies (see 2.1.P.8.3, stability studies of the validation batches according to ICH guideline) consists of the following components:

- a round plastic container with a threaded neck made of white high-density polyethylene (HDPE) and a nominal capacity of 50 mL
- a round plastic child-resistant tamper-evident screw cap made of polypropylene (PP) with a mounted desiccant (2 g silica gel)

All components conform to the current requirements of food and medicinal products packaging.

The specifications are presented in Section 2.1.P.7.

2.1.P.2.5 Microbiological Attributes

The manufacturing process of Canemes 1.0 mg and 0.25 mg capsules and all processing steps have been optimised to prevent microbial contamination of the product taking into consideration that this is a non-sterile process.

All validation batches have been tested for microbiological attributes. Please refer to Section 2.1.P.5.4 for results.

2.1.P.2.6 Compatibility

The drug product is not to be administered with a dosage device or to be reconstituted before administration; this chapter is thus not relevant for Canemes capsules.

2.1.P.3 Manufacture (Nabilone, 1 mg and 0.25 mg capsules)

2.1.P.3.1 Manufacturer

The manufacture and testing of Canemes 1 mg and 0.25 mg capsules drug product is being performed at:

Site	Responsibilities
SwissCo Services AG Bahnhofstraße 14 4334 Sisseln Switzerland	• Manufacture of drug product • Testing of drug product • Packaging of drug product
Swiss Caps AG Eptingerstraße 51 4132 Muttenz Switzerland	• Testing of drug product
Eurofins Scientific AG Parkstrasse 10 5012 Schönenwerd Switzerland	• Testing of drug product, microbial control
AOP Orphan Pharmaceuticals AG Wilhelminenstrasse 91/IIf 1160 Wien Austria	• Batch release
Meditop Pharmaceutical Ltd. Ady Endre utca 1. 2097 Pilisborosjenő, Hungary	• Additional secondary packaging site
Kwizda Pharmadistribution GmbH Achauer Straße 2 2333 Leopoldsdorf Austria	• Additional secondary packaging site

2.1.P.3.2 Batch Formula (Nabilone, 1 mg and 0.25 mg capsules)

The batch formula for the commercial batch size (100,000 capsules) of Nabilone 1 mg is provided in the table below.

Table 1: Batch Formula (100,000 cps of Nabilone 1mg)

Ingredient	Amount		Function
	Per capsule [mg]	Per batch [kg] (100,000 pcs)	
Nabilone	1.0	0.100	Active Ingredient
Povidone (K25)	10.0	1.000	Dispersion Matrix
Corn starch, pre-gelatinised	136.1	13.610	Filler
Ethanol[1]	---	(2.360 to 2.560)	Granulation Solvent
Total	147.1	14.710	---

[1] Ethanol serves as a granulation solvent and is not present in the final product.
The quantity of Ethanol added to each batch depends on the viscosity of the granulation solution and is therefore adapted within the given range on a batch to batch basis.

If Nabilone 0.25 mg is manufactured, the final granulate is split up to a ratio of 50:50. One part of the granulate is filled into size 2 capsules with a filling weight of 147.1 mg for Nabilone 1 mg capsules and the second part of the granulate is filled into size 4 capsules with a filling weight of 36.78 mg for Nabilone 0.25 mg capsules.

Table 2: batch formula for highest split ratio of 50:50

Granulate [kg]	147.1	
Strength	Nabilone 1 mg capsules	Nabilone 0.25 mg capsules
Split ratio	75%	25%
Granulate [kg]	7.355	7.355
Capsules, qty.	50,000	200,000

Ingredient	Amount (1 mg capsules)		Amount (0.25 mg capsules)		Function
	Per capsule [mg]	Per batch [kg] (50,000 pcs)	Per capsule [mg]	Per batch [kg] (200,000 pcs)	
Nabilone	1.0	0.05	0.25	0.05	Active Ingredient
Povidone (K25)	10.0	0.500	2.50	0.500	Dispersion Matrix
Corn starch, pre-gelatinised	136.1	6.805	34.03	6.805	Filler
Ethanol[1]	---	(1.180 to 1.280)	---	(1.180 to 1.280)	Granulation Solvent
Total	147.1	7.355	36.78	7.355	---

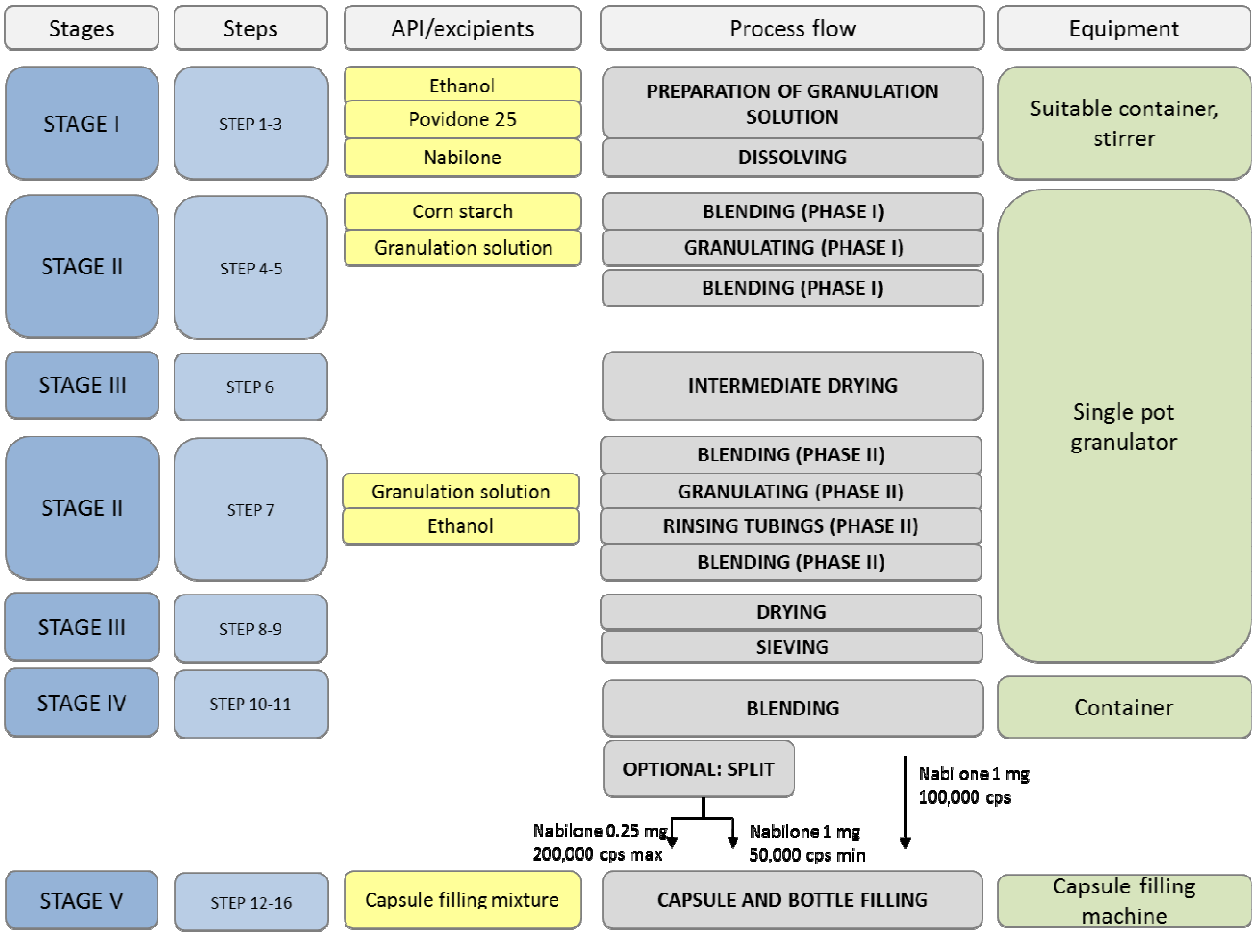
2.1.P.3.3 Description of Manufacturing Process and Process Controls (Nabilone, 1 mg and 0.25 mg capsules)

The manufacturing of Nabilone 1.0 mg and 0.25 mg capsules can be divided into the following stages:

Stage	Manufacturing step
Stage I	Preparation of granulation solution for granulate
Stage II	Wet granulation
Stage III	Granular drying and Sieving
Stage IV	Final blending
Stage V	Encapsulation and bottle filling

If Nabilone 0.25 mg capsules are produced, the granulate received in Stage IV is split up to a ratio of 50:50. One part of the granulate is filled into size 2 capsules with a filling weight of 147.1 mg for Nabilone 1 mg capsules and the second part of the granulate is filled into size 4 capsules with a filling weight of 36.78 mg for Nabilone 0.25 mg capsules.

An overview of the manufacturing process is shown below:



2.1.P.3.3.1 Description of the manufacturing process in steps (without split)

Step 1-3

Preparation of granulation solution

Item	Ingredients	Per batch [kg]
1	Ethanol	1.970 to 2.170
2	Povidone (K25)	1.000
3	Nabilone	0.100

Temperature of Ethanol (Item 1) is measured. Consecutively, Povidone K25 (Item 2) is dissolved in Ethanol under stirring. Mixing time is recorded. Afterwards the active ingredient Nabilone (Item 3) is added and dissolved under stirring until the solution appears clear and yellow. Mixing time is recorded.

IPC: TEMPERATURE OF ETHANOL (≤ 25°C)

IPC: APPEARANCE (complete dissolving)

Step 4-5

Wet granulation, Phase I

Item	Ingredients	Per batch [kg]
4	Corn starch, pre-gelatinised	13.610

Pre-gelatinised corn starch (Item 4) is added into the single pot granulator and is mixed. Afterwards half of granulation solution is pumped through spraying nozzles into the single pot granulator (at 200g/min). The granulate is stirred during the whole spraying process.

Step 6

Intermediate drying

Intermediate drying step is performed under vacuum. The drying duration is defined with 6 minutes at least.

After the intermediate drying phase residues of the granulate, which stuck on the internal vessel walls of the single pot granulator, are scrapped off and added to the granulate. Afterwards granulation is continued.

Step 7

Wet granulation, Phase II

Item	Ingredients	Per batch [kg]
5	Ethanol	0.390

The second half of the granulation solution is pumped through spraying nozzles into the single pot granulator (at 200g/min). The tubing and nozzles are finally rinsed with Ethanol (as defined under item 5). The mixture is stirred during the whole spraying process.

Step 8-9

Drying and sieving

The granulate is dried under conditions listed below until a humidity of ≤ 6% is reached.

Setting parameter:

Temperature (heating jacket)	NMT 50°C*
Product temperature	NMT 30°C

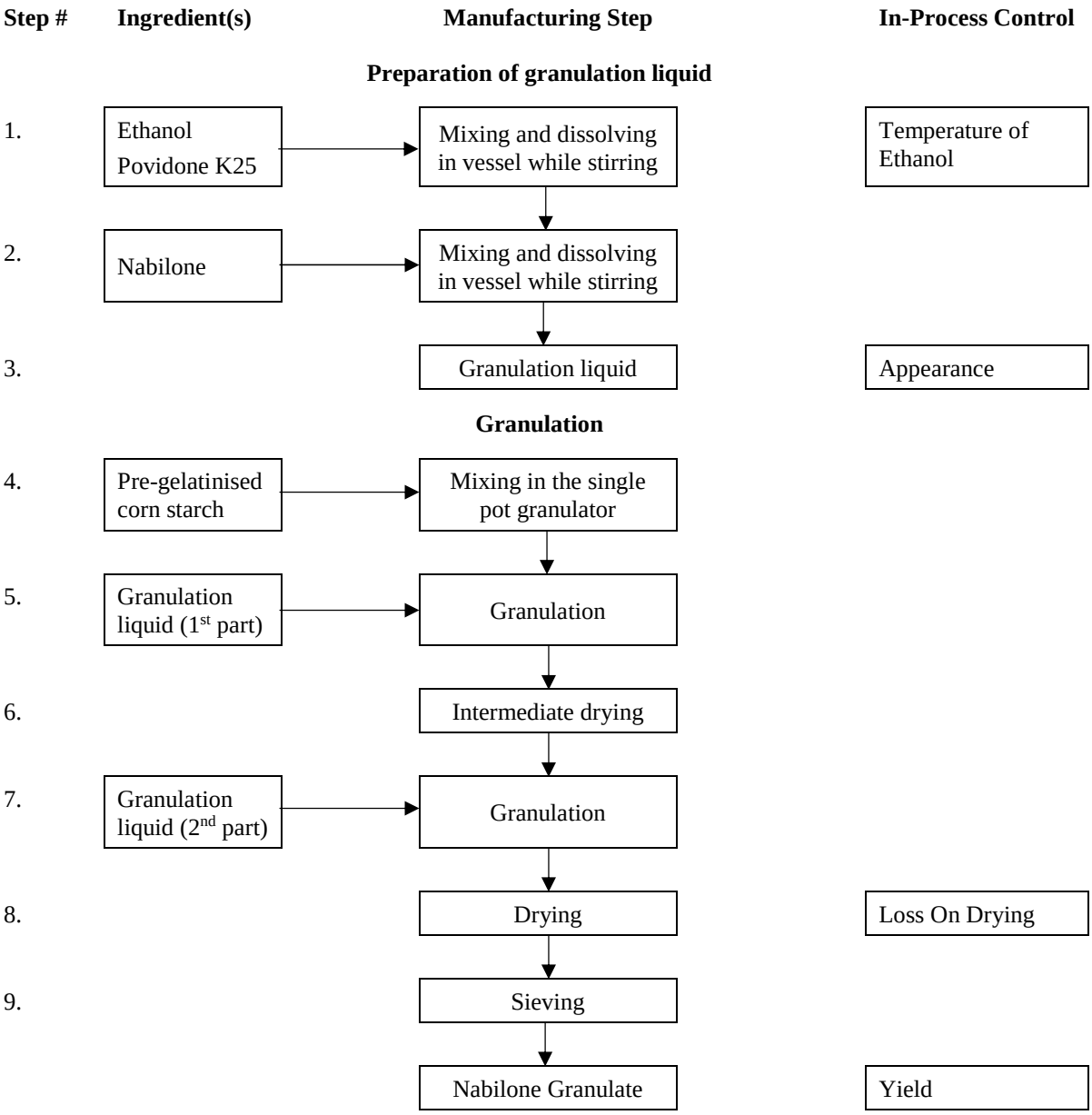
	<table><tr><td>Stirrer</td><td>ON/OFF Modus</td></tr><tr><td>Vacuum</td><td>ON</td></tr></table> *equipment specific parameter In-process-controls are performed. IPC: LOSS ON DRYING (≤ 6%) IPC: YIELD (98% to 102%) Subsequently the granulate is sieved over a mesh size of 2 mm.
Step 10-11	**<u>Final blending and storage</u>** A final blending step is performed before encapsulation. Until encapsulation, the granulate is stored in a PE bag.
Step 12-16	**<u>Encapsulation and filling</u>** The granulate is filled into hard gelatine capsules of size 2 using an automatic encapsulation system. IPC: APPEARANCE of capsules (non-transparent capsules with yellow cap and white body) IPC: AVERAGE MASS (147.1 mg + weight of empty capsules) ± 2.5% IPC: CAPSULE LENGTH (17.9 mm, 17.5 to 18.3 mm) IPC: CONFORMITY OF MASS (RSD ≤ 3.0%) Finally 28 capsules are filled into HDPE-bottles and sealed with the corresponding cap. The bottles are individually packaged into a carton (folding) box.

