Quali-G™

TECHNICAL MANUAL

Hard two-piece gelatin capsules for pharmaceutical applications

Qualicaps

Quali-G™ capsules are designed to meet the demanding requirements of the pharmaceutical industry

R&D

100% bovine bone gelatin.
Preservative-free.
Compatible with excipients being used currently.

Production

Run on automatic high-speed filling and packaging equipment.
Unique POSILOK® design prevents separation of cap and body.

Regulatory

Patented composition and manufacturing process.
Approved by the FDA.
In compliance with Pharmacopoeia USP/EP.
DMF registered for the USA and Canada.
Kosher and Halal certifications available.
EXCiPACT certificate.

Marketing

Pork-free, compatible with certain religious restrictions.
Effective and attractive product identity.
Available in a wide range of colours and printing options.

The information contained in this document applies to the Quali-G™ products (depending on the product, specific data such as moisture content may vary, please contact us for more information).

CONTENTS

1 Official Accreditations

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1.1 Quality System

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

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

The quality 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 11090 for USA
DMF 1998 - 096 for Canada
ISO 9001:2015 certificate (Quality)
ISO 14001:2015 certificate (Environmental)
EXCiPACT certificate (GMP)


CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

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

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

ISO 9001:2015

The Quality Management System is applicable to:

Manufacture of gelatin and hypromellose capsule shells for the Pharmaceutical and Consumer Health industries.

Approval Certificate No: SGI 2936271
Original Approval: 15 July 1994
Current Certificate: 01 July 2018
Certificate Expiry: 30 June 2021

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

Certificate of ISO 9001:2015


Certificate of Approval

This is to certify that the Management System of:

Qualicaps Europe, S.A.U.

ISO 14001:2015

Certificate of ISO 14001:2015


AENOR

EXCiPACT Certification Standard for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices 2012

EXC-2018/0001

QUALICAPS EUROPE, S.A.U.

Certificate of EXCiPACT

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

DMF 21632 for USA
DMF 2008 - 109 for Canada
GMP certification
ISO 9001:2015 certificate (Quality)
ISO 14001:2015 certificate (Environmental)
EXCiPACT certificate (GMP)

Certificate of ISO 9001:2015

Certificate of ISO 14001:2015

Certificate of EXCiPACT

2 Capsule Characteristics

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2.1 Quali-G™ Capsule Design

Quali-G™ capsules have a unique locking feature, the first to be introduced in the market.

This feature ensures that the contents are securely contained within the capsules, having been designed to promote optimum performance in the pre-locked state prior to filling on high speed machines. The dimensions of the POSILOK® capsule are carefully monitored throughout the manufacturing process to bolster runnability on today's filling machines.

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.

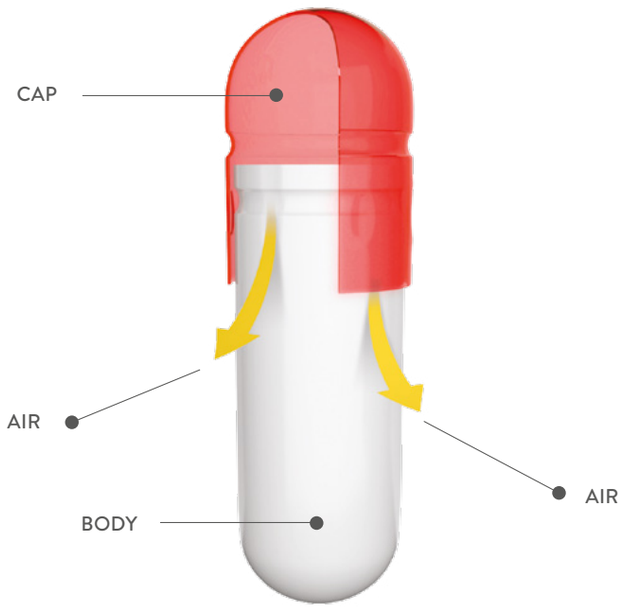
POSILOK®

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 such as:

