Quali-V®-I
Inhalation

TECHNICAL MANUAL

Hard two-piece HPMC capsules for pharmaceutical applications in inhalation

Qualicaps Engineered to perform

Quali-V®-I hypromellose capsules offer significant benefits for new and existing pharmaceutical product formulations for inhalation applications

R&D

Chemically stable.
No cross-linking.
Maintain physical stability at low moisture content.
Preservative-free.
Compatible with excipients being used currently.
Strict microbiological control.
Excellent puncturing characteristics.
Aerosolization parameters enable effective drug delivery to the lungs.

Production

Run on automatic high-speed filling and packaging equipment.
Comparable filling performance to two-piece HPMC and gelatin capsules in oral dosage form.

Regulatory

Patented composition and manufacturing process.
Approved by the FDA.
In compliance with Pharmacopoeia USP/EP/JP.

Marketing

100% plant-based; free of animal origin.
Effective and attractive product identity.
Available in translucent colours, allowing patients to verify correct powder emptying.

CONTENTS

1 Official Accreditations

1 Official Accreditations

1.1 Quality System

Quali-V®-I capsules are manufactured in a validated continuous production environment in compliance with Good Manufacturing Practices (GMP).

The objective of the Qualicaps® quality control system is to ensure consistency, uniformity and conformance to specifications through careful process control and monitoring.

The quality control system is designed to maintain specified Acceptable Quality Levels (AQL), and to ensure that Qualicaps® capsule manufacturing complies with current Good Manufacturing Practices (cGMP) and the norms of the International Organization for Standardization (ISO).

1.2 Official Accreditations

The Qualicaps® manufacturing site in Spain has the following accreditations:

DMF 4765 for USA
DMF 2003 092 for Canada
ISO 9001:2008 certificate (Quality)
ISO 14001:2004 certificate (Environmental)

Lloyd's Register LRQA

CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

QUALICAPS EUROPE, S.A.U.
Avda. Monte Valdelatas, 4
28108 Alcobendas, Madrid
Spain

has been approved by Lloyd's Register Quality Assurance to the following Quality Management System Standard:

ISO 9001:2008

The Quality Management System is applicable to:

Manufacture of gelatine and cellulose empty hard capsules for the pharmaceutical industry.

Approval Certificate No: SGI 2936271

Original Approval: 15 July 1994
Current Certificate: 01 July 2015
Certificate Expiry: 30 June 2018

Issued by: LRQA España, S.L.
For and on behalf of: Lloyd's Register Quality Assurance Limited

UKAS 001

C/ Princesa, 29 – 1ª - 28008 Madrid, España
For and on behalf of 1 Trinity Park, Bickenhill Lane, Birmingham B37 7ES, United Kingdom

Certificate of ISO 9001:2008

Lloyd's Register LRQA

CERTIFICATE OF APPROVAL

This is to certify that the Environmental Management System of:

QUALICAPS EUROPE, S.A.U.
Avda. de Valdelatas, 4
28108 Alcobendas, Madrid
Spain

has been approved by Lloyd's Register Quality Assurance to the following Environmental Management System Standard:

ISO 14001:2004

The Environmental Management System is applicable to:

Manufacture of gelatine and cellulose empty hard capsules for the pharmaceutical industry.

Approval Certificate No: SGI 6004085

Original Approval: 01 April 2005
Current Certificate: 01 June 2014
Certificate Expiry: 30 May 2017

Issued by: LRQA España, S.L.
For and on behalf of: Lloyd's Register Quality Assurance Limited

UKAS 001

C/ Princesa, 29 – 1ª - 28008 Madrid, España
For and on behalf of Hiramford Middlemarch Office, Village Sidon Drive, Coventry CV3 4FJ United Kingdom

Certificate of ISO 14001:2004

The Qualicaps® manufacturing site in Japan has the following accreditations:

DMF 12900 for USA
DMF 2002 068 for Canada
ISO 9001:2008 certificate (Quality)
ISO 14001:2004 certificate (Environmental)


Quality Management System
CERTIFICATE OF CONFORMITY
COPY
JCQA
Certificate No.: JCQA-0309 Registration Date: 1998.3.16
Renewal Date: 2016.3.16 Expiry Date: 2019.3.15
Name of Registered Organization: Qualicaps Co., Ltd. Nara Plant et al.
Address of Registered Organization: 321-5, Ikezawa-cho, Yamatokoriyama-shi, Nara, 639-1032, Japan et al.
JAPAN CHEMICAL QUALITY ASSURANCE LTD. certifies that the Quality Management System of the above organization specified in the appendix, has been assessed and verified to be in accordance with the requirements of the quality management system standards as shown below:
Quality Management System Standards: JIS Q 9001:2008 ISO 9001:2008
The Date of Issue: 2016.3.7
JAPAN CHEMICAL QUALITY ASSURANCE LTD. (JCQA)
Nittoshi-Uchisaiwaicho BLDG. 7F, 1-2-1, Uchisaiwaicho, Chiyoda-ku, Tokyo, 100-0011, JAPAN
JCQA
T. Tamada
Tadanori Tamada
PRESIDENT REPRESENTATIVE DIRECTOR