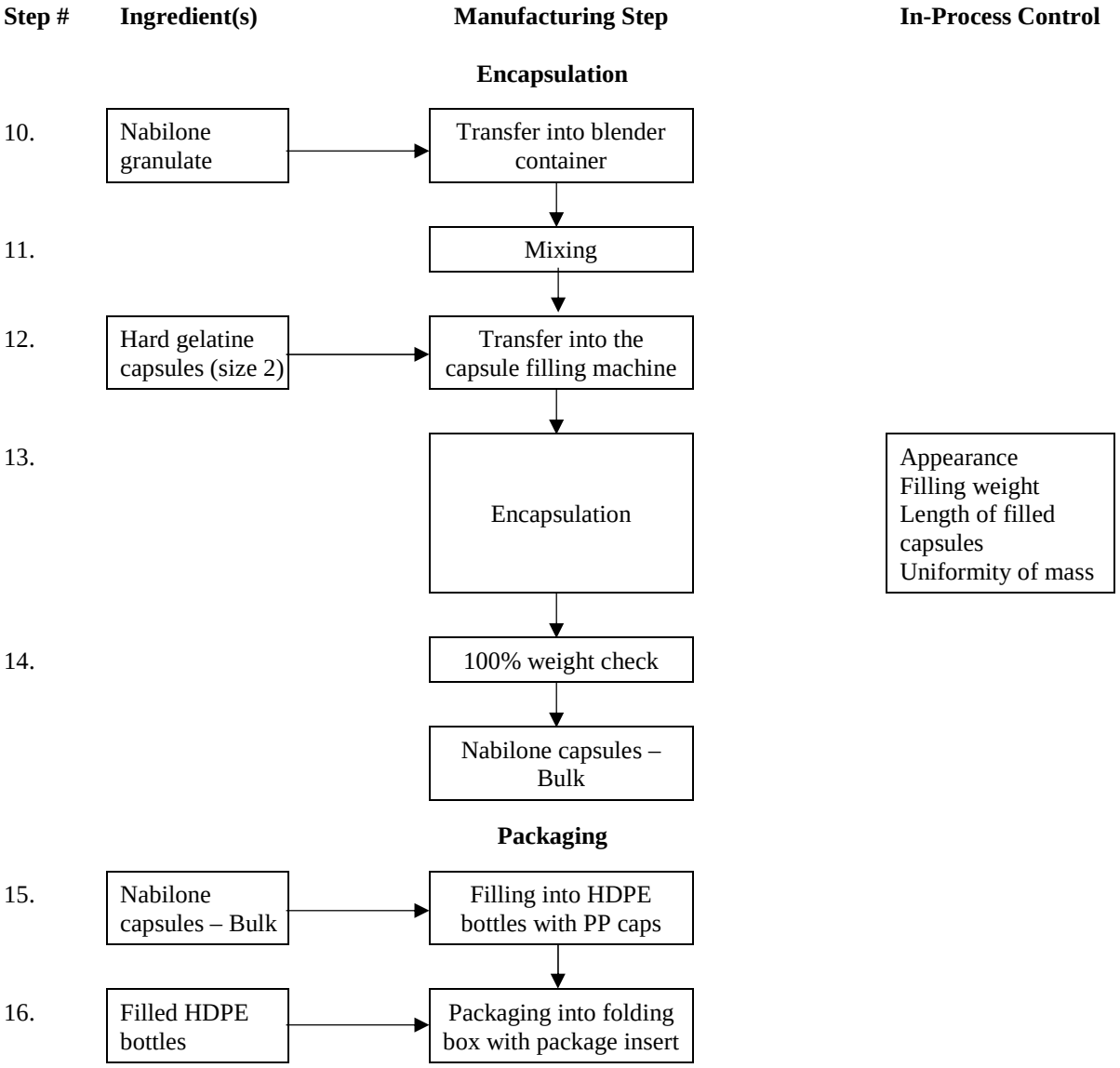
2.1.P.3.3.2 Description of the manufacturing process in steps (with split)

Step 1-11 stays as described in the chapter above. After final blending the granulate is divided into two parts. One part of the granulate is filled into size 2 capsules with a filling weight of 147.1 mg for Nabilone 1 mg capsules as described in the chapter above for step 12-16.
The second part of the granulate is filled into size 4 capsules with a filling weight of 36.78 mg for Nabilone 0.25 mg capsules.

Step 12-16 **(0.25 mg capsules)**	**<u>Encapsulation and filling</u>** The granulate is filled into hard gelatine capsules of size 4 using an automatic encapsulation system. IPC: APPEARANCE of capsules (non-transparent capsules with white cap and white body) IPC: AVERAGE MASS (36.775 mg + weight of empty capsules) ± 2.5% IPC: CAPSULE LENGTH (14.1 mm, 13.8 to 14.4 mm) IPC: CONFORMITY OF MASS (RSD ≤ 3.0%) Finally 28 capsules are filled into HDPE-bottles and sealed with the corresponding cap. The bottles are individually packaged into a carton (folding) box.

2.1.P.3.3.3 Flow chart (without split)




Step #
Ingredient(s)
Manufacturing Step
In-Process Control
Encapsulation
10.
Nabilone granulate
Transfer into blender container
11.
Mixing
12.
Hard gelatine capsules (size 2)
Transfer into the capsule filling machine
13.
Encapsulation
Appearance
Filling weight
Length of filled capsules
Uniformity of mass
14.
100% weight check
Nabilone capsules – Bulk
Packaging
15.
Nabilone capsules – Bulk
Filling into HDPE bottles with PP caps
16.
Filled HDPE bottles
Packaging into folding box with package insert

2.1.P.3.4 Control of Critical Steps and Intermediates (Nabilone, 1 mg and 0.25 mg capsules)

The in-process controls for the manufacture of Nabilone 1 mg and 0.25 mg capsules are listed in the table below.

Table 1: Overview of In-Process Controls

Process Step	Process Control	Limit
Preparation of granulation solution	Temperature of ethanol	≤ 25°C
	Appearance of solution	No lumps, clear yellowish, viscous solution
Granulation	Loss on Drying	≤ 6%
	Yield	98 – 102%
Encapsulation	Appearance	1 mg capsules non-transparent capsules with yellow cap and white body
		0.25 mg capsules non-transparent capsules with white cap and white body
	Filling weight	1 mg capsules (147.1 mg + weight of empty capsules) ± 2.5%
		0.25 mg capsules (36.8 mg +weight of empty capsules) ± 2.5%
	Length of filled capsules	1 mg capsules: 17.9 ± 0.4 mm
		0.25 mg capsules: 14.1 ± 0.3 mm
	Uniformity of Mass	RSD ≤ 3.0%

Additional sampling performed during process validation is described in section 2.1.P.3.5.

2.1.P.3.5 Process Validation and Evaluation (Nabilone, 1 mg and 0.25 mg capsules)

The manufacturing process was transferred from Nycomed in Oranienburg, Germany to SwissCo Services AG, Sisseln, Switzerland. A process validation according to the current PIC/S GMP Guidelines and to the SwissCo internal SOP for the validation of production processes and process steps was performed.

The process validation will focus on the granulation and encapsulation steps. The process validation will be performed using API from both registered drug substance manufacturers, LOBA and CPL Sachse.

The manufacture of Nabilone 1 mg and 0.25 mg Capsules will be performed at SwissCo Services AG according to the released manufacturing instructions and test methods. The batch size is 100,000 capsules of Nabilone 1 mg capsules without split.

For Nabilone 0.25 mg the final granulate is split and divided into two parts. One part is filled in size 2 capsules with a filling weight of 147.1 mg for Nabilone 1 mg capsules; the second part is filled into size 4 capsules with a filling weight of 36.775 mg for Nabilone 0.25 mg capsules.

The batch formula is provided in section 2.1.P.3.2., the manufacturing process is described in section 2.1.P.3.3.

An overview of the validation batches for Nabilone 1 mg (full batch size) is given below:

Table 2: Overview of the validation batches for Nabilone 1 mg capsules

Batch No.	Manufacturing date	Batch size	Purpose
09030016	April 2016	Production scale (100’000 capsules)	Process validation and ICH-stability
09010016	April/May 2016	Production scale (100’000 capsules)	Process validation and ICH-stability
090xxxxx[1]	On customers demand	Production scale (100’000 capsules)	Process validation

[1] Batch number of third validation batch will be reported in the final process validation report

Subject of the process validation for the Nabilone 0.25 mg capsules will only be the process step encapsulation. The validation of the prior process steps (granulation/preparation of encapsulation blend) is performed within process validation of Nabilone 1 mg capsules. The formulation, respectively composition of the encapsulation blend of Nabilone 1 mg and 0.25 mg is dose-linear, hence the starting material of the encapsulation process is equivalent. For the purpose of the validation of the Nabilone 0.25 mg capsules the manufactured encapsulation blends will be split. As two API sources are registered for the manufacture of the drug product, the manufacture of validation batches will be performed with API from both suppliers

The following table provides an overview of the blend spitting for the 3 split validation batches.

Table 3: Overview of planned batch splitting

			Batch splitting	
Batch	**API supplier**	**Encapsulation blend quantity**	**Quantity intended for encapsulation of Nabilon 1 mg capsules** [1]	**Quantity intended for encapsulation of Nabilon 0.25 mg capsules**
1st split batch	CPL	14.71 kg	11.03 kg ≙ 75’000 capsules	3.68 kg ≙ 100’000 capsules
2nd split batch	CPL or LOBA	14.71 kg	11.03 kg ≙ 75’000 capsules	3.68 kg ≙ 100’000 capsules
3rd split batch	LOBA	14.71 kg	7.36 kg ≙ 50’000 capsules	7.36 kg ≙ 200’000 capsules

[1] Not part of this process validation of the 0.25 mg capsules

Table 4: Overview of planned validation batches for 0.25 mg Nabilone capsules

Batch N°	**Manufacturing date**	**Batch size**	**Purpose**
09010017	April 2017	Production scale (100’000 capsules)	Process validation and ICH-stability
09010027	June 2017	Production scale (100’000 capsules)	Process validation and ICH-stability
09030017	On customer’s demand	Production scale (200’000 capsules)	Completion of process validation and ICH-stability

A summary of the validation plan for Nabilone 1 mg capsules is provided on the following pages.

2.1.P.3.5.1 Setting of critical process parameters

Table 5: Critical Process Parameters for Nabilone 1 mg capsules

Critical process parameter	Setting	The process parameter has a potential impact on
Complete dissolving of Povidone and Nabilone in the granulation liquid	No lumps, clear yellowish, viscous solution	Content uniformity and assay of capsules
Residual humidity after drying	LOD: ≤ 6%	Stability of the drug product
Filling weight	Mean mass (147.1 mg + weight of empty capsules) ± 2.5%	Uniformity of mass, content uniformity and assay of capsules
Capsule dimensions	Capsule size 2 Capsule length: 17.9 mm (17.5 to 18.3 mm)	Stability of the drug product; opening of the primary packaging

Table 6: Additional Critical Process Parameters for Nabilone 0.25 mg capsules

Critical process parameter	Setting	The process parameter has a potential impact on
Filling weight	Mean mass (36.775 mg + weight of empty capsules) ± 2.5%	Uniformity of mass, content uniformity and assay of capsules
Capsule dimensions	- capsule size 4 - capsule length: 14.1 mm (13.8 – 14.4 mm)	Stability of the drug product; opening of the primary packaging.

2.1.P.3.5.2 Sampling plan, in- process controls, additional tests and acceptance criteria per batch

In the following tables, the tests to be performed, the samples to be taken and the test methods with the respective acceptance criteria are given. The location of the samples to be taken for the uniformity of content analysis of the final blend is described in Figure 1

<u>In- process control to manufacturing step a) Preparation of granulation liquid</u>

Table 7: IPC tests – a) Preparation of granulation liquid

Test	Method	Acceptance criteria
Appearance	Visual inspection	Complete dissolving
Temperature of Ethanol	Thermometer	≤ 25°C

Sampling plan, sampling positions, in- process controls and acceptance criteria to manufacturing step b) Granulation

Table 8: Sampling plan – b) Granulation

Test	Sampling time point and location	Sample amount
Bulk density	From the middle of the container containing the granulate	250 g (± 5 g)
Tapped density	From the middle of the container containing the granulate	
Sieve analysis	From the middle of the container containing the granulate	
Uniformity of content of the compression blend in the mixing container	After mixing the granulate from locations according to Figure 1	3 x 147.1 – 441.3 mg per location[1]

[1]Two samples per position are taken as retention sample.

The bulk and tapped density are analysed with the same sample (100 g), the sieve analysis is done with 100 g and 50 g are taken as back-up.

Table 9: IPC tests – b) Granulation

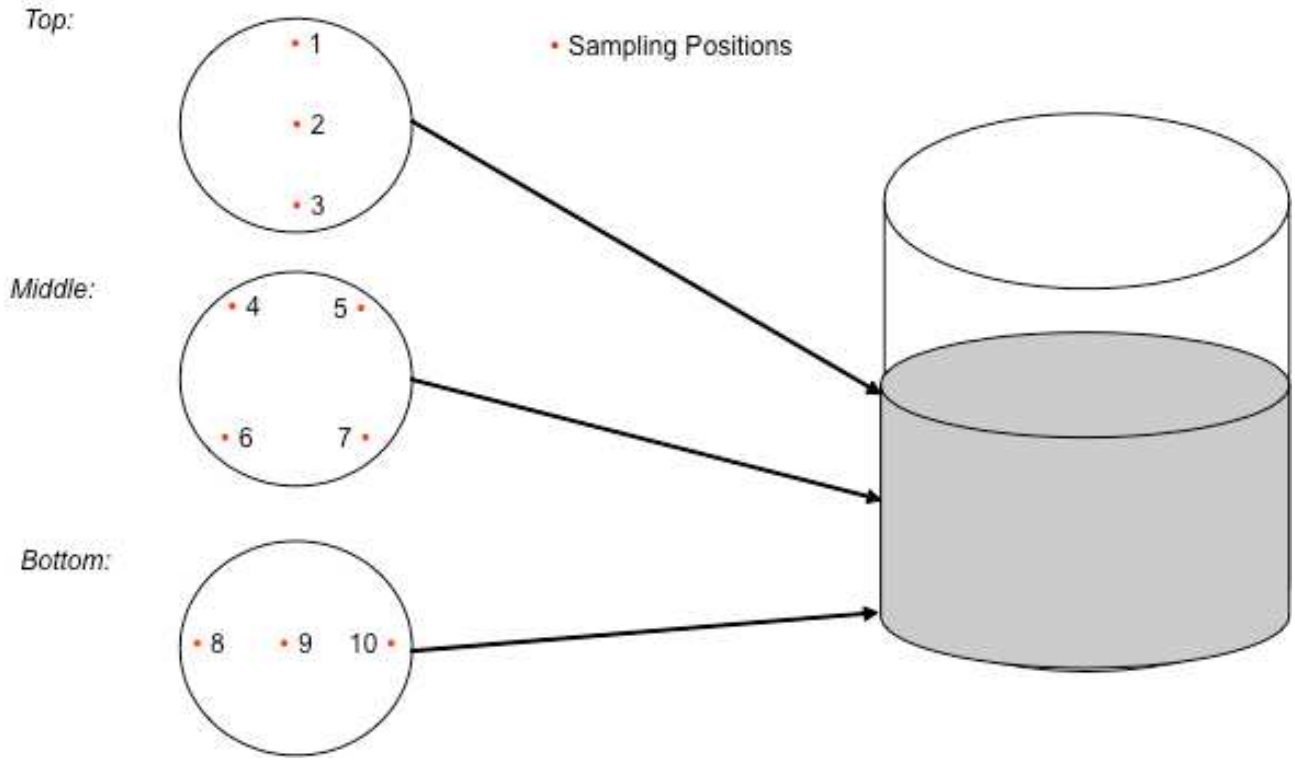
Test	Method	Acceptance criteria
Loss on drying	Internal method (Halogen moisture analyzer)	≤ 6%
Yield	Weighing comparison theoretical weight and actual weight	98 – 102%

Table 10: Additional tests – b) Granulation

Test	Method	Acceptance criteria
Bulk density	Ph. Eur. 2.9.34	Report
Tapped density	Ph. Eur. 2.9.34	Report
Sieve analysis	Internal method	Report
Uniformity of content (blend uniformity)	Ph. Eur. 2.9.6 (Relative standard deviation (RSD))	Must comply (RSD for information)

Figure 1: Sampling positions from container containing the granulates

–



Sampling plan, additional tests and acceptance criteria to manufacturing step c) Encapsulation

During the filling of the capsules, samples from 3 time points of the process will be drawn for additional tests within this process validation. The additional test, which will be performed during the process validation only, is mentioned in Table 15.