- Powders
- Pellets
- Tablets

SECURE LOCKING

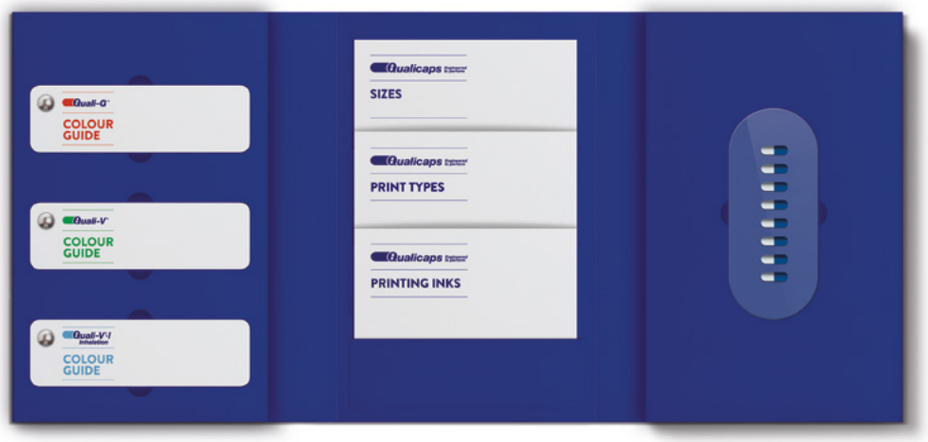
Efficient packing relies on consistent product quality. The POSILOK® capsule is designed to remain securely closed to a precise length, ready for subsequent handling that ensures efficient placement in blister packages, minimal product loss during packaging and no separation.



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-G™ capsules, is available upon request to assist customers with the choice of colour combinations.



2.3 Capsule Sizes

Quali-G™ capsules are available in sizes ranging from 00E to 4.

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.

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

GELATIN

Quali-G™ capsules are made from gelatin that complies with the European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP/NF).

The gelatin is supplied exclusively by member companies of the Gelatin Manufacturers of Europe (GME) Association and complies with the latest EMA CPMP/CVMP guidance.

Each of our gelatin suppliers has obtained “Certificates of Suitability” from the European Directorate for the Quality of Medicines (EDQM). This confirms that their gelatins comply with the monograph “Products with risk of transmitting agents of animal spongiform encephalopathies” in the European Pharmacopoeia.

COLOURANTS

The colourants used are in compliance with the EC 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

Sodium Lauryl Sulphate, used as a wetting agent, complies with the EP and USP/NF. In addition, Sodium Lauryl Sulphate could be used as surface lubricant on the capsules.

PRINTING INKS

Qualicaps® uses edible printing inks that contain pigments and the lake form of dyes used 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-G™ Capsule Specifications