Certificate of ISO 9001:2008


Environmental Management System
CERTIFICATE OF CONFORMITY
COPY
JCQA
Certificate No.: JCQA-E-0322 Registration Date: 2001.12.25
Renewal Date: 2013.12.25 Expiry Date: 2016.12.24
Name of Registered Organization: Qualicaps Co., Ltd. Nara Plant
Address of Registered Organization: 321-5, Ikezawa-cho, Yamatokoriyama-shi, Nara, 639-1032, Japan
JAPAN CHEMICAL QUALITY ASSURANCE LTD. certifies that the Environmental Management System of the above organization specified in the appendix, has been assessed and verified to be in accordance with the requirements of the environmental management system standards as shown below:
Environmental Management System Standards: JIS Q 14001:2004 ISO 14001:2004
The Date of Issue: 2013.12.9
JAPAN CHEMICAL QUALITY ASSURANCE LTD. (JCQA)
Nittoshi-Uchisaiwaicho BLDG. 7F, 1-2-1, Uchisaiwaicho, Chiyoda-ku, Tokyo, 100-0011, JAPAN
JCQA
T. Tamada
Tadanori Tamada
PRESIDENT REPRESENTATIVE DIRECTOR

Certificate of ISO 14001:2004

2 Capsule Characteristics

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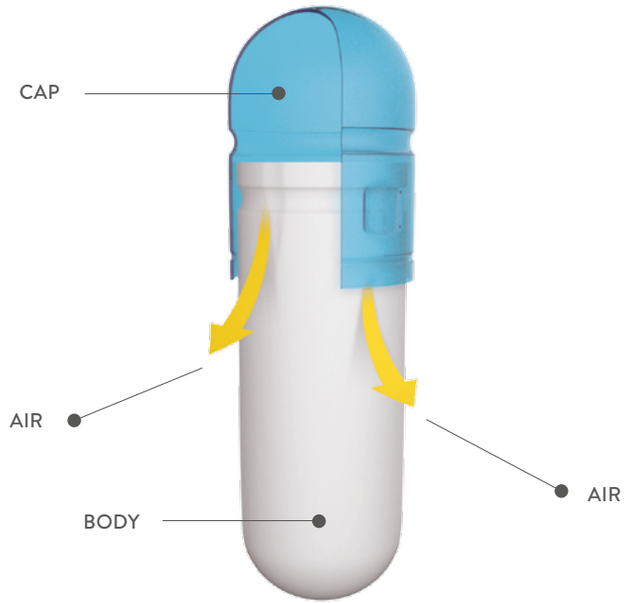
2.1 Quali-V®-I Capsule Design

Quali-V®-I capsules have a unique locking feature, the first to be introduced in the market.



PRE-LOK®

Favourable machine performance relies on empty capsules not separating during transportation and handling. The PRE-LOK® feature holds the cap and body together in the correct position prior to filling, maintaining a uniform length and preventing unwanted separation before filling.

The first stage in the filling process is the separation of the cap and body of the empty capsule. The empty body is then received by a filling device and dosed with material.

POSILOK®

After filling the body, the two parts of the capsule are rejoined. The POSILOK® design helps to further reduce the risk of reopening and to maintain a constant closed joined length, enabling the filling of different types of formulations.

SECURE LOCKING

Efficient packing relies on consistent product quality. The POSILOK® capsule is designed to remain securely closed to a precise length, ready for subsequent handling that ensures efficient placement in blister packages, minimal product loss during packaging and no separation.

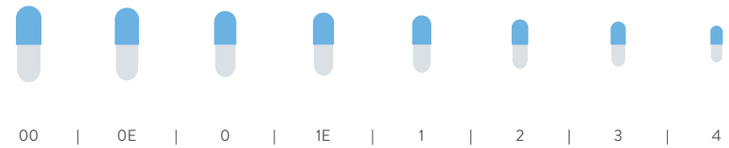
2.2 Colour Selection

Qualicaps® manufactures capsules to customer colour specifications and can match existing formulations or colour appearances.

The “SPECIALIST GUIDE”, which displays a representative sample of the recommended colours for Quali-V®-I capsules, is available upon request to assist customers with the choice of colour combinations.

2.3 Capsule Sizes

Quali-V®-I capsules are available in sizes ranging from 00 to 4, though the standard for use in most Dry Powder Inhalers is size 3. Sizes 2 and 0 are also available when higher doses are required.



Note Other sizes may be available. Images are not to scale.

2.4 Capsule Print Types

Qualicaps® offers the perfect opportunity for product identification through capsules imprinted with the company name, logo, product brand, dosage information, etc.

Five types of printing are available:

- **AXIAL-PRINT:** Axial printing, coverage up to 42°. Single ink colour. Ideal for simple branding and dosage information.
- **MAGNI-PRINT:** Axial printing, double size print, coverage up to 84°. Single ink colour. Company name or logo can be twice the size allowed in AXIAL-PRINT.
- **ROTOPRINT:** Rectified radial printing, almost 300° coverage for the maximum printable area and legibility. Single ink colour.
- **ROTOCOLOR:** Rectified radial printing, combines almost 300° coverage with different colours of ink on cap and body. Provides the best opportunity for displaying product identity.

- **LASER PRINT:** Based on UV laser technology and void of contact with the capsule surface. Coverage up to 54°. Handles a variety of print designs, including letters, numbers and logos.

AXIAL-PRINT

42°

MAGNI-PRINT

84°

ROTOPRINT

300°

ROTOCOLOR

300°

LASER PRINT

54°

Qualicaps® Technical Services can assist customers regarding print options and capabilities according to selected designs.