Table 11: Sampling plan – c) Encapsulation of Nabilone 1 mg capsules

Test	Sampling time point	Sample amount
Tests according to Table 14	After approx. 10’000 capsules (Beginning)	50 capsules
	After approx. 50’000 capsules (Middle)	50 capsules
	After approx. 90’000 capsules (End)	50 capsules

Table 12: Sampling plan – c) Encapsulation of Nabilone 0.25 mg capsules

Test	Sampling time point	Sample amount
Tests according to Table 14	After approx. 10'000 or 20'000 capsules (B)	3x28 capsules
	After approx. 50'000 or 100'000 capsules (M)	3x28 capsules
	After approx. 90'000 or 180'000 capsules (E)	3x28 capsules

Table 13: IPC tests – c) Encapsulation of 1 mg capsules

Test	Method	Acceptance criteria
Appearance of Capsules	Visual inspection	Non-transparent capsules with yellow cap and white body
Average mass (n=10)	Weighing	147.1 mg + weight of empty capsules ± 2.5%
Capsule length (n=10)	Caliper	17.9 mm (17.5 – 18.3 mm)
Uniformity of Mass (n=20)	Weighing	RSD ≤ 3.0%

Table 14: IPC tests – c) Encapsulation of 0.25 mg capsules

Test	Method	Acceptance criteria
Appearance of Capsules	Visual inspection	Non-transparent capsules with white cap and white body
Average mass (n=10)	Weighing	36.8 mg + weight of empty capsules ± 2.5%
Capsule length (n=10)	Caliper	14.1 mm (13.8 – 14.4 mm)
Uniformity of Mass (n=20)	Weighing	RSD ≤ 3.0%

Table 15: Additional tests – c) Encapsulation for Nabilone 1 mg and 0.25 mg capsules

Test	Samples to be analysed	Method	Acceptance criteria
Uniformity of dosage units	Test to be performed with samples: Beginning (B), Middle (M), End (E) (Total: 3 tests per batch)	Internal method	Ph. Eur. 2.9.40

2.1.P.3.5.3 Release tests

The release tests are performed on capsules from a pooled sample, consisting of samples from the whole filling process. Please refer to Section 2.1.P.5.1 for the release specification.

2.1.P.3.5.4 Documentation

Before the start of the process validation, training for all the persons involved in the manufacture of the product has to be done by the responsible person for the process validation or authorized staff. The training has to be documented.

The sampling according to this process validation protocol has to be documented in a sampling protocol.

The documentation of the manufacturing process and IPC is done following the master batch documentation and according to standard operation procedures. The documentation of the analytical tests performed for the process validation only is done following the corresponding standard operation and/or testing procedures.

The test results of the in-process controls, the additional tests and the release tests will be summarized and discussed in a process validation report that will be compiled upon completion of the process validation.

The performance of the validation will be assessed and a statement on the validity of the manufacturing process will be given.

2.1.P.3.5.5 Preliminary Observations and Results of the Process Validation

2.1.P.3.5.5.1 Addition of Solvent to the Granulation Liquid

During the manufacture of the first validation batch of Nabilone 1 mg, the granulation liquid was prepared according to the protocol, dissolving 1 kg of Povidone (K25) and 100 g of Nabilone in 1970 g of Ethanol. This granulation liquid was sprayed through a spraying device with a 1.0 mm nozzle diameter onto the components. However, the spraying process had to be interrupted as clogging of the 1.0 mm nozzle was observed due to the high concentration of API and excipient in the granulation liquid. A nozzle with a larger diameter was not available, therefore the 1.0 mm nozzle was cleaned and the spraying process was resumed subsequently.

In order to reduce the risk of clogging of the nozzle by API crystallization, the use of a more diluted granulation liquid was considered as an appropriate measure and implemented during the manufacture of the second validation batch. The increased quantity of ethanol required for the granulation solution is reflected in the batch formula presented in Section 2.1.P.3.2.

Previous feasibility trials have shown that the risk for a potential over-wetting of the granulate was low. Furthermore, the drying step after granulation to reach a specified loss on drying value ensures a sufficient solvent evaporation.

2.1.P.3.5.5.2 Low Assay Values at Release

During the release testing of the first two validation batches (B/N 09030013 and 09010036), low assay values were observed: 96.1% and 96.5 %, respectively. No degradation was observed; the total of related compounds remained below the reporting threshold of 0.1% for both batches (Refer to Section 2.1.P.5.4 for further details).

During the evaluation of the trial batches, it had already been observed that the analytical method for the determination of content uniformity was leading to lower assay values and that an additional rinsing step of the capsules could be beneficial (Please refer to chapter 2.1.P.2.3.3.6 in Section 2.1.P.2.3 for more details). Therefore investigations were initiated on the analytical method for the determination of assay (and related substances) and as a result, the sample preparation was optimized to include a rinse step of the capsule shell. The changes made to the sample preparation are described in Table 16.

Table 16: Comparison of the old vs new sample preparation for the assay method

Old sample preparation	New sample preparation
Weigh accurately the content of 10 capsules and determine the average weight. Homogenize the granulate by mixing with a spatula. Weigh accurately about 147 mg (equivalent to the content of one capsule) of the granulate into a 10 ml volumetric flask, acetonitrile (about 7 ml) is added, vigorously shaken and the solution is sonicated for 5 min. Fill up to mark with acetonitrile	The content of 10 capsules is transferred into a 100 ml volumetric flask; the body and cap of each capsule is rinsed each with 2 x 1 m acetonitrile, the rinse solution is then added to the flask and the flask filled to approximately 40 ml with acetonitrile. The flask is then sonicated for 5 min at ambient temperature and filled to volume with acetonitrile

At the 3 months stability time point, stability samples were prepared according to both methods of preparation in order to compare the assay results thus obtained. The results are summarized in the Table 17 below.

Table 17: Comparison of Assay Results at T = 3 months

Batch	Conditions	Assay results (n=2)		Δ
		Old sample preparation	New sample preparation	
09030016	25°C/60%	99.3%	99.7%	+ 0.4 %
	40°C/75%	95.9%	98.9%	+ 3.0 %
09010036	25°C/60%	98.1%	100.9%	+ 2.8 %
	40°C/75%	98.4%	100.5%	+ 2.1 %

All assay results are within the acceptance criteria of 95.0 to 105.0%. However, the newly optimised sample preparation lead to assay results 0.4% to 3.0% higher than those obtained with the old sample preparation and generally closer to 100%, which is expected when no degradation is observed (please refer to Section 2.1.P.8.3 for detailed results).

Validation of the new sample preparation was performed and the validation report is provided in Section 2.1.P.5.3. The new sample preparation will be implemented for the testing of all future stability timepoints.

2.1.P.4 Control of Excipients (Nabilone, 1mg and 0.25 mg capsules)

2.1.P.4.1 Specifications

The excipients used in the drug product formulation comply with the current valid edition of the Ph. Eur., with the exception of yellow iron oxide (E172) which complies with the Commission Regulation (EU) No 231/2012 of 9 March 2012.

The regulation No 231/2012 lays down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council.

Table 1: Compendial Quality Standard of Excipients

Excipient	Quality Standard	Supplier*
Povidone (K25)	Ph. Eur.	BASF SE Ludwigshafen, Germany
Corn starch	Ph. Eur.	Colorcon Dartford Kent, England
Ethanol	Ph. Eur.	Alcosuisse Bern, Switzerland
Capsules (Nabilone 1 mg) Gelatine Titanium dioxide, E171 Yellow Iron Oxide, E172	 Ph. Eur. Ph. Eur. EU No 231/2012	Capsugel QA: Bornem, Belgium
Capsules (Nabilone 0.25 mg) Gelatine Titanium dioxide, E171	 Ph. Eur. Ph. Eur.	Capsugel QA: Bornem, Belgium

*Current supplier. The applicant reserves the right to source inactive ingredients from other manufacturers; the grade of material will be equivalent and the supplier(s) suitably qualified.

CoA Povidone (K25)

BASF
We create chemistry

KONTROLLIERT AM 23. FEB. 2016

Certificate of Analysis

BASF SE

Please note that the certificates of analysis are also conveniently available online and around the clock at www.worldaccount.basf.com

Pharmachemicals Handels GmbH

Hauptstr. 36

85399 Hallbergmoos-Goldach

Germany

2015-10-09
GMC/AV
Fr. Dr. Anna Maria Fournier
+49 621 60-79321
Certificate No 6683
Page 1 of 3

Certificate of Analysis according to DIN 55350-18-4.2.2

Kollidon® 25

25KG Boxes Fibreboard
Purchase Order/Customer Product#
115-3056-01102015

Material	57254799
Order	3011674582 000010
Delivery	3095368732 000010
Lot	75997636W0
Lot/Qty	2000.000 KG
Total	2000.000 KG
Transport	LD-G7760//

Test Parameter	Requirements	UoM	Results
Identification (IR)	must conform		conforms
Appearance of solution	clear, not more intensely colored than reference solution BY6/B6/R7		conforms
pH-value	Min.: 3.0 Max.: 5.0		3.6
K-value	Min.: 22.5 Max.: 27.0		25.1
Aldehydes	Max.: 500	mg/kg	82
Peroxides	Max.: 400	mg/kg	46
Hydrazine	Max.: 1	mg/kg	<1
2-pyrrolidone (impurity B)	Max.: 3.0	g/100g	1.9
Vinylpyrrolidone (impurity A)	Max.: 10	mg/kg	2
Heavy metals *	must conform (max.: 10 mg/kg)		conforms
Lead *	must conform (max.: 10 mg/kg)		conforms

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

This is a computer-generated document. No signature is required.

BASF
We create chemistry

KONTROLLIERT AM 23. FEB. 2016

Certificate of Analysis

BASF SE

Please note that the certificates of analysis are also conveniently available online and around the clock at www.worldaccount.basf.com

Pharmachemicals Handels GmbH

Hauptstr. 36

85399 Hallbergmoos-Goldach

Germany

2015-10-09
GMC/AV
Fr. Dr. Anna Maria Fournier
+49 621 60-79321
Certificate No 6683
Page 2 of 3

Certificate of Analysis according to DIN 55350-18-4.2.2

Kollidon® 25

25KG Boxes Fibreboard
Purchase Order/Customer Product#
115-3056-01102015

Material	57254799
Order	3011674582 000010
Delivery	3095368732 000010
Lot	75997636W0
Lot/Qty	2000.000 KG
Total	2000.000 KG
Transport	LD-G7760//

Test Parameter	Requirements	UoM	Results
Water	Max.: 5.0	g/100g	2.1
Residue on ignition / Sulphated ash *	must conform (max.: 0.1 g/100g)		conforms
Residual solvent formic acid	Max.: 0.5	g/100g	0.4
Total aerobic microbial count (TAMC) Test method Ph.Eur., 2.6.12	Max.: 200	CFU/g	<10
Total combined yeasts/moulds count (TYMC) Test method Ph.Eur., 2.6.12	Max.: 20	CFU/g	<10
Nitrogen (anhydrous basis)	Min.: 11.5 Max.: 12.8	g/100g	12.6

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

This is a computer-generated document. No signature is required.

BASF
We create chemistry

KONTROLLIERT AM 23. FEB. 2016

Certificate of Analysis

BASF SE

Please note that the certificates of analysis are also conveniently available online and around the clock at www.worldaccount.basf.com

Pharmachemicals Handels GmbH

Hauptstr. 36

85399 Hallbergmoos-Goldach

Germany

2015-10-09
GMC/AV
Fr. Dr. Anna Maria Fournier
+49 621 60-79321
Certificate No 6683
Page 3 of 3

Certificate of Analysis according to DIN 55350-18-4.2.2

Kollidon® 25

25KG Boxes Fibreboard
Purchase Order/Customer Product#
115-3056-01102015

Material	57254799	
Order	3011674582	000010
Delivery	3095368732	000010
Lot	75997636W0	
Lot/Qty	2000.000	KG
Total	2000.000	KG
Transport	LD-G7760//	

* This test is verified on random samples only.

The product meets the requirements of the following monographs:

"Povidone" of Ph.Eur. 8th edition, USP38/NF33, JP 16th.ed.

Manufacturer: BASF SE
Carl-Bosch-Str.38
67056 Ludwigshafen
Germany

QC-Reference-No.		15C08571
Production date	(YYYY-MM)	2015-07
Release date	(YYYY-MM-DD)	2015-08-05
Retest date	(YYYY-MM)	2019-07

BASF SE
Competence Center Analytic
Quality Control
sig. Hr. Sontag
QC-Represantative

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

Ethanol

Länggassstrassse 35 | 3000 Bern 9 | Tel. 031 309 17 17 | Fax 031 309 17 08

alcosuisse

Ein Profitcenter der Eidg. Alkoholverwaltung | Un centre de profit de la Régie fédérale des alcools | Un centro di profitto della Regia federale degli alcool | A profit centre of the Swiss Alcohol Board

Chargen-Nummer **10124**
Batch number

SwissCo Services AG
Pharma & Food Supplements
Bahnhofstrasse 14
CH-4334 Sisseln AG

Datum / Date 27.05.2016

Geht an / Attn. to: Viktoria Kanczok

Fax: certificates.sisseln@aenova-group.com

Ethanol-Analysenzertifikat / Certificate of analysis of the ethanol

F25-A Ethanol aus Agrarrohstoffen
F25-A Ethanol from agricultural raw material

Warenempfänger-Nr. / Consignee No.	17054
Herstellung / Production	04.02.2016
Freigabe / Release	05.02.2016
Ihre Bestellung vom / Your order of	23.05.2016
Ihre Bestell-Nr. / Your order No.	52528
Ihre Artikel-Nr. / Your article No.	1.0319.00
Lieferschein-Nr. / Delivery note No.	168173-1
Abgefüllt am / Filled on	25.05.2016
Geliefert am / Delivered on	27.05.2016
Netto-Gewicht total / Net weight total	750 kg
Transportgebinde / container of transport	IBC / IBC xf711443

geprüft 30. MAI 2016

(Gebinde und Lieferung / Container and delivery)

Haltbarkeit / Lenght of time to be kept

In Edelstahlbehältern 5 Jahre ab Abfülldatum /
In tanks of high grade steel 5 years from filling date

In Kanister Einweg von Alcosuisse 6 Monate ab Abfülldatum /
In canister one way of Alcosuisse 6 month from filling date

Beilage: Analysenzertifikat des Eidg. Institut für Metrologie METAS, Labor Alkohol
Enclosure: Certificate of analyses of the Federal institute of Metrology METAS, alcohol laboratory

Dokument ohne Unterschrift / Document without signature

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Institut für Metrologie METAS

Alcosuisse
Länggassstrasse 35
3000 Bern 9

Charge / Batch **10124**
METAS-Nr. / number 200027896

Seite / Page 1/1

Analysenzertifikat / Certificate of analysis
Für: F25 Ethanol
For: F25 Ethanol

Analysendatum / Date of analysis: 05.02.2016
Mustereingang / Sample Receipt: 05.02.2016

Parameter / parameter	Einheit / unit	Resultat / result	Spez. Ph. Eur. spec. Ph. Eur.	Spez. Alcosuisse spec. Alcosuisse	Methode / method
Organoleptische Eigenschaften Organoleptic characteristics		Kein feststellbarer Fremdgeschmack No detectable taste other than that of the raw material		Kein feststellbarer Fremdgeschmack No detectable taste other than that of the raw material	SLMB
Infrarot-Spektroskopie Infrared absorption		entspricht complies	entspricht complies	entspricht complies	Ph. Eur.
Aussehen Appearance		klar & farblos clear & colourless	klar & farblos clear & colourless	klar & farblos clear & colourless	Ph. Eur.
Aussehen nach Verdünnung mit Wasser Appearance after dilution with water		klar clear	klar clear	klar clear	Ph. Eur.
Säure, ausgedrückt als Essigsäure Acidity, expressed as acetic acid	mg/L	6	max. 30	max. 15	Ph. Eur.
Sauer oder alkalisch reagierende Substanzen / Acidity or alkalinity		entspricht complies	entspricht complies	entspricht complies	Ph. Eur.
Dichte (20 °C) Density (20 °C)	kg/m3	806.8		max. 807	SLMB / Ph. Eur.
Relative Dichte Relative density		0.8083	0.805 - 0.812	max. 0.809	SLMB
Ethanol-Gehalt Ethanol content	% m/m % vol	94.05 96.15	92.6 - 95.2 95.1 - 96.9	min. 94.0 min. 96.1	OIML
Absorption im UV: 240 nm 250 - 260 nm 270 - 340 nm		 0.21 0.09 0.01	 max. 0.40 max. 0.30 max. 0.10	 max. 0.40 max. 0.30 max. 0.10	Ph. Eur.
Absorptionskurve Absorption curve		gleichmässig smooth	gleichmässig smooth	gleichmässig smooth	Ph. Eur.
Acetaldehyd + Acetal Acetaldehyde + acetal	ppm V/V (mg/L)	<5 (<4)	max. 10	max. 10 (max. 8)	Ph. Eur.
Methanol Methanol	ppm V/V (mg/L)	<5 (<4)	max. 200	max. 100 (max. 80)	Ph. Eur.
Benzol Benzene	ppm V/V	<1	max. 2	max. 1	Ph. Eur.
Andere flüchtige Verunreinigungen Other volatile impurities	ppm V/V	<5	max. 300	max. 150	Ph. Eur.
Verdampfungsrückstand Residue on evaporation	mg/L	<10	max. 25	max. 10	Ph. Eur.