Size		00E*	00	0E	0	1E*	1	2	3	4
Weight	Target weight (mg)	130.0	126.0	106.0	98.0	83.0	76.0	63.0	50.0	40.0
	Weight limits (mg)	120.3 – 139.8	116.6 – 135.5	98.1 – 114.0	90.7 – 105.4	76.8 – 89.2	70.3 – 81.7	58.3 – 67.7	46.3 – 53.8	37.0 – 43.0
Capacity	Approximate body volume (ml)	1.00	0.93	0.77	0.69	0.54	0.50	0.37	0.28	0.21
	Powder fill weight (mg)									
	Powder density 0.6 g/ml	598	558	462	414	324	300	222	168	126
	Powder density 0.8 g/ml	798	744	616	552	432	400	296	224	168
	Powder density 1.0 g/ml	997	930	770	690	540	500	370	280	210
	Powder density 1.2 g/ml	1196	1116	924	828	648	600	444	336	252
Outside diameter	Cap diameter (mm)	8.56	8.56	7.66	7.66	6.95	6.95	6.38	5.85	5.34
	Cap diameter limits (mm)	8.50 – 8.62	8.52 – 8.60	7.62 – 7.70	7.62 – 7.70	6.91 – 6.99	6.91 – 6.99	6.34 – 6.42	5.81 – 5.89	5.30 – 5.38
	Body diameter (mm)	8.21	8.21	7.36	7.36	6.65	6.65	6.08	5.60	5.07
	Body diameter limits (mm)	8.15 – 8.27	8.17 – 8.25	7.32– 7.40	7.32 – 7.40	6.61 – 6.69	6.61 – 6.69	6.04 – 6.12	5.56 – 5.64	5.03 – 5.11
Length	Cap length (mm)	12.95	11.70	12.00	10.90	10.60	9.70	8.90	7.90	7.20
	Cap length limits (mm)	12.65 – 13.25	11.40 – 12.00	11.70 – 12.30	10.60 – 11.20	10.30 – 10.90	9.40 – 10.00	8.60 – 9.20	7.60 – 8.20	6.90 – 7.50
	Body length (mm)	22.20	20.10	20.90	18.60	17.70	16.70	15.30	13.50	12.40
	Body length limits (mm)	21.90 – 22.50	19.80 – 20.40	20.60 – 21.20	18.30 – 18.90	17.40 – 18.00	16.40 – 17.00	15.00 – 15.60	13.20 – 13.80	12.10 – 12.70
Closed joined length	Closed joined length (mm)	25.30	23.50	24.00	21.80	20.40	19.50	17.80	15.80	14.50
	Closed joined length limits (mm)	25.00 – 25.60	23.20 – 23.80	23.70 – 24.30	21.50 – 22.10	20.10 – 20.70	19.20 – 19.80	17.50 – 18.10	15.50 – 16.10	14.20 – 14.80

*Not available for powders with fine particle size.

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

- **Weight:** The average weights shown in the table are determined from the gross weight of a sample of 100 capsules at the standard moisture content of 13.0% to 16.0%. The average weight of the capsules can vary by ± 7.5% from the target value. These values are not applicable to individual capsules but rather to the average of the batch. Customers should determine tare weights for filling by testing samples from in-house batches.

- **Capacity:** Quali-G™ capsules can be filled with a range of materials with different physical properties: powders, granules and pellets. The fill weight of powders can be estimated by multiplying the capsule body volume by the tapped bulk density of the formulation. This holds true for most types of filling machines despite their different dosing mechanisms. Total internal capsule volume is another useful value that allows the formulator to estimate the porosity of the powder fill. When filling liquids, the working capacity is 90% of the body volume to reduce the risk of spillage during machine movement.

- **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 will 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 through 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	Critical	0.010%
	Major	0.040%
	Minor	0.25%

INSPECTION MODE AND ASSOCIATED INSPECTION TIME

Visual inspection is performed in segments of approximately 400 units each by unaided eyes, at a distance of about 30 cm. Qualicaps® visual control booths have transparent polymethyl methacrylate 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:

- **Critical:** Affects the performance of a capsule as a package for the final product, or could contribute to a major subjective problem in filling.
- **Major:** 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

CRITICAL	
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 long 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	
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 gelatin > 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

Critical Defects

CRACKED

DOUBLE CAP

HOLE

LONG CAP

LONG BODY

MASHED

SHORT CAP

SHORT BODY

SPLIT

TELESCOPE

TRIMMING

UNCUT CAP

UNCUT BODY

UNJOINED

Major Defects

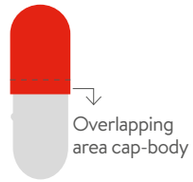
DAMAGED EDGE

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)**
  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.