Qualicaps® produces artwork in the actual size that will appear on the capsule for use in the imprinting process.

Qualicaps® uses only edible printing inks. Ink colourants meet applicable regulatory requirements.

3 Capsule Specifications

3 Capsule Specifications

Qualicaps® follows the latest editions of the EP and the USP/NF for raw materials specifications.

3.1 Raw Materials Specifications

HYPROMELLOSE

Quali-V®-I capsules are made from hypromellose that complies with the principal Pharmacopoeiae: the United States Pharmacopoeia (USP/NF), the European Pharmacopoeia (EP) and the Japanese Pharmacopoeia (JP).

Quali-V®-I capsules are made from plant products. This eliminates the need for additional compliance with USA and European requirements for using materials of animal origin, thus minimizing regulatory obligations.

COLOURANTS

The colourants used are in compliance with the EU Directives and when required with the requirements of the EP, USP/NF.

PURIFIED WATER

The water used by Qualicaps® is in compliance with the requirements of the EP, USP/NF and JP.

ADDITIVES

Quali-V®-I capsules contain small amounts of carrageenan as a gelling agent and potassium chloride as a gelling promoter. In addition carnauba wax is applied as a surface lubricant on the capsules. These additives comply with the requirements of the following regulations: carrageenan - the EEC food regulations, USP/NF, and Japanese Pharmaceutical Excipients (JPE) regulations; potassium chloride - the EP, USP/NF and JP; carnauba wax and/or maize (corn) starch - the EP, USP/NF and JP.

PRINTING INKS

Qualicaps® uses edible printing inks that contain pigments and the lake form of dyes employed in capsule shell manufacture which are dispersed in shellac solutions. The residual solvents in the ink applied to a capsule comply with limits stated in ICH Q3C Guideline for Residual Solvents.

3.2 Quali-V®-I Capsule Specifications

Size		00	0E	0	1	2	3	4
Weight	Target weight (mg/100 capsules)	120.0	110.0	90.0	72.0	61.0	49.0	38.0
	Weight limits (mg/100 capsules)	108.0 – 132.0	99.0 – 121.0	81.0 – 99.0	64.8 – 79.2	54.9 – 67.1	44.1 – 53.9	34.2 – 41.8
Capacity	Approximate body volume (ml)	0.93	0.76	0.67	0.48	0.37	0.28	0.21
	Powder fill weight (mg)							
	0.6 mg/ml	0.560	0.455	0.400	0.290	0.220	0.170	0.125
	0.8 mg/ml	0.745	0.610	0.535	0.385	0.295	0.225	0.170
	1.0 mg/ml	0.930	0.760	0.670	0.480	0.370	0.280	0.210
	1.2 mg/ml	1.115	0.910	0.805	0.575	0.445	0.335	0.250
Outside diameter	Cap diameter (mm)	8.57	7.69	7.68	6.92	6.36	5.83	5.33
	Body diameter (mm)	8.23	7.34	7.34	6.61	6.07	5.56	5.06
	Tolerance (mm)	± 0.06	± 0.06	± 0.06	± 0.06	± 0.06	± 0.06	± 0.06
Length	Cap length (mm)	11.84	11.99	10.72	9.78	8.94	8.08	7.21
	Body length (mm)	20.17	20.98	18.44	16.61	15.27	13.59	12.19
	Tolerance (mm)	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30
Closed joined length	Closed joined length (mm)	23.6	24.2	21.7	19.4	18.0	15.9	14.3
	Tolerance (mm)	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30	± 0.30

Note Tailor-made specifications may be possible, upon request.

- **Weight:** Capsule weight can vary by ± 10% from the target value. The values are determined by weighing a sample of 100 capsules at the standard moisture content of 4.0% to 6.0%. Customers should determine tare weights for filling by testing samples from in-house batches. These values are not applicable to individual capsules but rather to the average of the batch.

- **Capacity:** Quali-V®-I capsules are normally filled with powders. As such, the approximate maximum fill weight can be estimated by multiplying the capsule body volume for the particular size by the tapped bulk density of the formulation. This relationship holds true even for products filled on automatic machines where the dose measuring mechanism is independent of the capsule.

- **Outside diameters:** The outside diameters, provided as a guideline for evaluating packaging material dimensions, are measured by passing the caps and bodies through calibrated bushes under specified conditions that simulate those of filling machines. This dimension should never be considered as an approval/rejection criterion.

- **Length:** Capsule lengths are controlled in the manufacturing process and audited for each batch.

- **Closed joined length:** This value is given as a filling machine set-up recommendation and not as an approval/rejection criterion for empty capsules. The closed joined length has been calculated to ensure the correct location of the special positive locking features on the cap and body. If the filling machine is set so that the capsules are closed to a shorter length, then the cap or body may be damaged and the locking mechanism may fail; if longer, they may come apart. It is recommendable to provide this value to packaging equipment manufacturers prior to making a decision on blister pocket specifications.

3.3 Visual Quality

The visual quality of a capsule batch is determined using sampling plans defined in ANSI/ASQ Z 1.4–2008 (normal inspection level, single sampling plan).

The specifications are derived from the ANSI/ASQ Z 1.4–2008 and assessed on a combined sample taken randomly throughout the batch from √N + 1 cartons (N is the total number of cartons in the controlled batch).

Qualicaps® capsules are controlled statistically to ensure conformance to the following specifications.