Ph. Eur.: Europäische Pharmakopöe / Pharmacopée européenne / European Pharmacopoeia
OIML: Organisation Internationale de Métrologie Légale
SLMB: Schweizerisches Lebensmittelbuch / manuel suisse des denrées alimentaires / Swiss food manual

Die Prüfergebnisse beziehen sich nur auf das vom Prüflaboratorium untersuchte Muster.
The results relate only to the items tested.

Die Resultate wurden im reinen Ethanol ermittelt, allfällige Denaturierungen sind nicht berücksichtigt.
The results are determined in the pure ethanol, eventually added denaturants are not respected.

Angaben zur Messunsicherheit werden dem Auftraggeber auf Anfrage angegeben.
Dokument ohne Unterschrift / Document without signature

geprüft 30. MAI 2016

Für die Analyse:
Sharona Perrin, Wissenschaftliche Mitarbeiterin, Bereich Analytische Chemie/Labor Alkohol

Eidgenössisches Institut für Metrologie METAS
Lindenweg 50, 3003 Bern-Wabern, Schweiz
Navigationsadresse: 3084 Wabern
Tel. +41 58 387 01 11, www.metas.ch
info@metas.ch

Labor Alkohol-AZ10124

Corn starch

KONTROLLIERT AM 21. MRZ. 2016

Colorcon

Page 1 of 2

Certificate of Analysis

Product Name:	STARCH 1500® PARTIALLY PREGELATINIZED MAIZE STARCH 2001
Product Number:	2001
Material Description:	White Powder
Lot No:	IN531237
VBN:	IN531237
Quantity Supplied:	50 KG
Ship To:	Swissco Services AG CH
Bill To:	Swissco Services AG CH
Sales Order No:	CCUK1169646
Customer PO NO:	49786
Customer Item:	1.241.00

Compliance Statement: This Product meets all agreed upon specifications

		Specifications			
Test	**Method**	**Minimum**	**Maximum**	**Result**	**Analyst**
BULK DENSITY (TAPPED), g/ml	IN-QAC-TM-5381	0.80	1.05	0.85 g/ml	BP
COLD WATER SOLUBLES AVERAGE, %	IN-QAC-TM-5382	10.0	20.0	15.7 %	BP
DENSITY, g/cc	IN-QAC-TM-5381	0.55	0.75	0.63 g/cc	BP
IDENTIFICATION PH EUR	PH EUR	POSITIVE		POSITIVE	BM
IDENTIFICATION USP/NF	USP/NF	POSITIVE		POSITIVE	BP
IRON, %	USP/NF	NMT 0.0010		NMT 0.0010 %	BP
LOSS ON DRYING AVERAGE, %	IN-QAC-TM-5364	0.00	14.00	8.10 %	BP
FOREIGN MATTER	PH EUR	CONFORMS		CONFORMS	BM
MICRO AEROBIC TPC, CFU	IN-QAC-TM-6374	0	100	30 CFU	BM
MICRO E. COLI	IN-QAC-TM-6373	ABSENT		ABSENT	BM
MICRO M&Y, CFU	IN-QAC-TM-6374	0	100	<10 CFU	BM
MICRO P. AERUGINOSA	IN-QAC-TM-6369	ABSENT		ABSENT	BM
MICRO S. AUREUS	IN-QAC-TM-6376	ABSENT		ABSENT	BM
MICRO SALMONELLA	IN-QAC-TM-6371	ABSENT		ABSENT	BM
OXIDIZING SUBSTANCES	USP/NF	NEGATIVE		NEGATIVE	BP
PH	USP/NF	4.5	7.0	5.5	BP
PROTEIN, %	FCC	< 0.5		GM	N/A

12.02.16

This Product was manufactured in a facility that is registered with the United States FDA under the provisions of the Bioterrorism Preparedness and Response Act.

The information contained in this document is proprietary to Colorcon, Inc. and may not be used or disseminated inappropriately.

Manufactured By:	COLORCON	**Date Of Manufacture:**	17-SEP-2015
Manufacturing Site:	Indianapolis, IN, USA	**Re-evaluation Date:**	16-SEP-2019

The above analytical data has been reviewed and authenticated electronically by an authorised representative of the Quality Unit as evidence by the application of an electronic signature.

Approved By: Joshua Cardinal **Date:** 05-OCT-2015

Electronic Signature ID: 1694659-1626244

Chris Fowler
QA Doc Controller

Flagship House Victory Way, Crossways Dartford Kent DA2 6QD England Tel: 44-1322-293000 Fax: 44-1322-627200 www.colorcon.com

KONTROLLIERT AM 21. MRZ. 2016

Colorcon

Page 2 of 2

Certificate of Analysis

Product Name:	STARCH 1500® PARTIALLY PREGELATINIZED MAIZE STARCH 2001
Product Number:	2001
Material Description:	White Powder
Lot No:	IN531237
VBN:	IN531237
Quantity Supplied:	50 KG
Ship To:	Swissco Services AG CH
Bill To:	Swissco Services AG CH
Sales Order No:	CCUK1169646
Customer PO NO:	49786
Customer Item:	1.241.00

Compliance Statement: This Product meets all agreed upon specifications

Specifications

Test	Method	Minimum	Maximum	Result	Analyst
PARTICLE SIZE RETAINED ON 8 MESH, %	IN-QAC-TM-5378	0.0	0.0	0.0 %	BP
PARTICLE SIZE RETAINED ON 40 MESH, %	IN-QAC-TM-5378	0.0	0.5	0.0 %	BP
PARTICLE SIZE THROUGH 100 MESH, %	IN-QAC-TM-5378	90.0	100.0	93.4 %	BP
PARTICLE SIZE THROUGH 270 MESH, %	IN-QAC-TM-5378	25.0	100.0	37.2 %	BP
RESIDUE ON IGNITION, %	USP/NF	0.0	0.5	0.3 %	BP
SULPHUR DIOXIDE, %	USP/NF	NMT 0.001		GM	N/A

Meets all specifications of Pregelatinized Starch, Current NF / Current PhEur.
Colorcon warrants Starch 1500 partially pregelatinized maize starch to meet current NF and PhEur Requirements for Pregelatinized Starch. Colorcon supports this claim through method equivalency studies between the NF methods and PhEur methods and quarterly audit testing for all the PhEur requirements.
This product is produced using identity preserved, non genetically enhance dent maize. The identity preservation process includes: grower certification of the origin of the seeds planted, documentation of storage and handling of grain, and PCR testing of grain delivered to the raw material supplier's plant. The raw material supplier's plant only accepts identity preserved maize.

This product meets ICH Q3C and current USP/NF requirements for Organic Volatile Impurities.

Regarding the solvents identified in the ICH Guideline on Residual Solvents Q3C and in the USP/NF General Chapter <467> Residual Solvents, none of the solvents are expected to be present in this product.
GM: Manufacturer guarantees compliance based on process knowledge and audit testing.

This Product was manufactured in a facility that is registered with the United States FDA under the provisions of the Bioterrorism Preparedness and Response Act.

Manufactured By:	COLORCON	**Date Of Manufacture:**	17-SEP-2015
Manufacturing Site:	Indianapolis, IN, USA	**Re-evaluation Date:**	16-SEP-2019

The above analytical data has been reviewed and authenticated electronically by an authorised representative of the Quality Unit as evidence by the application of an electronic signature.

Approved By: Joshua Cardinal **Date:** 05-OCT-2015

Electronic Signature ID: 1694659-1626244

Chris Fowler
QA Doc Controller

Flagship House Victory Way, Crossways Dartford Kent DA2 6QD England Tel: 44-1322-293000 Fax: 44-1322-627200 www.colorcon.com

Capsules (Nabilone 1mg)

TO THE ATTENTION OF: **SwissCo Services AG**
QA

CAPSUGEL®

CERTIFICATE OF ANALYSIS

Page: 1 of 2

The capsules are produced under very carefully controlled conditions. Controls are performed continuously throughout the process and guarantee that capsules conform to the highest quality standards. The capsules described below conform to the specifications as defined in the current edition of the Capsugel "Technical Reference File" for empty hard gelatin capsules.

PRODUCT DESCRIPTION Empty Hard Gelatin Capsules (Bovine and/or Porcine Origin)

Customer:	SwissCo Services AG	Lot Number:	34373931
Product Name:	HGK GR.2 WEISS/GELB	Customer Reference:	49505
Product Code:	1.1301.00	Product Size:	2
Manufacturing Date:	12-Jan-2016	Type:	CONI-SNAP
Expiration Date:	Jan 2021		
BODY		**CAP**	
Code:	44.000	Code:	41.357
Name:	WHITE OP.	Name:	RICH YELLOW OP. C357

Body Composition		**Cap Composition**	
Titanium dioxide	2.0000 %	Titanium dioxide	1.1200 %
GELATIN	qsp 100 %	Yellow iron oxide	0.7840 %
		GELATIN	qsp 100 %

Due to the nature of raw materials, their sourcing, and technology improvements, the color composition data indicated are target values and actual values may vary to insure the consistency of lot color. Capsugel supports the expiry date if recommendations for warehousing and transportation are observed (recommended : 15°C - 25°C and 35% - 65% relative humidity)

Ingredient / Reference	**E Nr**	**C.I. Nr**	**Function**	**Regulatory References**
Titanium dioxide	E171	77891	Opacifier	(EU) 231/2012, 21 CFR, EP, JP, USP/NF
Yellow iron oxide	E172	77492	Colorant	(EU) 231/2012, 21 CFR, JPE, USP/NF
GELATIN			Structure	EP, JP, USP/NF

ANALYTICAL DATA

Characteristics	**Test Method**	**Units**	**Specifications**	**Results**
Identification of gelatin	CP010		Positive	pass *
Identification of TiO2	CP011		Conforms to composition	pass *
Identification of iron oxides	CP013		Conforms to composition	pass *
Sulphated ash	CP015	%	Less than 7	pass *
Arsenic	CP017A	ppm	Less than 1	pass *
Cadmium	CP017B	ppm	Less than 0.5	pass *
Lead	CP017C	ppm	Less than 1	pass *
Mercury	CP017D	ppm	Less than 0.1	pass *
Lubricant content	CP019	%	Less than 0.5	0.06 *
Sulphur dioxide	CP020	ppm	Less than 50	1 *
Disintegration time	CP001	min/sec	Less than 15:00	3:05 *
Loss on drying	CP014	%	13.0 to 16.0	14.8
Average weight	CP003	mg	57 to 65	60.8
Total Aerobic Microbial Count	CP031	cfu / g	Less than 1000	< 10
Escherichia coli	CP033		Absence in 1 gram	pass *
Salmonella	CP034		Absence in 10 gram	pass *
Staphylococcus aureus	CP035		Absence in 1 gram	pass *
Pseudomonas aeruginosa	CP036		Absence in 1 gram	pass *
Total Yeasts/Moulds Count	CP032	cfu / g	Less than 100	< 10 *

*** Reduced frequency testing**

CAPSUGEL®

CERTIFICATE OF ANALYSIS

Customer Name: SwissCo Services AG

Lot Nr: 34373931

Capsugel hard gelatin capsules are meeting not more than 2 ppm Chromium as defined in the Chinese pharmacopoeia for Vacant Gelatin Capsules.
In accordance with ICH Q3C residual solvent guideline , Class 3 Solvents may be used according to good manufacturing practices such that their cumulative value does not exceed 5000ppm or 0.5%, under option 1 as defined in ICH Q3C, USP<467>, and EP General Text 5.4.

Physical Characteristics

This product conforms to established A.Q.L.'s for Physical Attributes.
Appearance - Clean empty capsules, meeting the specified requirements of color and size.
Odor - Free of disagreeable odor.
The reported disintegration time is subjective, and is provided to indicate Pass/Fail status for 15 minutes.
Tests for color, solubility and acidity conform to Japanese Pharmacopeia requirements.

TSE/BSE Regulations

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is in full compliance with all pharmaceutical regulatory statutes.
Specifically, Capsugel fully complies with the following where applicable:

- Commission Directive 2003/63/EC/ Note for guidance EMA/410/01 compliance demonstrated by "Certificate of Suitability".
- Regulation (EC) No 853/2004 on specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 as regards specified risk material.
- United States FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Materials Derived from Cattle in Medical Products.
- United States FDA - 21 CFR Parts 189 and 700 related to Use of Materials Derived From Cattle in Human Food and Cosmetics.
- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210, Notification No. 1002-27 as of November 25th 2014.
- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

- Rousselot R1 CEP 2000-027
- Rousselot R1 CEP 2000-029
- Rousselot R1 CEP 2001-332
- PB Gelatins R1 CEP 2000-045
- PB Gelatins R1 CEP 2002-110
- Gelita group R1 CEP 2001-424
- Gelita group R1 CEP 2003-172
- Sterling Gelatin R1-CEP 2001-211
- Nitta Gelatin R1-CEP 2000-344
- Nitta Gelatin R1 CEP 2005-217
- Nitta Gelatin R1 CEP 2004-247
- Nitta Gelatin R1 CEP 2004-320

Manufacturing Processes:
No Addition of Preservatives
No Ethylene Oxide Treatment
No Irradiation Treatment

Capsugel Belgium NV
Sophie De Keersmaeker - Quality Assurance
Rijksweg 11 - 2880 Bornem -Belgium
Tel: +32 (0)3 8900588

Digitally approved by Moernaut, Roel (Feb 09 2016, 13:52:49)

Authorized Signer

Capsules (Nabilone 0.25mg)

TO THE ATTENTION OF:

CAPSUGEL®

CERTIFICATE OF ANALYSIS

Page: 1 of 2

The capsules are produced under very carefully controlled conditions. Controls are performed continuously throughout the process and guarantee that capsules conform to the highest quality standards. The capsules described below conform to the specifications as defined in the current edition of the Capsugel "Technical Reference File" for empty hard gelatin capsules.

PRODUCT DESCRIPTION	Empty Hard Gelatin Capsules (Bovine and/or Porcine Origin)		
Customer:		Lot Number:	34435641
Product Name:		Customer Reference:	
Product Code:		Product Size:	4
Manufacturing Date:	26-Apr-2016	Type:	CONI-SNAP
Expiration Date:	Apr 2021		
BODY		**CAP**	
Code:	44.000	Code:	44.000
Name:	WHITE OP.	Name:	WHITE OP.

Body Composition		**Cap Composition**	
Titanium dioxide	2.0000 %	Titanium dioxide	2.0000 %
GELATIN	qsp 100 %	GELATIN	qsp 100 %

Due to the nature of raw materials, their sourcing, and technology improvements, the color composition data indicated are target values and actual values may vary to insure the consistency of lot color. Capsugel supports the expiry date if recommendations for warehousing and transportation are observed (recommended : 15°C - 25°C and 35% - 65% relative humidity)

Ingredient / Reference	**E Nr**	**C.I. Nr**	**Function**	**Regulatory References**
Titanium dioxide	E171	77891	Opacifier	(EU) 231/2012, 21 CFR, EP, JP, USP/NF
GELATIN			Structure	EP, JP, USP/NF

ANALYTICAL DATA

Characteristics	**Test Method**	**Units**	**Specifications**	**Results**
Identification of gelatin	CP010		Positive	pass *
Identification of TiO2	CP011		Conforms to composition	pass *
Sulphated ash	CP015	%	Less than 7	pass *
Arsenic	CP017A	ppm	Less than 1	pass *
Cadmium	CP017B	ppm	Less than 0.5	pass *
Lead	CP017C	ppm	Less than 1	pass *
Mercury	CP017D	ppm	Less than 0.1	pass *
Lubricant content	CP019	%	Less than 0.5	0.04 *
Sulphur dioxide	CP020	ppm	Less than 50	2 *
Disintegration time	CP001	min/sec	Less than 15:00	2:48 *
Loss on drying	CP014	%	13.0 to 16.0	14.5
Average weight	CP003	mg	35 to 41	38.4
Total Aerobic Microbial Count	CP031	cfu / g	Less than 1000	< 10
Escherichia coli	CP033		Absence in 1 gram	pass *
Salmonella	CP034		Absence in 10 gram	pass *
Staphylococcus aureus	CP035		Absence in 1 gram	pass *
Pseudomonas aeruginosa	CP036		Absence in 1 gram	pass *
Total Yeasts/Moulds Count	CP032	cfu / g	Less than 100	< 10 *

*** Reduced frequency testing**

CAPSUGEL®

CERTIFICATE OF ANALYSIS

Customer Name: Lot Nr: 34435641

Capsugel hard gelatin capsules are meeting not more than 2 ppm Chromium as defined in the Chinese pharmacopoeia for Vacant Gelatin Capsules.
In accordance with ICH Q3C residual solvent guideline , Class 3 Solvents may be used according to good manufacturing practices such that their cumulative value does not exceed 5000ppm or 0.5%, under option 1 as defined in ICH Q3C, USP<467>, and EP General Text 5.4.