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

INSPECTION MODE AND ASSOCIATED INSPECTION TIME

Visual inspection is performed in segments of approximately 400 units each by unaided eyes, at a distance of about 30 cm. Qualicaps® visual control booths have transparent polymethyl methacrylate 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 PRINT DEFECTS

Print defects are classified according to the following definitions:

- **Critical print defects:**
  Unprinted capsules or incorrect logo.
- **Major 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

CRITICAL	MAJOR	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

CRITICAL: UNPRINTED

The entire image is missing.

MAJOR / 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 defect.

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

MAJOR / 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 defect.

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

MAJOR / MINOR: MULTIPLE IMAGES

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

Minor defect if the image is still legible.

MAJOR / MINOR: PARTIAL IMAGE

Part of the image is missing.

Major 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 / MINOR: SMUDGED IMAGE

The image is smudged or smeared.

Major 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: PET/aluminium foil/polyethylene. foil. This is heat-sealed after inserting the capsules, creating a container that is moisture proof.

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

Capsule size	00E	00	0E	0	1E	1	2	3	4
Capsules per carton in 000's**	65	75	75	100	120	135	175	225	300

Cartons size: 60 cm long x 40 cm wide x 75 cm high
* Polypropylene carton box upon request
** 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 relevant data.

The delivery label on the box contains two easily-removable adhesive stickers 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-G™ capsules maintain their quality during this period.

TRANSPORTATION

Quali-G™ capsules are supplied in sturdy cardboard cartons, each having heat-sealed, moisture-proof liners. These cartons may be grouped on an European size case pallet.

WAREHOUSING CONDITIONS

The ideal condition for the storage of capsules is at a temperature between 15°C and 30°C (59°F and 86°F). Care should also be taken to maintain the capsules at an even temperature. The containers should be kept away from exposure to direct heat and sunlight, as they may cause localised heating and moisture migration within the capsules, possibly resulting in dimensional changes that affect performance on the filling machine.

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

Capsules stored correctly in Qualicaps® packaging will give the optimum performance in production.

CAPSULE SHELF LIFE

Quali-G™ capsules under the aforementioned storage conditions, will have a satisfactory 5-year shelf life from the date of manufacture. The temperature of the environment should not exceed the recommended limits to avoid water migration inside the vapour-proof liners that may lead to possible capsule wall distortions.

The maintenance of the moisture content between 13.0% and 16.0% is necessary for two reasons: firstly, it maintains the capsule dimensions within specifications, and secondly, the growth of micro-organisms is discouraged at moisture less than 16.0%, because the water activity is too low.

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 13.0% to 16.0% for Quali-G™.

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-G™ capsules are manufactured with the greatest care to ensure optimum running on filling machines.

The capsule specifications described previously are the result of extensive tests performed with different equipment manufacturers on machines adjusted to normal filling conditions with bushes or segments within official diameter limits.

To achieve the best results, it is recommendable to check the bores in the bushes on the filling machine to ensure that they are within the machine manufacturer's specifications (consult with the machine manufacturer or your Qualicaps® Technical Services engineer).

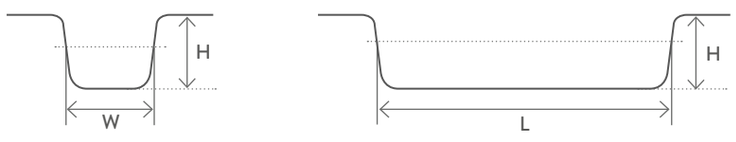
Care should be taken to close the capsules to the correct closed joined length after filling. If the capsules are over-closed, faults may occur as a result of distortion of the shells, with the possibility of cracking, splitting or reopening. If the capsules are under-closed, due to incorrect machine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

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	00E	0E	0	1E	1	2	3	4
H	9.1	9.2	8.2	8.1	7.5	7.4	6.9	6.3	5.8
L	25.0	26.8	25.1	22.8	22.2	20.5	18.8	16.8	15.5
W	9.8	9.9	8.9	8.8	8.2	8.1	7.6	7.0	6.5