AQL DEFINITIONS AND VALUES

Acceptable Quality Level (AQL)
AQL as defined in ANSI/ASQ Z 1.4-2008, is the maximum percent of defective units that for the purpose of sampling inspection can be considered satisfactory as a process average. A normal inspection level, single sampling plan is used.

	Defect classification	AQL
Visual Quality Specifications	Major A	0.010%
	Major B	0.040%
	Minor	1.0%

INSPECTION MODE AND ASSOCIATED INSPECTION TIME

Visual inspection is performed in segments of 400 units each by unaided eyes, at a distance of approximately 30 cm. Qualicaps® visual control booths have transparent Plexiglas table tops with diffused lighting underneath. To verify or measure a possible deviation (e.g. the size of a speck), an eye-piece magnifier with graticule can be used. Capsules are not opened during inspection; capsules are lying sideways and moved using manual vibrations of the table during inspection. The sample of 1,250 units is inspected for approximately 3 minutes.

DEFINITION OF VISUAL DEFECTS

Visual defects are classified according to the following definitions:

- **Major A:** Affects the performace of a capsule as a package for the final product, or could contribute to a major subjective problem in filling.
- **Major B:** Would cause a problem on a capsule filling machine.
- **Minor:** Has no effect on the performance of a capsule as a package; it is a slight blemish that makes the capsule visually imperfect.

CLASSIFICATION AND DESCRIPTIONS OF VISUAL DEFECTS

MAJOR A	
Cracked	A cap or body with many splits
Double cap	A capsule with an additional cap covering the body end
Double dip	Extra thick cap due to being dipped twice
Failure to separate	A joined cap and body that does not separate properly
Hole	An irregular opening in the cap or body
Joined in lock	A capsule in locked position
Large strings	Strings > 4 mm at the cutting edge
Long cap/body	Length of cap or body 1 mm more than specified length
Mashed	A mechanically damaged capsule that has been squashed flat
Pinched	Inward cap or body pinches > 3 mm
Short cap	Cap length 1 mm less than specified length
Short body	Body length 0.4 mm less than specified length
Split	A split in the film starting from the cap or body edge
Telescope	A closed capsule with a protruding piece of either cap or body produced by a double split
Thin spot (cap shoulder)	A thin area in the cap shoulder that may rupture when the capsule is filled
Trimming	A piece of, or the whole trimmed end of a cap or body inside a closed capsule
Uncut cap/body	An untrimmed cap or body
Unjoined	A single cap or body

MAJOR B	
Damaged edge-large	Roughly trimmed cap edge. The imperfection at its greatest is > 1 mm into the specified length
Different dye speck	A coloured spot different from the colour of cap or body
Grease	Mould release aid spots on the inside of capsule
Inverted end	A cap or body with the end pushed inwards
Long joined	A capsule not closed sufficiently to engage the prelock
Small pinched	Inward cap or body pinches < 3 mm
Thin spot	A thin area in the cap or body wall which may rupture when the capsule is filled
Turned edge	Folded-over edge on body cut line

MINOR	
Black speck	A non-contaminant black spot > 1 mm
Bubble	An air bubble in the visible part of the capsule with a diameter > 0.4 mm (excluding overlapping area between cap and body)
Chips, tails	Small fragments of hypromellose > 3 mm still attached or free within the capsule
Crimp	Cap or body has external surfaces crimped > 3 mm
Damaged edge-small	Roughly trimmed cap edge. The imperfection is V shaped and < 1 mm into the specified length
Dent	A depression formed in the end of cap or body. The dent is less than half of the diameter of the capsule part
Dye speck	A colour spot from the colour of the cap or body > 1 mm
Grease light	Small grease marks > 3 mm
Scrape	A scratch mark on the surface of a cap or body
Starred end	An individual imperfection of the tip of cap or body > 3 mm generated by turbidity or surface deformation
Strings	Strings between 3-4 mm at the cutting edge
Wrinkles	Longitudinal wrinkles > 5 x 5 mm, visible from a distance of 30 cm

VISUAL DEFECTS DIAGRAMS

Major A Defects

CRACKED

DOUBLE CAP

HOLE

LONG CAP

LONG BODY

MASHED

SHORT CAP

SHORT BODY

SPLIT

TELESCOPE

TRIMMING

UNCUT CAP

UNCUT BODY

UNJOINED

Major B Defects

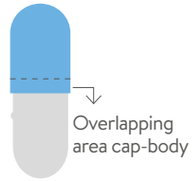
DAMAGED EDGE

DIFFERENT DYE SPECK

INVERTED END

THIN SPOT

Minor Defects



BUBBLE

DENT

SCRAPE

3.4 Print Quality

The print quality of a capsule batch is determined using statistical sampling plans defined in the ANSI/ASQ Z 1.4–2008 (normal inspection level, single sampling plan).

The specifications are derived from the ANSI/ASQ Z 1.4–2008 and assessed on a combined sample taken randomly throughout the batch from √N + 1 cartons (N is the total number of cartons in the controlled batch).

Qualicaps® printed capsules are controlled statistically to ensure compliance with the following specifications.

AQL DEFINITIONS AND VALUES

- **Acceptable Quality Level (AQL)**
  QL as defined in ANSI/ASQ Z 1.4-2008, is the maximum percent of defective units that for the purpose of sampling inspection can be considered satisfactory as a process average. A normal inspection level, single sampling plan is used.