Physical Characteristics

This product conforms to established A.Q.L.'s for Physical Attributes.
Appearance - Clean empty capsules, meeting the specified requirements of color and size.
Odor - Free of disagreeable odor.
The reported disintegration time is subjective, and is provided to indicate Pass/Fail status for 15 minutes.
Tests for odor, solubility and acidity conform to Japanese Pharmacopeia requirements.

TSE/BSE Regulations

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is in full compliance with all pharmaceutical regulatory statutes.
Specifically, Capsugel fully complies with the following where applicable:
· Commission Directive 2003/63/EC/ Note for guidance EMA/410/01 compliance demonstrated by "Certificate of Suitability".
· Regulation (EC) No 853/2004 on specific hygiene rules for food of animal origin.
· Regulation (EC) No 999/2001 as regards specified risk material.
· United States FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Materials Derived from Cattle in Medical Products.
· United States FDA - 21 CFR Parts 189 and 700 related to Use of Materials Derived From Cattle in Human Food and Cosmetics.
· Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", MHLW Notice No.0327-2 of March 27, 2015.
· Japanese Ministry of Health, Labor and Welfare - Notification No. 210, Notification No. 1002-27 as of November 25th 2014.
· The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:
· Rousselot R1 CEP 2000-027
· Rousselot R1 CEP 2000-029
· Rousselot R1 CEP 2001-332
· PB Gelatins R1 CEP 2000-045
· PB Gelatins R1 CEP 2002-110
· Gelita group R1 CEP 2001-424
· Gelita group R1 CEP 2003-172
· Sterling Gelatin R1-CEP 2001-211
· Nitta Gelatin R1-CEP 2000-344
· Nitta Gelatin R1 CEP 2005-217
· Nitta Gelatin R1 CEP 2004-247
· Nitta Gelatin R1 CEP 2004-320

Manufacturing Processes:
No Addition of Preservatives
No Ethylene Oxide Treatment
No Irradiation Treatment

Capsugel Belgium NV
Sophie De Keersmaeker - Quality Assurance
Rijksweg 11 - 2880 Bornem -Belgium
Tel: +32 (0)3 8900588

Digitally approved by Soontjens, Chris (May 03 2016, 12:24:46)
Authorized Signer

2.1.P.4.2 Analytical Procedures (Nabilone, 1 mg and 0.25 mg capsules)

For the excipients described in the Ph. Eur., the analytical procedures are identical with those mentioned in the respective monographs.

The yellow iron oxide (E172), which is an excipient only used for the 1mg Nabilone capsules, is described in the COMMISSION REGULATION (EU) No 231/2012 of 9 March 2012 laying down specifications and analytical procedures for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council.

2.1.P.4.3 Validation of Analytical Procedures (Nabilone, 1 mg and 0.25 mg capsules)

All analytical procedures are performed according to the current Ph. Eur, excipient monographs or the Commission Regulation (EU) No 231/2012 (9 March 2012) and are therefore considered suitable for their intended use.

2.1.P.4.4 Justification of Specifications (Nabilone, 1 mg and 0.25 mg capsules)

The excipient specifications are equivalent to those of their respective Ph. Eur. Monographs or Commission Regulation (EU) No 231/2012 (9 March 2012) and are therefore considered suitable for their intended use. No further justification is deemed necessary.

2.1.P.4.5 Excipients of Human or Animal Origin (Nabilone, 1 mg and 0.25 mg capsules)

The only material of human or animal origin is the gelatine used for manufacture of the capsule shell material. The gelatine used by the current manufacturer Capsugel can contain blends of several pharmaceutical gelatines. When bovine gelatine is used, it is in full compliance with all pharmaceutical regulatory requirements.

Regulatory declaration by Capsugel regarding BSE safety is attached on the following pages.

CAPSUGEL®

Regulatory Information & Documents

> Subject – Regulatory declaration – BSE safety

Valid as of September 2015

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is pharmaceutical grade, and in full compliance with all pharmaceutical regulatory statutes. Specifically, Capsugel fully complies with the following where applicable:

- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), which is published by the European Commission following Commission Directive 2003/63/EC, (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), Annex I, Part I, paragraph 3.2.2.4. Control of excipients.
  These Directives require that applicants for Marketing Authorisation must demonstrate that medicinal products are manufactured in accordance with the latest version of this Note for Guidance and compliance is demonstrated by the "Certificate of Suitability" issued to the manufacturer of the bovine gelatin by the European Directorate for the Quality of Medicines (EDQM). As such, Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

  - Rousselot R1-CEP 2000-027
  - Rousselot R1-CEP 2000-029
  - Rousselot R1-CEP 2001-332
  - PB Gelatins R1-CEP 2000-045
  - PB Gelatins R1-CEP 2002-110
  - Gelita Group R1-CEP 2001-424
  - Gelita Group R1-CEP 2003-172
  - Sterling Gelatin R1-CEP 2001-211
  - Nitta Gelatin R1-CEP 2000-344
  - Nitta Gelatin R1-CEP 2004-247
  - Nitta Gelatin R1-CEP 2004-320
  - Nitta Gelatin R1-CEP 2005-217

- Regulation (EC) No 853/2004 laying down specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies.

- United States Food and Drug Administration (FDA) – Proposed Rule on "Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants," 72 Fed. Reg. 1582 (Jan. 12, 2007) (to be codified at 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271).
- United States Food and Drug Administration (FDA) – Interim Final Rule on "Use of Materials Derived From Cattle in Human Food and Cosmetics," 69 Fed. Reg. 42256 (July 14, 2004), as amended and codified at 21 CFR §§ 189.5, 700.27; and Final Rule on "Recordkeeping Requirements for Human Food and Cosmetics Manufactured From, Processed With, or Otherwise Containing, Material From Cattle," 71 Fed. Reg. 59653 (Oct. 11, 2006), codified at 21 CFR §§ 189.5, 700.27.

Colmar, FRANCE
10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Bornem, BELGIUM
Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

Greenwood, USA
535 North Emerald Road
SC-29646 Greenwood
T (888) 783 6361
F (888) 783 6360

Boulevard 18 de Noviembre
1030A
Puebla, Peubla
México 72270
T +52 (222) 372 1545

CAPSUGEL®

Regulatory Information & Documents

- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", Chapter 2, Article 7 and Article 10 "Specifications and Standards for Food or additives" revised and announced by MHLW Notice No.0327-2 of March 27, 2015.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of the MHLW issued on May 20, 2003 and the latest version by Notification No. 1002-27 about the partial amendment of the criteria eliminating source country restrictions, applicable from November 25th 2014.

  Capsugel bovine bone gelatin suppliers certify vertebrae removal independent from the age of the animals.

- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel continuously monitors all regulatory activities; please let us know if there are further questions or clarification needed.

For further information, please consult your customer service representative.

Valid as of
September, 2015

Colmar, FRANCE
10, Rue Timken
FR-68027 Colmar Cedex
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Bornem, BELGIUM
Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

Greenwood, USA
535 North Emerald Road
SC-29646 Greenwood
T (888) 783 6361
F (888) 783 6360

Boulevard 18 de Noviembre
1030A
Puebla, Peubla
México 72270
T +52 (222) 372 1545

2.1.P.4.6 Novel Excipients (Nabilone, 1 mg and 0.25 mg capsules)

No novel excipients are used in the formulation.

2.1.P.5 Control of Drug Product (Nabilone, 1 mg capsules and 0.25 mg capsules)

2.1.P.5.1 Specifications

Release and shelf-life specifications for Canemes 1 mg and 0.25 mg capsules are presented in the tables below.

Release Specifications for Canemes 1 mg and 0.25 mg

Test	Specifications	Method
Appearance	Nabilone 1 mg capsules: Opaque capsules size 2, body white, cap yellow; filled with a white powder Nabilone 0.25 mg capsules: Opaque capsules size 4, body white, cap white; filled with a white powder	Visual inspection
Identification HPLC RT HPLC UV (DAD)	The retention time complies with the retention time of the reference substance The UV spectrum complies with the UV spectrum of the reference substance	In-house HPLC method based on Ph. Eur. 2.2.29
Assay (HPLC)	95.0 – 105.0%	In-house HPLC method based on Ph. Eur. 2.2.29
	Nabilone 1 mg capsules: 0.950 – 1.050 mg/capsule Nabilone 0.25 mg capsules: 0.2375 – 0.2625 mg/capsule	
Related Compounds (HPLC): Single unknown RC Sum RC	 NMT 0.3% [1] NMT 1.0%	
Uniformity of dosage units	n=10: AV NMT 15.0% n=30: AV NMT 15.0% and no unit less than 0.75 M more than 1.25 M	Ph. Eur. 2.9.40
Dissolution test	NLT 70% (Q) after 60 min Level S_1, S_2 or S_3 must comply	Ph. Eur. 2.9.3
Water content (KF)	NMT 10.0%	Ph. Eur. 2.5.12, Method A
Ethanol content (GC)	NMT 0.5%	Internal GC method
Microbiological quality [2] TAMC TYMC *E.Coli*	 NMT 10^3 CFU/g NMT 10^2 CFU/g Absent in 1 g	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13

[1] based on the designated amount of Nabilone
[2] to be tested on the first three validation batches and subsequently on every 5th batch

Shelf-life specifications for Canemes 1 mg and 0.25 mg

Test	Specifications	Method
Appearance	Nabilone 1 mg capsules: Opaque capsules size 2, body white, cap yellow; filled with a white powder Nabilone 0.25 mg capsules: Opaque capsules size 4, body white, cap white; filled with a white powder	Visual
Assay (HPLC)	95.0 – 105.0%	In-house HPLC method based on Ph. Eur. 2.2.29
	Nabilone 1 mg capsules: 0.950 – 1.050 mg/capsule Nabilone 0.25 mg capsules: 0.2375 – 0.2625 mg/capsule	
Related compounds (HPLC): Single unknown RC Total RC	 NMT 0.3% [1] NMT 1.0%	
Dissolution test	NLT 70% (Q) after 60 min Level S_1, S_2 or S_3 must comply	Ph. Eur. 2.9.3
Water content (KF)	NMT 10.0%	Ph. Eur. 2.5.12, Method A
Microbiological quality [2] TAMC TYMC *E.Coli*	 NMT 10^3 CFU/g NMT 10^2 CFU/g Absent in 1 g	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13

[1] based on the designated amount of Nabilone
[2] to be tested on the first three validation batches (beginning and end of stability study) and subsequently on every 5th batch

2.1.P.5.2 Analytical Procedures (Nabilone, 1 mg and 0.25 mg capsules)

The analytical procedures used to analyse Nabilone capsules are listed in the table below. A description of the in-house HPLC and GC methods is provided on the following pages.

Test	**Analytical Procedures**
Appearance	Visual
Identification HPLC-RT HPLC UV (DAD)	In-house HPLC method based on Ph. Eur. 2.2.29
Assay	In-house HPLC method based on Ph. Eur. 2.2.29
Related Compounds Single unknown RC Total RC	In-house HPLC method based on Ph. Eur. 2.2.29
Uniformity of dosage units	Ph. Eur. 2.9.40
Dissolution test	Ph. Eur. 2.9.3
Water Content	Ph. Eur. 2.5.12, Method A
Ethanol Content	Internal GC Method
Microbiological quality TAMC TYMC *E.Coli*	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13

2.1.P.5.2.1 Appearance

Ten (10) capsules per batch are inspected visually; the shells as well as the content are examined for appearance.

2.1.P.5.2.2 Identity Nabilone (HPLC, Retention Time)

The test is performed on the test solution (b1) – refer to the HPLC method description under 3.2.P.5.2.4.

The retention time of the Nabilone peak from the test solution (b1) is compared to those of the reference solution (b1) (mean RT of the first three injections). The %RSD of the retention time from the test solution (b1) and of the reference solution (b1) should not exceed 1.5%.

2.1.P.5.2.3 Identity Nabilone (HPLC, UV-Spectrum)

The test is performed on the first injection of the test solution (b1) – refer to the HPLC method description under 3.2.P.5.2.4.

The UV spectrum of the Nabilone peak from the test solution (b1) should comply with the UV spectrum of the Nabilone peak of the first injection of the reference solution (b1).

2.1.P.5.2.4 Assay Nabilone and Related Substances

All solutions which contain Nabilone, i.e. test and reference solutions, must be light protected by using brown glass volumetric flasks.

Preparation of Reference Solutions

Reference stock solution (a)

10.0 mg Nabilone reference standard are weighed into a 10 ml volumetric flask. Acetonitrile (about 7 ml) is added, vigorously shaken, the solution is sonicated for 5 min and filled up to mark with acetonitrile.

Concentration: 1.0 mg/ml Nabilone.

Prepare the solution in duplicate and name (a1) and (a2).

Reference solution (b)

1.0 ml of reference stock solution (a) is diluted to 10.0 ml with acetonitrile. Each solution (a) is diluted.

Concentration: 0.1 mg/ml Nabilone.

Prepare the solution in duplicate, and name (b1) and (b2).

The reference solution (b1/b2) is stable for 108 hours (4.5 days) when stored in the autosampler brown glass HPLC vials at room temperature. The reference solution (b1/b2) is stable for 7 days when stored in a brown glass flask in the refrigerator (2-8 °C).

Reference stock solution (c)

10.0 mg Impurity C reference standard are weighed into a 10 ml volumetric flask. Acetonitrile (about 7 ml) is added, vigorously shaken, the solution is sonicated for 5 min and filled up to mark with acetonitrile.

Concentration: 1.0 mg/ml Impurity C.

Prepare the solution once.

Reference solution (d) – Resolution solution

5.0 ml of reference stock solution (a1) and 1.0 ml of reference stock solution (c) are transferred into the same 50 ml volumetric flask and diluted to volume with acetonitrile.

Concentration: 0.1 mg/ml Nabilone and 0.02 mg/ml Impurity C.

Prepare the solution once.

Reference solution (e) – Reporting limit solution

2.0 ml of reference solution (b1) is diluted to 50.0 ml with acetonitrile. 5.0 ml of the diluted solution is further diluted to 200.0 ml with acetonitrile.

Concentration: 0.0001 mg/ml Nabilone.

Prepare the solution once.

Preparation of Test Solutions

Test solution (a) (content uniformity)

The content of 1 capsule is transferred completely into a 10 ml volumetric flask, the body and cap of the capsule is rinsed each with 2 x 1 ml acetonitrile, the rinse solution is then added to the flask. Acetonitrile (about 3 ml) is added to the same volumetric flask, vigorously shaken and the solution is sonicated for 5 min.The sample solution is filtered (Macherey and Nagel, Chromophil RC 45/25 or equivalent).

Concentration: 0.1 mg/ml Nabilone.

Prepare ten (10) test solutions.

The test solution is stable for 108 hours (4.5 days) when stored in the autosampler in brown glass HPLC vials at room temperature. The test solution is stable for 7 days when stored in a brown glass flask in the refrigerator (2-8 °C).

Test solution (b) (assay, related substances)

The content of 10 capsules is transferred in a 100 ml volumetric flask; the body and cap of each capsule is rinsed each with 2 x 1 ml acetonitrile, the rinse solution is then added to the flask. Acetonitrile (about 30 ml) is added to the same volumetric flask, vigorously shaken and the solution is sonicated for 5 min. The flask filled to approximately 40 ml with acetonitrile. The sample solution is filtered (Macherey and Nagel, Chromophil RC 45/25 or equivalent).

Concentration: 0.1 mg/ml Nabilone.

Prepare the solution in duplicate.

The test solution is stable for 108 hours (4.5 days) when stored in the autosampler in brown glass HPLC vials at room temperature. The test solution is stable for 7 days when stored in a brown glass flask in the refrigerator (2-8 °C).

HPLC Conditions

Column dimensions	250 mm x 4.0 mm
Column material	Octadecylsilyl silica gel for chromatography *R;* particle size: 5 µm, Supelco or equivalent
Pre-column	Octadecylsilyl silica gel for chromatography *R;* particle size: 5 µm, Supelguard Discovery C18 20 mm x 4mm from Supelco or equivalent
Detection wavelength	208 nm for assay/related substances 190 - 370 nm for UV spectrum of Nabilone
Flow rate	1.0 ml/min
Run time	55 min*
Data integration	until 29 min
Injection volume	20 µl
Column temperature	50°C
Auto sampler temperature	≤ 25°C
Mobile phase A	Acetonitrile
Mobile phase B	Water
Gradient	

Time [min]	Mobile phase A	Mobile phase B
0	60	40
15	65	35
25	65	35
30	90	10
45	90	10
46	60	40
50*	60	40

**following additional 5 min conditioning (60:40) to have total run time of 55 min*

System Suitability Tests (SST)

Repeatability

The relative standard deviation of the respective response (area Nabilone corrected by standard weights) of the 6 injections of reference solution (b), i.e. three injections of reference solution (b1) and three injections of reference solution (b2) is ≤ 2.0 %.

Standard Recovery $r_{korr, rel}$

The average of the respective response of Nabilone of the three injections of reference solution (b2) must not differ more than 2.0 % from the average of the respective response of Nabilone of the first three injections of reference solution (b1).

$$r_{korr,rel} = \frac{\left|\bar{x}_1 - \bar{x}_2\right|}{(\bar{x}_1 + \bar{x}_2) : 2} \cdot 100\,\%$$

$r_{korr, rel}$ Standard Recovery
$\bar{x}_1$ Average response of reference solution (b1)
$\bar{x}_2$ Average response of reference solution (b2)

Variability S

The variability of the three injections of reference solution (b1) and reference solution (b2) must not be greater than 2.0%.

$$S = \frac{x_{max} - x_{min}}{x_{mean}} \cdot 100\,\%$$

S Variability
x_{max} maximum area of the three injections of reference solution (b1) respectively (b2)
x_{min} minimum area of the three injections of reference solution (b1) respectively (b2)
x_{mean} mean area of the three injections of reference solution (b1) respectively (b2)

Precision throughout the run

The Nabilone peak area of the check standards (b1) do not differ more than 2.0 %.

The deviation (r_{rel}) of the replicate injections of reference solution (b1) has to be calculated as outlined:

$$r_{rel} = \frac{\left|\bar{x}_1 - x_{1\mathrm{Re}\,plication}\right|}{\bar{x}_1} \cdot 100\,\%$$

$\bar{x}_1$ Average area of the first three injections of reference solution (b1)
$x_{1Replication}$ Area of the injection of every replicate injection of reference solution (b1) (check standard)

Resolution

From the injection of the reference solution (d) the resolution between Impurity C and Nabilone is ≥ 1.5.

S/N Ratio

From the injection of the reference solution (e) the S/N ratio for the Nabilone peak is ≥ 10:1.

Table of Retention Times

The RRTs are given with reference to Nabilone (retention time = about 22.5 min)

Designation	RRT
Impurity C	0.93
Nabilone	1.00

Calculation and Reporting

Get the chromatograms of reference solution (b), test solution (a), test solution (b) and integrate the peak area. Peaks below the reporting limit are not taken into account for calculation of impurities.

The calculation is done with reference of the average respective response of the first 6 injections of reference solution (b), i.e. average of three injections of reference solution (b1) and three injections reference solution (b2).

Note: 1 capsule is equivalent to 147 mg.

mg/cps Nabilone (assay) =

$$\frac{(Area\ Spl\ (b))(m\ Std\ (a)\ [mg])(\frac{\%\ Activity\ Std}{100})(1\ ml)(10\ ml)}{(Area\ Std\ (b))(10 capsules)(10\ ml)(10\ ml)}$$

% Nabilone (assay) =

$$\frac{(\text{Area Spl (b)})(\text{m Std (a)}\,[\text{mg}])(\frac{\%\ \text{Activity Std}}{100})(1\,\text{ml})(10\,\text{ml})(100\,\%)}{(\text{Area Std (b)})(10\ \text{capsules})(10\,\text{ml})(10\,\text{ml})(1\,\text{mg/cps})}$$

% Nabilone (content uniformity) =

$$\frac{(\text{Area Spl (a)})(\text{m Std (a)}\,[\text{mg}])(\frac{\%\ \text{Activity Std}}{100})(1\,\text{ml})(10\,\text{ml})(100\,\%)}{(\text{Area Std (b)})(1\,\text{capsule})(10\,\text{ml})(10\,\text{ml})(1\,\text{mg/capsule})}$$

% Impurity C =

$$\frac{(\text{Area Spl (b)})(\text{m Std (a)}\,[\text{mg}])(\frac{\%\ \text{Activity Std}}{100})(1\,\text{ml})(10\,\text{ml})(\text{Average Cps weight}\,[\text{mg}])(100\,\%)}{(\text{Area Std (b)})(\text{m Spl (b)}\,[\text{mg}])(10\,\text{ml})(10\,\text{ml})(1\,\text{mg/cps})}$$

% Single Unknown Impurity (IRC) =

$$\frac{(\text{Area Spl (b)})(\text{m Std (a)}\,[\text{mg}])(\frac{\%\,\text{Activity Std}}{100})(1\,\text{ml})(10\,\text{ml})(\text{Average Cps weight}\,[\text{mg}])(100\,\%)}{(\text{Area Std (b)})(\text{m Spl (b)}\,[\text{mg}])(10\,\text{ml})(10\,\text{ml})(1\,\text{mg/cps})}$$

% Total impurities = Summarize the percentage of all impurities.

where:

Area Spl (a)	peak area of Nabilone in test solution (a)
Area Spl (b)	peak area of Nabilone or the resp. Impurity in test solution (b)
Area Std (b)	peak area of Nabilone in reference solution (b)
m Std (a)	weight Nabilone (mg) in reference solution (a)
m Spl (b)	weight sample (mg) in test solution (b)
1 mg/cps	theoretical label strength: 1.0 mg/cps

For the evaluation, the individual determinations are calculated; each determination must be documented with one (1) decimal place more as given in the specification.

The reported result is the mean of the (unrounded) individual determinations. The reported result is rounded to the decimal places as given in the specification.

2.1.P.5.2.5 Uniformity of Dosage Units (Content Uniformity)

All solutions which contain Nabilone, i.e. test and reference solutions, must be light protected by using brown glass volumetric flasks.

For preparation of test, reference solutions and experimental, please refer to the method description for assay and related substances in 2.1.P.5.2.4.

The test is performed on 10 capsules. 10 individual ***test solutions (a) for content uniformity*** are prepared and the ***%Nabilone (content uniformity)*** is calculated for each.

Calculation and Reporting

Perform the calculation as indicated in Ph. Eur. 2.9.40 Uniformity of dosage units and report the AV value as well as the number of samples tested.

2.1.P.5.2.6 Dissolution with off-line HPLC Quantification

All solutions which contain Nabilone, i.e. test and reference solutions, must be light protected by using brown glass volumetric flasks and* brown *glass vessels. Transparent tubings must be protected with aluminium foil.

Preparation of Reference Solutions

Reference solution

Weigh 10 mg to 13 mg ± 0.1 mg Nabilone reference standard into a 10.0 ml volumetric flask; dissolve in 5 ml of Acetonitrile using an ultrasonic bath for approximately 30 s and fill up to volume with Acetonitrile. 1.0 ml of this solution is diluted to 10.0 ml with the mobile phase.

Concentration: 0.1 mg/ml Nabilone.

Prepare the solution in duplicate.

Reference solution for injection

Dilute 1.0 ml of Reference solution with Dissolution medium to 100.0 ml.

Concentration: 0.001 mg/ml Nabilone.

Prepare the solution in duplicate.

The reference solution for injection is stable for 24 hours when stored in an autosampler at room temperature.

Preparation of Dissolution Medium and Mobile Phase

Dissolution Medium (0.1 M HCl containing 0.1% SDS)

1000 ml of 1 M hydrochloric acid is dissolved to 10 l with water. 10.15 g sodium dodecyl sulphate are added and mixed.

Mobile Phase

Mix 90 volumes of acetonitrile and 10 volumes of 0.05 mol/l phosphoric acid. Filter through a filter of regenerated cellulose 0.45 µm.

Preparation of Test Solutions

After the given dissolution time point, sampling is performed using an autosampler with on-line filtration through glass microfiber filter GF/D (Whatman cat. no. 1823-025 or equivalent). An aliquote of approximately 1.5 ml is transferred into a brown glass HPLC vial and analyzed.

Alternatively, sampling is performed manually as follows: after the given dissolution time point a sample amount of approx. 10 ml is drawn with a 10 ml syringe and immediately filtrated through a filter of regenerated cellulose. An aliquote of 1.5 ml is transferred into a brown glass HPLC vial and analyzed.

The test solution is stable for 24 hours when stored in an autosampler at room temperature.

Dissolution Test Conditions

Apparatus	Basket apparatus
Stirring rate	75 rpm/min
Medium	0.1 M hydrochloric acid containing 0.1 % sodium dodecyl sulphate
Temperature	37°C
Volume	1000 ml
Sample drawing	After 60 min / 1.5 ml

HPLC Test Conditions

Column dimensions	250 mm x 4.6 mm
Column material	Octadecylsilyl silica gel for chromatography *R;* particle size: 3 µm, Nucleodur 100-3 C-18 or equivalent
Column temperature	25°C
Autosampler temperature	≤ 25°C
Mobile phase	Acetonitrile : 0.05 mol/l phosphoric acid – 90 : 10 (V:V)
Flow rate	1.0 ml/min
Injection volume	20 µl
Detection	UV-Vis 208 nm
Run time	12 min
Gradient	Isocratic

System Suitability Test (SST)

Retention time for Nabilone: 7 min

Repeatability

The relative standard deviation of the areas of 5 injections of reference solution for injection 1 shall not exceed 2.0 %.

Recovery Rate

From the first injection of the reference solution for injection 2 the recovery rate is calculated and shall be within 95.0 % and 105.0 %.

$$\%\ \text{Recovery rate} = \frac{(\text{Area Std 2})(\text{m Std 1}[\text{mg}])(100\%)}{(\text{Average Area Std 1})(\text{m Std 2}[\text{mg}])}$$

Where:

Average Area Std 1	Average of Nabilone peak areas of 5 injections of reference solution for injection 1
Area Std 2	Nabilone peak area of first injection of reference solution for injection 2
m Std 1	Net weight of Nabilone in reference solution 1
m Std 2	Net weight of Nabilone in reference solution 2

Standard Recovery

The average of the respective response of Nabilone of the three injections of reference solution for injection 2 must not differ more than 4.0 % from the average of the respective response of Nabilone of the first three injections of reference solution for injection 1.

$$r_{korr,rel} = \frac{|\bar{x}_1 - \bar{x}_2|}{(\bar{x}_1 + \bar{x}_2) : 2} \cdot 100\%$$

$r_{korr,rel}$	Standard Recovery
$\bar{x}_1$	Average response of reference solution for injection 1 (first three injections)

$\bar{x}_2$ Average response of reference solution for injection 2 (three injections)

Precision throughout the run

The Nabilone peak area of the check standards (reference solution for injection 1) do not differ more than 4.0 %. The deviation (rrel) of the replicate injections of reference solution for injection 1 has to be calculated as outlined:

$$r_{rel} = \frac{\left| \bar{x}_1 - x_{1Replication} \right|}{\bar{x}_1} \cdot 100\,\%$$

$\bar{x}_1$ Average area of the first three injections of reference solution for injection 1

$x_{1Re plication}$ Area of the injection of every replicate of reference solution for injection 1 (check standard)

Calculation

Get the chromatograms of reference solution and sample solutions and integrate the peak area.

The calculation is done with reference to the average respective response of the first three injections of reference solution for injection 1 and the three injections of reference solution for injection 2.

% Nabilone / capsule =

$$\frac{(\text{Area Spl})(\text{m Std}\,[\text{mg}])\left(\frac{\%\,\text{Activity Std}}{100}\right)(1)(1)(1000)(100\,\%)}{(\text{Area Std})(10)(10)(100)(1\ \text{cps})(1\text{mg/cps})}$$

where:

Area Spl	peak area of Nabilone in sample solution
Area Std	peak area of Nabilone in reference solution for injection
m Std	weight Nabilone (mg) in reference solution
1 mg/cps	theoretical label strength: 1.0 mg/cps

Reporting

For the evaluation, the individual determinations are calculated; each determination must be documented with one (1) decimal place more as given in the specification.

The reported result is the mean of the (unrounded) individual determinations, and it is calculated up to the decimal places as given in the specification.

The test must comply with Ph. Eur. 2.9.3.

2.1.P.5.2.7 Water Content (KF Titration)

The test is performed according to Ph. Eur. 2.5.12, Method A on a 150 ± 10 mg sample size (content of 1 capsule).

Two individual titrations are performed, the results reported to two decimal places. The reported result is the mean of the individual results rounded to the decimal place given in the specification.

2.1.P.5.2.8 Ethanol Content

Solutions

Sample solution:

Accurately weigh the content of one capsule (approx. 150 mg) into a headspace vial and add 5.0 ml of water.

Concentration: 30 mg/ml capsule powder.

Prepare the solutions in duplicate.

Reference solution:

Accurately weigh about 150 mg of ethanol reference standard into a 100 ml volumetric flask, containing about 50 ml water, fill to the mark with water and homogenize. Transfer 10.0 ml of this solution into a 100 ml volumetric flask, fill to the mark with water and homogenize. Transfer 5.0 ml of this solution into a headspace vial.

Concentration: 0.15 mg/ml Ethanol.

Prepare the solutions in duplicate.

Equipment / Chromatographic Parameters

<table>
<tr><th colspan="5">GC Parameter</th></tr>
<tr><td>Column dimensions</td><td colspan="4">30 m x 320 µm x 1.8 µm</td></tr>
<tr><td>Column type</td><td colspan="4">Capillary column, coated with 6 % Cyanopropylphenyl, 94 % dimethylpolysiloxane, e.g. Agilent DB-624</td></tr>
<tr><td>Oven temperature</td><td colspan="4">Temperature program
<table>
<tr><th>Time [min]</th><th>Temperature [°C]</th><th>Holding Time [min]</th><th>Rate [°C/min]</th></tr>
<tr><td>0</td><td>45</td><td>5</td><td>--</td></tr>
<tr><td>5</td><td>45</td><td>--</td><td>45</td></tr>
<tr><td>8.4</td><td>200</td><td>5</td><td>--</td></tr>
<tr><td>13.4</td><td>200</td><td>--</td><td>45</td></tr>
<tr><td>16.9</td><td>45</td><td>2</td><td>--</td></tr>
<tr><td>19</td><td>45</td><td>--</td><td>--</td></tr>
</table></td></tr>
<tr><td>Injector temperature</td><td colspan="4">250 °C</td></tr>
<tr><td>Detector temperature</td><td colspan="4">270 °C</td></tr>
<tr><td>Carrier gas</td><td colspan="4">Helium</td></tr>
<tr><td>Column flow</td><td colspan="4">2 mL/min</td></tr>
<tr><td>Injection volume</td><td colspan="4">1.00 mL, see head space</td></tr>
<tr><td>Split flow</td><td colspan="2">HPW (GC Perkin Elmer):</td><td colspan="2">2 mL/min</td></tr>
</table>

GC Parameter		
	KIR (GC Agilent):	0.2 mL/min
Detector	FID (Range 1 / Attenuation 1)	
Detector gases	Hydrogen 30 mL/min; Synthetic air 300 mL/min	
Run time	19 min	
Head space Parameter		
Needle temperature	100 °C	
Oven temperature, sample	80 °C	
Transfer temperature	120 °C	
Carrier pressure	120 kPa	
Thermostatting time	30 min (shaker on)	
Pressurisation time	20 min	
Injection time	0.05 min (3 s)	
Transfer flow	HPW (GC Perkin Elmer):	20 mL/min
	KIR (GC Agilent):	30 mL/min
Withdrawal time	0.1 min	
GC cycle time	25 min	

System suitability tests (SST)

Requirement for Standard Recovery $r_{korr,rel}$:

The respective response of Ethanol (area Ethanol corrected by standard weights) of the injection of reference solution 2 must not differ more than 4.0 % from the average of the respective response of Ethanol of the first three injections of reference solution 1.

$$r_{korr,rel} = \frac{|\bar{x}_1 - x_2|}{(\bar{x}_1 + x_2) : 2} \cdot 100\%$$

$r_{korr,rel}$ = Standard Recovery

$\bar{x}_1$ = Average response of reference solution 1 (first three injections)

x_2 = Response of reference solution 2 (one injection)

Requirement for Trend analysis:

The Ethanol peak area of the check standards (reference solution 1) do not differ more than 4.0 %. The deviation (r_{rel}) of the replicate injections of reference solution 1 has to be calculated as outlined:

$$r_{rel} = \frac{\left|\bar{x}_1 - x_{1\text{Re }plication}\right|}{\bar{x}_1} \cdot 100\,\%$$

$\bar{x}_1$ = Average area of the first three injections of reference solution 1

$x_{1\text{Re }plication}$ = Area of the injection of every replicate of reference solution 1 (check standard)

Evaluation and Calculation

Get the chromatograms of reference solution 1 and 2, and sample solution and integrate the peak area of the Ethanol peak. The retention time of ethanol is ca. 2.9 min.