	Print defect classification	AQL
Print Quality Specifications	Major A	0.010%
	Major B	0.040%
	Minor	1.0%

INSPECTION MODE AND ASSOCIATED INSPECTION TIME

Visual inspection is performed in segments of 400 units each by unaided eyes, at a distance of approximately 30 cm. Qualicaps® visual control booths have transparent Plexiglas table tops with diffused lighting underneath. To verify or measure a possible deviation (eg. the size of a speck), an eye-piece magnifier with graticule can be used. Capsules are not opened during inspection; capsules are lying sideways and moved using manual vibrations of the table during inspection. The sample of 1,250 units is inspected for approximately 3 minutes.

DEFINITION OF PRINT DEFECTS

Print defects are classified according to the following definitions:

- **Major A print defects:**
  Unprinted capsules or incorrect logo.
- **Major B print defects:**
  Illegible print or print that inhibits proper identification.
- **Minor print defects:**
  Cosmetic flaws that do not interfere with the identification of the product.

CLASSIFICATION OF PRINT DEFECTS

MAJOR A	MAJOR B	MINOR
Unprinted	Ink Line/Spot	Ink Line/Spot
Incorrect Image	Misplaced Image (off-register)	Misplaced Image (off-register)
	Multiple Images	Multiple Images
	Partial Image	Partial Image
	Smudged Image	Smudged Image

PRINT DEFECT DESCRIPTIONS AND DIAGRAMS

MAJOR A: UNPRINTED

The entire image is missing.

MAJOR B / MINOR: INK LINE / SPOT

An extra line or spot of ink that does not interfere with the legibility of the image.

An ink line or spot greater than 5 mm is a Major B defect.

An ink line or spot between 1 - 5 mm is a Minor defect.

MAJOR B / MINOR: MISPLACED IMAGE (OFF-REGISTER)

The image is not centred correctly between the cap cut edge and the end of a closed capsule.

A capsule with an image or images having missing characters that would result in misidentification, is a Major B defect.

A capsule with an image missing a part of a letter or logo that is still identifiable, is a Minor defect.

MAJOR B / MINOR: MULTIPLE IMAGES

Image printed more than once on the same capsule. Major B defect if the image is illegible.

Minor defect if the image is still legible.

MAJOR B / MINOR: PARTIAL IMAGE

Part of the image is missing.

Major B defect when at least half of the image is missing and it is illegible.

Minor defect when parts of the image are missing and it is still legible.

MAJOR B / MINOR: SMUDGED IMAGE

The image is smudged or smeared.

Major B defect when the image is illegible.

Minor defect when the image is still legible.

4 Capsule Post-Production Technical Information

4 Capsule Post-Production Technical Information

4.1 Packaging

CARTONS

Qualicaps® capsules are supplied in a package that has two components:

- An inner liner made of a laminate of pharmaceutical-grade materials: polyester/polyethylene/aluminium foil. This is heat-sealed after inserting the capsules, creating a container with minimal moisture transfer properties.

- A cuboid cardboard carton of standard dimensions. This protects the inner liner during transportation.

Capsule size	00	0E	0	1E	1	2	3	4
Capsules per carton in 000's*	75	75	100	120	135	175	225	300

Cartons size: 60 cm long x 40 cm wide x 75 cm high
* Tolerance: Capsule quantity variance is ± 5% per delivered carton box

PALLETS

A number of cartons can be assembled together with a protective covering and placed on a pallet.

The standard pallet assembly consists of eight or ten wrapped cardboard cartons on a Europallet base (1.20 m x 0.80 m) with a height varying between 0.85 m and 1.27 m.

IDENTIFICATION

Each carton and/or pallet is identified with a Qualicaps® label containing the relevant data.

The delivery label on the box contains an easily-removable adhesive sticker that can be used to identify the liner within each box.

4.2 Storage

Qualicaps® packaging is designed to maintain the quality of the empty capsule between manufacturing and filling. It is essential to read and understand the following information in order to ensure that Quali-V®-I capsules maintain their quality during this period.

TRANSPORTATION

Quali-V®-I capsules are supplied in sturdy cardboard cartons, each having heat-sealed, moisture-proof liners. These cartons may be grouped on a European size case pallet.

WAREHOUSING CONDITIONS

The conditions in the areas in which capsules are stored or filled can affect the machinability of the Quali-V®-I capsule. The ideal temperature for the storage of capsules should be between 15°C and 30°C (59°F and 86°F). The containers should be kept away from exposure to direct heat, sunlight and moisture.

Maintaining the capsules within the liner bag (without perforations) safeguards them from both light degradation and loss of moisture, regardless of ambient humidity.

Properly stored and sealed containers will provide optimum capsule performance in production.

CAPSULE SHELF LIFE

Under the aforementioned storage conditions, Quali-V®-I capsules will maintain their quality for five years from the date of manufacture.

INCOMING QUALITY CONTROL AND SAMPLING

The integrity of the packaging is also important in maintaining the quality of the capsules. Taking samples for incoming inspection must be done with care.

Sampling plans require that a number of cartons have to be opened, e.g. the square root of the number of cartons plus one. When the inner liner has been opened, it loses its moisture barrier properties.

It is recommendable to make the smallest cut possible in the liner when taking a sample. It should then be reclosed in the most adequate manner, preferably by heat-sealing, which restores the moisture barrier properties of the liner. If this is not possible, then special heat adhesive tape or other types of sealing should be used to once again secure the liner.