The calculation is done with reference to the average respective response of the first 4 injections of the reference solution (average of three injections of reference solution 1 and the first injection of reference solution 2).

$$\textbf{\% Ethanol} = \frac{(\text{Area Spl})(\text{m Std [mg]})(\frac{\text{\% Activity Std}}{100})(5)\,(100\,\%)}{(\text{Area Std})(\text{m Spl [mg]})(1000)}$$

where:

Area Spl	= peak area of Ethanol in sample solution
Area Std	= peak area of Ethanol in reference solution
m Std	= weight Ethanol (mg) in reference solution
m Spl	= weight sample (mg)
% Activity	= Assay Ethanol reference standard % as is

Documentation

For the evaluation, the individual determinations are calculated; each determination must be documented with one (1) decimal place more as given in the specification.

The reported result for ethanol is the mean of the determinations, and it is calculated up to the decimal places as given in the specification.

2.1.P.5.2.9 Microbiological Quality (TAMC, TYMC, *E. Coli*)

The tests are carried out according to Ph. Eur. 2.6.12 and Ph. Eur. 2.6.13. The microbiological tests will be performed on the first three batches, then on every fifth batches.

2.1.P.5.3 Validation of Analytical Procedures (Nabilone, 1mg and 0.25mg capsules)

The methods listed below were transferred from the manufacturer Haupt Pharma Wolfratshausen GmbH, Germany to SwissCo Services AG, Switzerland. The method transfer report and, where appropriate, the method verification reports are provided as attachments.

Method	Document	Document No.	Appendix No.
Identity, Assay, Related Substances, Content Uniformity and Dissolution by HPLC	Method Transfer Report	MTRC_2014/002_1_0_ENG	2.1.A.5
	Addendum to Method Transfer Report – Validation of the new test solution preparation	AO-01-MVAR_02_V01	2.1.A.6
Water Content by KF	Method Verification Report	AO-01_MVER_01_V01	2.1.A.7
Ethanol Content by GC	Method Transfer Report	MTRC_2015/008_1_0_ENG	2.1.A.8
Microbiological Quality	Method Validation Report	Report No. 1	2.1.A.9

The methods for Nabilone 0.25mg capsules were validated at SwissCo Services AG, Switzerland.

Method	Document	Document No.	Appendix No.
ID, Assay, Related Substances by HPLC	Method Validation Report	AO-02_MVAR_03_V01	2.1.A.10
Content uniformity	Method Validation Report	AO-02_MVAR_02_V01	2.1.A.11
Dissolution	Method Validation Report	AO-02_MVAR_01_V01	2.1.A.12
Water Content by KF	Method Validation Statement	AO-02-MVES-01_V01	2.1.A.13
Ethanol Content by GC	Method Validation Statement	AO-02-MVAS-01_V01	2.1.A.14

All other analytical procedures used to test Canemes 1mg and 0.25mg capsules are performed according to common Ph. Eur. procedures, and are therefore considered suitable for their intended use.

2.1.P.5.4 Batch Analysis (Nabilone, 1 mg and 0.25 mg capsules)

Strength		**1 mg**	**1 mg**	**0.25 mg**
Test	**Specification**	**09030016** DoM: 06.04.2016 Process Validation Batch 1	**09010036** DoM: 23.06.2016 Process Validation Batch 2	**09010017** DoM: 24.04.2017 Process Validation Batch 1
Appearance	Nabilone 1 mg capsules: Opaque capsules size 2, body white, cap yellow; filled with a white powder	Conforms	Conforms	NA
	Nabilone 0.25 mg capsules: Opaque capsules size 4, body white, cap white; filled with a white powder	NA	NA	Conforms
Identification				
HPLC RT	The retention time complies with the retention time of the reference substance	Positive	Positive	Positive
HPLC UV (DAD)	The UV spectrum complies with the UV spectrum of the reference substance	Positive	Positive	Positive
Assay (HPLC)	Nabilone 1 mg: 95.0 – 105.0% (0.950 – 1.050 mg/capsule)	96.1% (0.961 mg/capsule)	96.5% (0.965 mg/capsule)	NA
	Nabilone 0.25 mg capsules: 95.0 – 105.0% (0.2375 – 0.2625 mg/capsule)	NA	NA	98.0% (0.2451 mg/capsule)
Related Compounds (HPLC)				
Single unknown RC	NMT 0.3%	< 0.1%	< 0.1%	< 0.1%
Sum RC	NMT 1.0%	< 0.1%	< 0.1%	< 0.1%
Uniformity of Dosage Units	n=10: AV ≤ 15.0 n=30: AV ≤ 15.0 and no unit less than 0.75 M or more than 1.25 M	Complies AV 5.5%	Complies AV 7.0%	Complies AV 5.5%
Dissolution test	Q=70% after 60 min Level S_1, S_2 or S_3 must comply	85%	91%	97%
Water Content (KF)	NMT 10.0%	4.9%	4.7%	5.0%

Strength		**1 mg**	**1 mg**	**0.25 mg**
Test	**Specification**	**09030016** DoM: 06.04.2016 Process Validation Batch 1	**09010036** DoM: 23.06.2016 Process Validation Batch 2	**09010017** DoM: 24.04.2017 Process Validation Batch 1
Ethanol	NMT 0.5%	0.2%	0.2%	0.2%
Microbiological quality				
TAMC	NMT 10^3 CFU/g	< 1 CFU/g	< 10 CFU/g	< 10 CFU/g
TYMC	NMT 10^2 CFU/g	< 1 CFU/g	< 10 CFU/g	< 10 CFU/g
E.Coli	Absent in 1 g	absent	absent	absent

2.1.P.5.5 Characterization of Impurities

Please refer to the drug substance Section 3.2.S.3.2 for a discussion of potential and actual impurities in the drug substance.

Potential Degradation Products

The Maximum Daily Dose for Nabilone is 6 mg; therefore, according to ICH Q3B (R2), the identification and qualification thresholds are 0.3% and 0.8%, respectively. No impurities have been reported above the identification threshold during stability studies (Please refer to Section 2.1.P.8.1 and 2.1.P.8.3.). Consequently, no impurities have been identified or specified in the drug product.

2.1.P.5.6 Justification of Specification (Nabilone, 1 mg and 0.25 mg Capsules)

The specifications for the drug product are in compliance with general pharmacopoeial and ICH guidelines requirements. The justification for the specifications is presented.

Test	Specifications	Method	Justification
Appearance	For Nabilone 1 mg: Opaque capsules size 2, body white, cap yellow; filled with a white powder For Nabilone 0.25 mg: Opaque capsules size 4, body white, cap white; filled with a white powder	Visual inspection	According to ICH Q6A
Identification HPLC RT HPLC UV (DAD)	The retention time complies with the retention time of the reference substance The UV spectrum complies with the UV spectrum of the reference substance	In-house HPLC method based on Ph. Eur. 2.2.29	According to ICH Q6Aand Note for Guidance on Specifications two independent methods for identifications should be used
Assay (HPLC)	For Nabilone 1 mg: 95.0 – 105.0% (0.950 – 1.050 mg/capsule) For Nabilone 0.25 mg: 95.0 – 105.0% (0.2375 – 0.2625 mg/capsule)	In-house HPLC method based on Ph. Eur. 2.2.29	According to ICH Q6A

Test	Specifications	Method	Justification
Related compounds (HPLC) Single unknown RC Sum RC	 NMT 0.3% NMT 1.0%		According to ICH Q3B (R2) and Note for Guidance on Impurities in new Drug Products
Uniformity of dosage units	n=10: AV NMT 15.0% n=30: AV NMT 15.0% and no unit less than 0.75 M more than 1.25 M	Ph. Eur. 2.9.40	According to ICH Q6A and Ph. Eur. 2.9.40
Dissolution test	NLT 70% (Q) after 60 min Level S_1, S_2 or S_3 must comply	Ph. Eur. 2.9.3	According to ICH Q6A and Ph. Eur. 2.9.3, Table 2.9.3.-1. Q = 70 (release after 60 min) due to delayed release of Nabilone from the PVP-complex
Water content (KF)	NMT 10.0%	Ph. Eur. 2.5.12, Method A	According to ICH Q6A
Ethanol	NMT 0.5%	Internal GC method	According to ICH Q6A
Microbiological quality TAMC TYMC *E. Coli*	 NMT 10^3 CFU/g NMT 10^2 CFU/g Absent in 1 g	 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13	According to ICH Q6A and Ph. Eur. 5.1.4

2.1.P.6 Reference Standards and Materials (Nabilone, 1 mg and 0.25 mg capsules)

The active reference standards used in the HPLC method transfer and in the evaluation of the batches of Canemes capsules presented in Section 3.2.P.5.4 are listed in the table below. The certificates of analysis are provided on the following pages. Pharmacopoeial standards or other reference or working standards of suitable purity with confirmed structure or suitably qualified may be used.

Table 1: Reference Standards

Reference Standard	Batch number	Supplier	Use
Nabilone	RS 070302 K1a1alpha, CPL A279	CPL Sachse	HPLC method transfer (Nabilone 1 mg) Release of batches 09030016 & 09010036
Nabilone Impurity C	FD 140122K1, CPL 797	CPL Sachse	HPLC method transfer (Nabilone 1 mg)
Nabilone	RS 070302 K1a1alpha, CPL A279	CPL Sachse	Analytical validation (Nabilone 0.25 mg) Release of split batches
Nabilone Impurity C	FD 140122K1, CPL A797	CPL Sachse	Analytical validation (Nabilone 0.25 mg)

RS-17003
2007.17/0

CPLSACHSE

Certificate of Analysis
CpL B 0051/17

Neues CoA nach Retest CpL

Nabilone	**Batch RS 070302 K1a1α, CpL A 279**	2017-02-17

CoA sprich i.O. 20.02.2017

General Information:

Name:	Nabilone	
Scope of application:	In-house primary standard for assay and purity	
Batch:	RS 070302 K1a1α	
CpL:	CpL 0054/17	
Manufacturer:	Chemisch-pharmazeutisches Labor, Rolf Sachse GmbH Stieffring 14, 13627 Berlin, Tel.: (0 30) 34 34 62-60	
Specification:	SP-0174-6	
Test instruction:	PA-0174-6	
Storage instructions:	Store in a tightly closed container, protected from light at room temperature	
Date of manufacture:	2007-03-02	Retest date: 2018-02-14

Test	**Description**	**Test Result**
Appearance	White or almost white, crystalline powder	White, crystalline powder

Test	**Acceptance criterion**	**Test Result**
Identity: ^{1}H NMR	Conforms to structure	Conforms to structure(1)
Identity: ^{13}C NMR	Conforms to structure	Conforms to structure(1)
Identity: MS	Conforms to structure	Conforms to structure(1)
Identity: IR	Conforms to structure	Conforms to structure(1)
Elemental analysis (CHN)	Calculated:	Found(1):
Carbon:	77.38 %	77.8 %
Hydrogen:	9.74 %	10.0 %
Oxygen:	12.88 %	13.1 %

(1) Test results of CpL B 0134/15 and tested by Solvias AG Switzerland, test report no 15-02744

CPLSACHSE

Certificate of Analysis
CpL B 0051/17

Nabilone	**Batch RS 070302 K1a1α, CpL A 279**	2017-02-17

Test	Specification	Test Result
Related substances (HPLC)	Impurity A: ≤ 0.10 %	< 0.05 % (RPT); complies
	Impurity B: ≤ 0.10 %	< 0.05 % (RPT); complies
	Impurity C: ≤ 0.15 %	< 0.05 % (RPT); complies
	Unknown single impurity: ≤ 0.10 %	Imp. RRT 0.54: 0.052 % Imp. RRT 0.87: 0.080 %; complies
	Total impurities: ≤ 1.0 %	0.13 %; complies
Sulphated ash	≤ 0.1 %	Complies (0.0 %)[2]
Loss on drying	≤ 0.5 %	Complies (0.05 %)[2]
Residual solvents (GC/MS-HS)	Dichloromethane: ≤ 0.06 % (600 ppm)	< 0.0004 % (4 ppm) (LOQ)[2]; complies
	n-Hexane: ≤ 0.029 % (290 ppm)	< 0.0002 % (2 ppm) (LOQ)[2]; complies
	Cyclohexane: ≤ 0.388 % (3880 ppm)	0.3661 % (3661 ppm)[2]; complies
	Ethyl acetate: ≤ 0.5 % (5000 ppm)	< 0.0014 % (14 ppm) (LOQ)[2]; complies
	Ethanol: ≤ 0.5 % (5000 ppm)	< 0.0008 % (8 ppm) (LOQ)[2]; complies
Content (as is) (calculated)	No limit	99.5 %[3]
Assay by q-NMR	No limit	99.3 % [1]

LOQ = Limit of quantitation RPT = Reporting threshold

(1) Test results of CpL B 0134/15 and tested by Solvias AG Switzerland, test report no 15-02744
(2) Test results of CpL B 0092/07
(3) Calculation: 100 % – 0.13 % (total impurities) – 0.3661 % (residual solvents)

The Certificate of Analysis replaces CpL B 0093/16 and refers to documents 372700 to 372755.

Appearance and related substances (HPLC) were updated.

The work associated with this report was completed between 2017-02-08 and 2017-02-15.

Chemisch-pharmazeutisches Labor, Rolf Sachse GmbH

Anja Rutkowski
Chief Test Administrator — Signature: A. Rutkowski

Roswitha Höfner
Quality Assurance — Signature — Date: 2017-02-17

CPLSACHSE

Certificate of Analysis
CpL B 0029/16

Nabilone Impurity C	**Batch FD 140122 K1, CpL A 797**	2016-01-22

General Information:

Name:	Nabilone impurity C
Scope of application:	In-house working standard for identity
Batch:	FD 140122 K1
CpL:	CpL 0028/16
Manufacturer:	Chemisch-pharmazeutisches Labor, Rolf Sachse GmbH
	Stieffring 14, 13627 Berlin, Tel.: (0 30) 34 34 62-60
Specification:	SP-0177-2
Test instruction:	PA-0177-2
Storage instructions:	Store in a tightly closed container, protected from light at 2 °C to 8 °C
Date of manufacture:	2014-01-22 Retest date: 2019-01-22

Test	**Description**	**Test Result**
Appearance	White to almost white powder	White powder(2)
Identity: Melting range	158 °C to 162 °C	161.3 °C to 162.0 °C(1)

Test	**Specification**	**Test Result**
Identity: UV spectrum	Identical with reference spectrum of primary standard batch RS 060824 K1, CpL A 271	Identical with reference spectrum(1); complies
	Maximum: 202 – 212 nm	Maximum: 208 nm(1); complies
Purity (HPLC)	≥ 90 area %	99.0 area %(2); complies

(1) Test results of CpL B 0043/14

(2) Test results of CpL B 0074/15

[NABIL418] Chemisch-pharmazeutisches Labor, Rolf Sachse GmbH Page 1 of 2
Stieffring 14, 13627 Berlin, Tel.: (0 30) 34 34 62-60

CPLSACHSE

Certificate of Analysis
CpL B 0029/16

Nabilone Impurity C	**Batch FD 140122 K1, CpL A 797**	2016-01-22

This Certificate of Analysis replaces CpL B 0074/15.

The purpose of the substance was restricted to identity and the retest date was updated according to SOP-A 088-3.1.

The work associated with this report was completed on 2016-01-22.

Chemisch-pharmazeutisches Labor, Rolf Sachse GmbH

Jessica Walkowiak	J. Walkowiak	
Chief Test Administrator	Signature	
Heike Stenschke	H. Stenschke	2016-01-25
Quality Assurance	Signature	Date

2.1.P.7 Container Closure System (Nabilone, 1 mg and 0.25 mg capsules)

The intended commercial packaging that was also used for the stability studies (see 2.1.P.8.3, stability studies of the validation batches according to ICH guideline) consists of the following components:

- a round plastic container with a threaded neck made of white high-density polyethylene (HDPE) and a nominal capacity of 50 mL
- a round plastic child-resistant tamper-evident screw cap made of polypropylene (PP) with a mounted desiccant (2 g silica gel)

All components conform to the current requirements of food and medicinal products packaging.