4.3 Capsule Filling

FILLING AREA CONDITIONS

The moisture content of capsules is directly related to the relative humidity of the air to which they are exposed. When capsules are removed from their original packaging (sealed aluminium liner) and exposed during the filling process, their moisture content will equilibrate to filling room conditions.

The ideal conditions for a filling area are a temperature between 20°C and 25°C and a relative humidity between 35% and 55%, which will maintain the moisture content of the capsules within the desired range of 4.5% to 6.5% for Quali-V®-I.

An important consideration is to expose the minimum number of capsules required for the process at any one time. Some filling machines can generate significant heat during running, and this may affect capsules in use.

The capsule filling machine may be located in a controlled area but the climatization system may be operated only during the working day. Empty capsules should preferably be removed from the hopper on the filling and/or intermediate conveying equipment if climatic conditions vary from the ideal during idle hours.

For capsule handling, it is best to avoid the use of plastic utensils because this could result in static electrical charging that could cause feeding problems on the filling machine.

FILLING EQUIPMENT SETTINGS

Quali-V®-I capsules are manufactured with the greatest care to ensure optimum running on filling machines.

However, Quali-V®-I capsules have a different behavior on filling machines than standard hard gelatin capsules. To achieve the best results, it is recommendable to check the segments or the bushes from the filling equipment to ensure that they are within the machine manufacturer's specifications (control can be performed by the machine manufacturer or by your Qualicaps® Technical Services engineer).

Care should be taken to close the capsules to the correct joined length after filling. If the capsules are over-closed, faults may occur as a result of distortion of the shells, with the possibility of cracking, splitting and reopening. If the capsules are under-closed, they may come apart causing problems during later production steps.

Qualicaps® also recommends increasing the level and quantity of vacuum in the capsule opening stage, making sure that the ends of the closing pins are concave instead of flat-shaped, confirming orientation station set-up, and finally, using specific parts designed for Quali-V®-I filling if available. Qualicaps® has extensive experience with Quali-V®-I encapsulation and offers technical support to attend first capsule filling sessions.

BLISTER PACKAGING

The chart below gives the recommended minimum dimensions for the die roll cavities for blister packaging of filled capsules. These values correspond to a film thickness of 0.1 mm. Variations in film thickness must be taken into account when determining actual measurements.

	00	0E	0	1E	1	2	3	4
H	9.10	8.20	8.10	7.50	7.40	6.90	6.30	5.80
L	25.0	25.1	22.8	22.2	20.5	18.8	16.8	15.5
W	9.80	8.90	8.80	8.20	8.10	7.60	7.00	6.50

H: Depth of cavity of blister die roll (mm)
L: Length of cavity of blister die roll measured at H/2 along the axis of the capsule (mm)
W: Width of cavity of blister die roll measured at H/2 along the perpendicular axis of the capsule (mm)

5 Chemical & Microbiological Test Methods

5 Chemical & Microbiological Test Methods

5.1 Chemical & Microbiological Specifications

Chemical specifications and references:

Test	Specification	Reference	Page
Loss on Drying (LOD)	4.5% - 6.5%	Based on European Pharmacopoeia 8th Edition	50
Identification of Organic Colourants	Meets test	Based on European Pharmacopoeia 8th Edition	51
Identification of Titanium Dioxide	Meets test	Based on European Pharmacopoeia 8th Edition	53
Identification of Iron Oxides	Meets test	Based on European Pharmacopoeia 8th Edition	54
Purity	Meets test	Japanese Pharmacopoeia 16th Edition	55
Capsule Description	Meets test	Based on Japanese Pharmacopoeia 16th Edition	56

Microbiological specifications and references (microbiological quality of non-sterile products for pharmaceutical use):

Test	Specification	Reference	Page
Total Aerobic Microbial Count (TAMC)	10^2 cfu/g	EP/USP/JP	57
Staphylococcus Aureus	Absence in 1 g	EP/USP/JP	58
Pseudomonas Aeruginosa	Absence in 1 g	EP/USP/JP	59
Total Combined Yeasts/Moulds Count (TYMC)	10^1 cfu/g	EP/USP/JP	60
Bile-Tolerant Gram-Negative Bacteria	Absence in 1 g	EP/USP/JP	61

5.2 Test Methods for Chemical Specifications

TEST: LOSS ON DRYING

SPECIFICATION 4.5% - 6.5%

PROCEDURE

Determined on a 1.0 g sample of capsules, by drying in an oven at 100 - 105°C for 2 hours.

Note Take the sample preferably just before performing the test. Keep it in a well sealed container and store it until the analysis is performed in a temperature controlled area.

1 Separate caps and bodies using gloves

2 Take a small jar with lid, previously dried in an oven and cooled to room temperature in a desiccator

3 Weigh the jar and the lid

4 Accurately weigh 1.0 g of capsules inside the jar and seal it with the lid

5 Place the sample inside an oven set at 100 - 105°C and open the jar

6 Leave the sample (lid and jar) in an oven for two hours

7 Replace the lid and remove the sample from the oven

8 Cool the sealed jar to room temperature inside a desiccator

9 Re-weigh the jar

10 Calculate the Loss on Drying percentage

INTERPRETATION OF RESULTS

Moisture content limit is 4.5% - 6.5%.

REFERENCE

Based on European Pharmacopoeia 8th Edition, Loss on Drying, 2.2.32.

TEST: IDENTIFICATION OF ORGANIC COLOURANTS

SPECIFICATION Must be positive for the colourants present in the formula

Note If the cap and body of capsules have the same colour, the test can be performed without separating the capsule parts. If the cap and body are of different colours, the cap and body must be tested separately.

PROCEDURE I

- **Extraction Solvent:** Methanol / Water (3:1 by volume).
- **Developing Solvent:** Dissolve 2 g of sodium citrate in 100 ml of purified water. To this solution, add 5 ml of concentrated ammonium hydroxide and mix.
- **Materials**
  - Chromatographic plates of cellulose
  - 1 micro-litre pipettes
  - Developing tanks
- **Sample Solution:** Take the required quantity of capsules (40 - 60 capsules or parts), preferably cut into pieces and placed in a suitable flask of 20 ml. Add 10 ml of the extraction solvent (or the amount necessary to cover the capsules). Place the flask in a dark place and leave for 30 - 60 minutes at room temperature (15°C - 30°C). Remove the capsule pieces and concentrate the solvent by evaporation. Re-dissolve by adding 2 - 3 drops of purified water. Apply 1 µl of each solution of the extract using a micropipette at a point approximately 2.5 cm from the base of the plate. The extract obtained (sample) is spotted onto a 20 cm x 20 cm thin-layer chromatographic cellulose plate. Develop for 10 cm - 12 cm in the developing solvent. Then, remove the plate, dry and examine.
- **Standard Solution**: Prepare a standard solution in the same conditions as the sample solution.

PROCEDURE II

- **Extraction Solvent:** Purified water.
- **Developing Solvent:** Mixture of isopenthyl alcohol (105 ml), acetone (81 ml), concentrated ammonium hydroxide (8 ml) and purified water (32 ml).
- **Materials**
  - Silica gel plates
  - 1 micro-litre pipettes
  - Beaker
  - Developing tanks
- **Sample Solution:** Place 0.5 g of capsules (or parts) into 20 ml of purified water at higher than 90°C for 1 minute or less. Filter 5 ml of the solution with a 0.45 µm pore size filter. Dry the filtrate and then redissolve in three drops of purified water. Spot 2 µl or 3 ml of the redissolved extract at the bottom of the silica gel plate. Allow the spots to dry completely. Place the plate into tank and allow the developing solution to migrate up the plate. Remove the plate from the developing solution and allow the plate to air dry.
- **Standard Solution:** Add 0.1 g of standard material in 100 ml of purified water and then dissolve. Operate this solution in the same conditions as the sample solution.

INTERPRETATION OF RESULTS

Examine and compare the plate to chromatograms of standard dyes. The dyes are identified by comparison between the test and standard spots in their appearance.

REFERENCE

Based on European Pharmacopoeia 8th Edition. Thin Layer-Chromatography, 2.2.27.

TEST: IDENTIFICATION OF TITANIUM DIOXIDE

SPECIFICATION Must be positive if present in the shell formulation

PROCEDURE

To approximately 2 g of capsule in a crucible, add 2 ml of concentrated sulphuric acid. Heat gently until thoroughly charred. Transfer the crucible to a muffle furnace and ignite it at 600°C until the carbon is gone. Cool the residue and add 8 ml of concentrated sulphuric acid and 2 ml of phosphoric acid. Heat until it just begins to boil. Centrifuge it if necessary. To 4 ml of this solution, add 5 ml of purified water and 0.25 ml of 30% hydrogen peroxide.

INTERPRETATION OF RESULTS

A yellowish to orange-yellowish colour appears if titanium dioxide is present.

REFERENCE

Based on European Pharmacopoeia 8th Edition. Titanium Dioxide Monograph.

TEST: IDENTIFICATION OF IRON OXIDES

SPECIFICATION Must be positive if present in the formulation

PROCEDURE

To approximately 2 g of capsule in a crucible, add 2 ml of concentrated sulphuric acid. Heat gently until thoroughly charred. Transfer the crucible to a muffle furnace and ignite it at 600°C until the carbon is gone. Cool the residue and add 8 ml of concentrated sulphuric acid and 2 ml of phosphoric acid. Heat until it just begins to boil. Centrifuge it if necessary. To 4 ml of this solution, add 5 ml of purified water and 1 ml of potassium ferrocyanide (5.3% w/v).

INTERPRETATION OF RESULTS

A bluish colour appears if iron oxides are present.

REFERENCE

Based on European Pharmacopoeia 8th Edition. Identification Reactions of Ions and Functional Groups. 2.3.1.

TEST: PURITY (ODOUR, SOLUBILITY, ACIDITY, ALKALINITY)

SPECIFICATION Capsules dissolve within 10 minutes

PROCEDURE

Place, without overlapping the parts, 1 capsule in a 100 ml conical flask, add 50 ml of water, and shake often, keeping the temperature at 37 ± 2°C. Perform this test 5 times.

INTERPRETATION OF RESULTS

All the capsules dissolve within 10 minutes. All the solutions obtained are odourless and neutral or slightly acidic.

REFERENCE

Japanese Pharmacopoeia 16th Edition.

TEST: CAPSULE DESCRIPTION

SPECIFICATION Capsules must be odourless and elastic

PROCEDURE

To check the following items:

- **Elastic test:** Take a capsule and hold it with the thumb and a finger, roll it between them and press to deform the shell walls. Remove the pressure and the capsule should return to its original shape with no deformation.