The following incoming testing of the primary packaging materials is applied by the drug product manufacturer:

Specification for Duma Twist-Off 50 mL Bottles

Test	**Specifications**
Type of Container	Duma Twist-Off 50 mL
Appearance	Free from foreign materials, metal residues, soil or dust. No burn marks, cracks or scratches/bubbles.
Colour	White
Dimensions	
Outer diameter	35.2 – 36.2 mm
Height	82.3 – 84.3 mm
Identity	IR-Spectrum must comply with reference spectrum of supplier

Specification for Duma Twist-Off Caps

Test	**Specifications**
Type of Cap	Duma Twist-Off with desiccant insert
Appearance	Free from foreign materials, soil or dust. Desiccant and sealing plate present and fitted correctly
Weight of desiccant	1.8 – 2.2 g
Colour	White
Dimensions	
Outer diameter	35.0 – 36.0 mm
Height	28.7 – 29.5 mm
Diameter inner ring w/o desiccant	18.75 – 19.05 mm
Identity	IR-Spectrum must comply with reference spectrum of supplier

The pack size is 28 capsules per container.

One container together with one patient leaflet is enclosed in a cardboard folding box.

2.1.P.8 Stability (Nabilone, 1mg and 0.25mg capsules)

2.1.P.8.1 Stability Summary and Conclusion

2.1.P.8.1.1 Batches Tested

The 1st and 2nd process validation batch (09030016 and 09010036) of Nabilone 1mg capsules were placed on stability at 25°C/60% RH for up to 36 months and at 40°C/75% RH for up to 6 months.

The process validation batches of Nabilone 0.25mg capsules and the 3rd validation batch of Nabilone 1 mg were placed on stability at 25°C/60% RH for up to 48 months and at 40°C/75% RH for up to 6 months.

Table 18: Nabilone 1 mg capsules

Batches Tested	Date of Manufacture	Batch Use	Available Data
09030016	04/2016	Process Validation	0, 3, (6, 9, 12, 18, 24, 36) months
09010036	06/2016	Process Validation	0, 3, (6, 9, 12, 18, 24, 36) months
tbd	04/2017	Process Validation	(0, 3, 6, 9, 12, 18, 24, 36,48) months

Table 19: Nabilone 0.25 mg capsules

Batches Tested	Date of Manufacture	Batch Use	Available Data
09010017	04/2017	Process Validation	0, (3, 6, 9, 12, 18, 24, 36, 48) months
09010027	June 2017	Process Validation	(0, 3, 6, 9, 12, 18, 24, 36, 48) months
09030017	Planned 08/2017	Process Validation	(0, 3, 6, 9, 12, 18, 24, 36, 48) months

2.1.P.8.1.2 Stability Protocols

Samples for stability testing are stored under long-term storage conditions at 25°C/60% RH, under intermediate conditions at 30°C/65% RH and accelerated conditions at 40°C/75% RH.

The analytical procedures used in the stability program include tests for appearance, assay, dissolution, water content, impurities and microbial count. The methods used for stability testing are the same as for batch release and are described in Section 2.1.P.5.2. The samples stored under intermediate conditions (30°C/65% RH) are only tested in case of OOS results at 40°C/75% RH.

The stability protocol for Nabilone 1 mg for the 1st and 2nd validation batch is summarized in the table overleaf:

Condition	Stability time point (month)							
	Initial	**3**	**6**	**9**	**12**	**18**	**24**	**36**
25°C / 60% RH	A, B	A	A	A	A	A	A	A, B
30°C / 65% RH	---	---	(A)*	(A)*	(A,B)*	---	---	---
40°C / 75% RH	---	A	A, B	----	---	----	---	---

A: appearance, assay, dissolution, water content, impurities
B: microbial and mould count
*only tested in case of OOS at 40°C / 75% RH

The stability protocol for Nabilone 1 mg (3rd validation batch) and Nabilone 0.25 mg (all validation batches) is summarized in the table overleaf:

Condition	Stability time point (month)								
	Initial	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**
25°C / 60% RH	A, B	A	A	A	A	A	A	A, B	A,B
30°C / 65% RH	---	---	(A)*	(A)*	(A,B)*	---	---	---	---
40°C / 75% RH	---	A	A, B	----	---	----	---	---	---

A: appearance, assay, dissolution, water content, impurities
B: microbial and mould count
*only tested in case of OOS at 40°C / 75% RH

2.1.P.8.1.3 Results and Discussion

The initial stability studies conducted at the first finished product manufacturer Nycomed GmbH, Germany (now Takeda) showed, that Nabilone 1 mg capsules are stable for up to 36 months. 6 months stability data for Nabilone 1 mg capsules are currently available for the finished product manufacturer SwissCo Services AG and the results are confirming the product stability so far.
For Nabilone 0.25 mg split batches were produced in 2017. The granulate for 1 mg and 0.25 mg capsules is the same, only the filling mass and the capsule size differ. The composition of the gelatine capsules for the both strengths is almost the same except for the colouring agent Yellow Iron Oxide, which is included in the cap composition of the 1mg Nabilone capsules. The primary packaging material is the same for both of the strengths. Due to the similarity of the both strengths and the stable nature of the product a shelf life of 36 months when stored at 25°C/60% RH is proposed.

2.1.P.8.2 Post Approval Stability Protocol and Stability Commitment (Nabilone, 1 mg and 0.25mg capsules)

The applicant commits to complete the stability studies on the validation batches as detailed in Section 2.1.P.8.1.

In addition, the applicant commits to perform post-approval stability studies at controlled room temperature (25°C±2°C/60%±5% RH) on one commercial lot of one strength on an annual basis as per the stability specifications given in Section 2.1.P.5.1.

2.1.P.8.3 Stability Data (Nabilone, 1 mg and 0.25 mg capsules)

2.1.P.8.3.1 Stability data for Nabilone 1 mg capsules

Stability results for 1st validation batch 09030016 – 25°C/60%RH

Test	Specification	Timepoints (Months)							
		0	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance	Opaque capsules size 2, body white, cap yellow; filled with a white powder	Complies	Complies	Complies					
Assay (HPLC)	95.0 – 105.0% (0.950 – 1.050 mg/capsule)	96.1% 0.961 mg/cps	99.3% 0.993 mg/cps	98.5% 0.985 mg/cps					
Related Compounds (HPLC)									
Single unknown RC	NMT 0.3%	< 0.1%	< 0.1%	< 0.1%					
Sum RC	NMT 1.0%	< 0.1%	< 0.1%	< 0.1%					
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	85%	90%	87%					
Water Content (KF)	NMT 10.0%	4.9%	4.9%	5.1%					
Microbiological quality									
TAMC	NMT 10^3 CFU/g	< 10 CFU/g	NA	NA					
TYMC	NMT 10^2 CFU/g	< 10 CFU/g	NA	NA					
E.Coli	Absent in 1 g	absent	NA	NA					

Stability results for 1st validation batch 09030016 – 40°C/75%RH

Test	Specification	Timepoints (Months)		
		0	**3**	**6**
Appearance	Opaque capsules size 2, body white, cap yellow; filled with a white powder	Complies	Complies	Complies
Assay (HPLC)	95.0 – 105.0% (0.950 – 1.050 mg/capsule)	96.1% (0.961 mg/cps)	95.9% (0.959 mg/cps)	97.4% (0.974 mg/cps)
Related Compounds (HPLC)				
Single unknown RC	NMT 0.3%	< 0.1%	< 0.1%	< 0.1%
Sum RC	NMT 1.0%	< 0.1%	< 0.1%	< 0.1%
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	85%	86%	86%
Water Content (KF)	NMT 10.0%	4.9%	5.8%	6.9%
Microbiological quality				
TAMC	NMT 10^3 CFU/g	< 10 CFU/g	NA	< 10 CFU/g
TYMC	NMT 10^2 CFU/g	< 10 CFU/g	NA	< 10 CFU/g
E.Coli	Absent in 1 g	absent	NA	absent

Stability results for 2nd validation batch 09010036 – 25°C/60%RH

Test	Specification	Timepoints (Months)							
		0	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Appearance	Opaque capsules size 2, body white, cap yellow; filled with a white powder	Complies	Complies	Complies					
Assay (HPLC)	95.0 – 105.0% (0.950 – 1.050 mg/capsule)	96.5% 0.965 mg/cps	98.1% 0.981 mg/cps	99.9% 0.999 mg/cps					
Related Compounds (HPLC)									
Single unknown RC	NMT 0.3%	< 0.1%	< 0.1%	< 0.1%					
Sum RC	NMT 1.0%	< 0.1%	< 0.1%	< 0.1%					
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	91%	91%	88%					
Water Content (KF)	NMT 10.0%	4.7%	4.9%	5.2%					
Microbiological quality									
TAMC	NMT 10^3 CFU/g	< 10 CFU/g	NA	NA					
TYMC	NMT 10^2 CFU/g	< 10 CFU/g	NA	NA					
E.Coli	Absent in 1 g	absent	NA	NA					

Stability results for 2nd validation batch 09010036 – 40°C/75%RH

Test	Specification	Timepoints (Months)		
		0	**3**	**6**
Appearance	Opaque capsules size 2, body white, cap yellow; filled with a white powder	Complies	Complies	Complies
Assay (HPLC)	95.0 – 105.0% (0.950 – 1.050 mg/capsule)	96.5% (0.965 mg/cps)	98.4% (0.984 mg/cps)	98.8% (0.988 mg/cps)
Related Compounds (HPLC)				
Single unknown RC	NMT 0.3%	< 0.1%	< 0.1%	< 0.1%
Sum RC	NMT 1.0%	< 0.1%	< 0.1%	< 0.1%
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	91%	82%	86%
Water Content (KF)	NMT 10.0%	4.7%	5.8%	7.2%
Microbiological quality				
TAMC	NMT 10^3 CFU/g	< 10 CFU/g	NA	< 10 CFU/g
TYMC	NMT 10^2 CFU/g	< 10 CFU/g	NA	< 10 CFU/g
E.Coli	Absent in 1 g	absent	NA	absent

2.1.P.8.3.2 Stability data for Nabilone 0.25 mg capsules

Stability results for 1st split validation batch 09010017– 25°C/60%RH

Test	Specification	Timepoints (Months)							
		0	3	6	9	12	18	24	36
Appearance	Opaque capsules size 4, body white, cap white; filled with a white powder	Conforms							
Assay (HPLC)	95.0 – 105.0% (0.2375 – 0.2625 mg/capsule)	98.00% (0.2451 mg/capsule)							
Related Compounds (HPLC)									
Single unknown RC	NMT 0.3%	<0.1%							
Sum RC	NMT 1.0%	<0.1%							
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	97%							
Water Content (KF)	NMT 10.0%	5.0%							
Microbiological quality									
TAMC	NMT 10^3 CFU/g	<10 CFU/g							
TYMC	NMT 10^2 CFU/g	<10 CFU/g							
E.Coli	Absent in 1 g	absent							

Stability results for 1st split validation batch 09010017 – 40°C/75%RH

Test	Specification	Timepoints (Months)		
		0	3	6
Appearance	Opaque capsules size 4, body white, cap white; filled with a white powder	Conforms		
Assay (HPLC)	95.0 – 105.0% (0.2375 – 0.2625 mg/capsule)	98.00% (0.2451 mg/capsule)		
Related Compounds (HPLC)				
Single unknown RC	NMT 0.3%	<0.1%		
Sum RC	NMT 1.0%	<0.1%		
Dissolution test	NLT 70% (Q) after 60 min Level S1, S2 or S3 must comply	97%		
Water Content (KF)	NMT 10.0%	5.0%		
Microbiological quality				
TAMC	NMT 10^3 CFU/g	<10 CFU/g		
TYMC	NMT 10^2 CFU/g	<10 CFU/g		
E.Coli	Absent in 1 g	absent		

2.1.P.8.3.3 **Supportive long term data of previous manufacturer Nycomed**

Batch: 380011

Batch size: 100,000
Packaging material: HDPE bottles with 28 capsules
Date of manufacture: 11.07.2008

Storage conditions: **25 °C / 60% RH**

Parameters	**Specifications**	**T0 (0 Months)**	**T3 (3 Months)**	**T6 (6 Months)**	**T9 (9 Months)**	**T12 (12 Months)**	**T18 (18 Months)**	**T24 (24 Months)**	**T36 (36 Months)**
Appearance	Opaque capsules, size 2, filled with white powder Cap: white, opaque Body: yellow, opaque	complies	complies	complies	complies	complies	n.a.	n.a.	n.a.
Assay	0.95 mg-1.05 mg/capsule	1.02	1.00	1.03	0.99	1.00	1.02	0.99	1.01
Greatest single unknown related compound	≤ 0.3%	0.1 (RRT 0.88)	0.1 (RRT 0.87)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1
Total related compounds	≤ 1.0%	0.1	0.1	0.2	0.2	0.1	0.1	0.1	0.1
Dissolution test	Q=70% after 60 min Level S1, S2 or S3 must comply	76 Level 2 corresponds	89 Level 1 corresponds	93 Level 1 corresponds	80 Level 1 corresponds	85 Level 1 corresponds	88 Level 1 corresponds	92 Level 1 corresponds	83 Level 1 Corresponds
Water content (KF)	≤ 10%	7.9	6.4	6.0	6.3	5.6	5.6	6.0	6.8
Microbiological quality	≤ 10^3TAMC (cfu per g) ≤ 10^2 TYMC (cfu per g) Absence of *E. coli* per g	1 cfu/g 0 cfu/g absent	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	5 cfu/g < 10 cfu/g absent

n.a. = not analysed

Batch: **480021**
Batch size: 100,000
Packaging material: HDPE bottles with 28 capsules
Date of manufacture: 13.10.2008

Storage conditions: **25 °C / 60 % RH**

Parameters	**Specifications**	**T0 (0 Months)**	**T3 (3 Months)**	**T6 (6 Months)**	**T9 (9 Months)**	**T12 (12 Months)**	**T18 (18 Months)**	**T24 (24 Months)**	**T36 (36 Months)**
Appearance	Opaque capsules, size 2, filled with white powder Cap: white, opaque Body: yellow, opaque	complies	complies	complies	complies	complies	n.a.	n.a.	n.a.
Assay	0.95mg-1.05mg/capsule	1.05	1.04	1.05	1.02	1.03	1.04	1.05	1.02
Greatest single unknown related compound	≤ 0.3%	0.1 (RRT 0.87)	n.d.	0.1 (RRT 1.58)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.2	0.1
Total related compounds	≤ 1.0%	0.1	n.d.	0.1	0.1	0.1	0.2	0.2	0.2
Dissolution test	Q=70% after 60 min Level S1, S2 or S3 must comply	75 Level 2 corresponds	96 Level 1 corresponds	87 Level 1 corresponds	92 Level 1 corresponds	88 Level 1 corresponds	94 Level 1 corresponds	89 Level 1 corresponds	96 Level 1 corresponds
Water content (KF)	≤ 10%	7.5	6.2	5.9	6.0	5.5	6.1	6.1	6.7
Microbiological quality	≤ 10^3TAMC (cfu per g) ≤ 10^2 TYMC (cfu per g) Absence of *E. coli* per g	18 cfu/g 0 cfu/g absent	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	< 10cfu/g <10cfu/g absent

n.d. = not detected
n.a. = not analysed

Batch: **480031**
Batch size: 100,000
Packaging material: HDPE bottles with 28 capsules
Date of manufacture: 13.10.2008

Storage conditions: **25 °C / 60 % RH**

Parameters	**Specifications**	**T0 (0 Months)**	**T3 (3 Months)**	**T6 (6 Months)**	**T9 (9 Months)**	**T12 (12 Months)**	**T18 (18 Months)**	**T24 (24 Months)**	**T36 (36 Months)**
Appearance	Opaque capsules, size 2, filled with white powder Cap: white, opaque Body: yellow, opaque	complies	complies	complies	complies	complies	n.a.	n.a.	n.a.
Assay	0.95mg-1.05mg/capsule	1.05	1.00	1.02	1.03	1.02	1.05	1.02	1.05
Greatest single unknown related compound	≤ 0.3%	0.1 (RRT 0.87)	n.d.	0.1 (RRT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.1 (RTT 0.88)	0.2	0.1
Total related compounds	≤ 1.0%	0.1	n.d.	0.1	0.1	0.1	0.1	0.2	0.2
Dissolution test	Q=70% after 60 min Level S1, S2 or S3 must comply	76 Level 2 corresponds	90 Level 1 corresponds	87 Level 1 corresponds	84 Level 1 corresponds	87 Level 1 corresponds	94 Level 1 corresponds	94 Level 1 corresponds	95 Level 1 corresponds
Water content (KF)	≤ 10%	7.4	6.1	6.1	5.6	5.4	6.1	6.0	6.6
Microbiological quality	≤ 10^3TAMC (cfu per g) ≤ 10^2 TYMC (cfu per g) Absence of *E. coli* per g	95 cfu/g 0 cfu/g absent	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.d. = not detected
n.a. = not analysed