- **Odour test:** Place a 1 g sample of capsules in a glass dish. They emit no discernable odour.

INTERPRETATION OF RESULTS

Capsules are odourless and elastic.

REFERENCE

Based on Japanese Pharmacopoeia 16th Edition.

5.3 Test Methods for Microbiological Specifications

TEST: TOTAL AEROBIC MICROBIAL COUNT (TAMC)

SPECIFICATION 10^2 cfu/g

PROCEDURE

Dissolve 10 g of capsules in Casein soya bean digest broth and adjust the volume to 100 ml with the same liquid using Petri dishes (9 cm in diameter). Add to each dish a mixture of 1 ml of the prepared solution and about 15 ml - 20 ml of liquefied Trypticase soya agar (Casein soya bean digest agar) at a maximum temperature of 45°C. Prepare at least two such Petri dishes using the same dilution and incubate at 30°C - 35°C for 3 - 5 days. Count the number of colonies that develop.

Note 250 colonies per plate is the maximum consistent with a reliable evaluation. For a greater number of colonies, proceed to make further dilution. Calculate the number of colonies per gram of product.

INTERPRETATION OF RESULTS

The prescribed limit to be interpreted is as follows:
10^2 CFU - maximum limit of acceptance: 200 CFU

REFERENCE

European Pharmacopoeia, 8th Edition, Microbial examination of non-sterile products 2.6.12. Harmonized Method.

TEST: STAPHYLOCOCCUS AUREUS

SPECIFICATION: Absence in 1 g

PROCEDURE

Prepare the product to be examined as described in the method for the total aerobic microbial count, and use 10 ml or the quantity corresponding to 1 g or 1 ml to inoculate 100 ml of Trypticase soya broth (Casein soya bean digest broth), homogenize and incubate at 30°C - 35°C for 18 - 24 hours. Subculture on a plate of Mannitol Salt agar and incubate at 30°C - 35°C for 18 - 72 hours.

INTERPRETATION OF RESULTS

The possible presence of S. aureus is indicated by the growth of yellow/white colonies surrounded by a yellow zone. This is confirmed by identification tests. The product complies with the test if colonies of the types described are not present or if the confirmatory identification tests are negative.

REFERENCE

European Pharmacopoeia, 8th Edition, Microbial examination of non-sterile products 2.6.13. Harmonized Method.

TEST: PSEUDOMONAS AERUGINOSA

SPECIFICATION: Absence in 1 g

PROCEDURE

Prepare the product to be examined as described in the method for the total aerobic microbial count and use 10 ml or the quantity corresponding to 1 g or 1 ml to inoculate 100 ml of Trypticase soya broth (Casein soya bean digest broth), homogenize and incubate at 30°C - 35°C for 18 - 24 hours. Subculture on a plate of Cetrimide agar and incubate at 30°C - 35°C for 18 - 72 hours.

INTERPRETATION OF RESULTS

Growth of colonies indicates the possible presence of Paeruginosa. This is confirmed by identification tests. The product complies with the test if colonies are not present or if the confirmatory identification tests are negative.

REFERENCE

European Pharmacopoeia, 8th Edition, Microbial examination of non-sterile products 2.6.13. Harmonized Method.

TEST: TOTAL COMBINED YEASTS AND MOLDS COUNT (TYMC)

SPECIFICATION: 10^1 CFU

PROCEDURE

Dissolve 10 g of capsules in Casein soya bean digest broth and adjust the volume to 100 ml with the same liquid. Using Petri dishes (9 cm in diameter), add to each dish a mixture of 1 ml of the prepared solution and about 15 ml - 20 ml of liquefied Sabouraud-dextrose agar at a maximum temperature of 45°C. Prepare at least two such Petri dishes using the same dilution and incubate at 20°C - 25°C for 5 - 7 days.

Note 50 colonies per plate is the maximum consistent with a reliable evaluation. For a greater number of colonies, proceed to make further dilution. Count the number of colonies which develop. Calculate the number of colonies per gram of product.

INTERPRETATION OF RESULTS

The prescribed limit to be interpreted is as follows:
10^1 cfu/g - maximum limit of acceptance: 20 CFU

REFERENCE

European Pharmacopoeia, 8th Edition, Microbial examination of non-sterile products 2.6.12. Harmonized Method.

TEST: BILE-TOLERANT GRAM-NEGATIVE BACTERIA

SPECIFICATION: Absence in 1 g

PROCEDURE

Prepare a dilution 1 in 10 dissolving 10 g of capsules in Casein soya bean digest broth. Mix and incubate at 20 - 25°C for a time sufficient to resuscitate the bacteria, but not enough to encourage multiplication of the organisms (usually 2 hours, but not more than 5 hours).
Use the volume corresponding to 1 g of the product (10 ml of diluted sample) to inoculate enterobacteria enrichment broth-Mossel. Incubate at 30 - 35°C for 24 - 48 hours. Subculture on plates of violet red bile glucose agar. Incubate at 30 - 35°C for 18 - 24 hours.

INTERPRETATION OF RESULTS

The product complies with the test if there is no growth of colonies.

REFERENCE

European Pharmacopoeia, 8th Edition, Microbial examination of non-sterile products 2.6.13. Harmonized Method.

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