Minimum die roll cavity dimensions (mm)



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
Identification of Gelatin	Meets test	French Pharmacopoeia 10th Edition	54
Odour	Meets test	European Pharmacopoeia 10th Edition	55
Loss on Drying (LOD)	13.0% - 16.0%	Based on European Pharmacopoeia 10th Edition	55
Identification of Organic Colourants	Meets test	Based on European Pharmacopoeia 10th Edition	56
Identification of Titanium Dioxide	Meets test	Based on European Pharmacopoeia 10th Edition	58
Identification of Iron Oxides	Meets test	Based on European Pharmacopoeia 10th Edition	59
Disintegration	< 15 min	European Pharmacopoeia 10th Edition	60
Sulphated Ash	< 3.0% for transparent capsules < 9.0% for opaque capsules	Based on European Pharmacopoeia 10th Edition	61
Arsenic	< 1 ppm	Based on European Pharmacopoeia 10th Edition	62
Heavy Metals	< 30 ppm	Based on European Pharmacopoeia 10th Edition	64
Elemental Impurities	HICH Q3D Guideline for Elemental Impurities. Permitted oral concentrations of elemental impurities. Option 1.	Based on European Pharmacopoeia 10th Edition	66
Lubricant Content	< 0.5%	French Pharmacopoeia 10th Edition	68
Sulphur Dioxide	< 0.1%	French Pharmacopoeia 10th Edition	69
Identification of Sodium Lauryl Sulphate	Meets test	Based on European Pharmacopoeia 10th Edition	70

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

Test	Specification	Reference	Page
Total Aerobic Microbial Count (TAMC)	10^3 cfu/g	EP/USP/JP	71
Escherichia Coli	Absence in 1 g	EP/USP/JP	72
Total combined Yeasts/Moulds Count (TYMC)	10^2 cfu/g	EP/USP/JP	73

5.2 Test Methods for Chemical Specifications

TEST: IDENTIFICATION OF GELATIN

SPECIFICATION Must be positive

PROCEDURE

- To 5 ml of purified water heated to 70°C, add 10 gelatin capsules. Shake until dissolved and allow to cool. A characteristic gel must appear.

- Shake to dissolve 1 g of capsules in 100 ml of purified water heated to about 70°C. Centrifuge. Take 2 ml of the supernatant whilst still warm. Add 2 ml of a solution of picric acid*. A turbidity is produced immediately.

Note Picric acid solution: prepare 100 ml of saturated picric acid and add 0.25 ml of concentrated sodium hydroxide solution.

INTERPRETATION OF RESULTS

- A characteristic gel appears if gelatin is present.

- A turbidity is produced if gelatin is present.

REFERENCE

French Pharmacopoeia, 10th Edition. Monograph for empty gelatin capsules (1986).

TEST: ODOUR

SPECIFICATION Practically odourless

PROCEDURE

On a watch glass, 6 cm to 8 cm in diameter, spread in a thin layer 0.5 g to 2.0 g of the capsules to be examined. After 15 minutes, determine if an odour is present or verify the absence of odour.

INTERPRETATION OF RESULTS

Capsules are practically odourless.

REFERENCE

European Pharmacopoeia, 10th Edition, Odour, 2.3.4.

TEST: LOSS ON DRYING (LOD)

SPECIFICATION 13.0% - 16.0%

PROCEDURE

Determined in an oven at 100°C - 105°C for 6 hours using 1.0 g of capsules, separated caps from bodies.

INTERPRETATION OF RESULTS

Moisture content limit is 13.0% - 16.0%.

REFERENCE

Based on European Pharmacopoeia, 10th Edition, Loss on Drying, 2.2.32

TEST: IDENTIFICATION OF ORGANIC COLOURANTS

SPECIFICATION Must be positive for the colourants present in the capsule

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

Use (a) or (b) of the chromatographic systems, depending upon the colourants present in the capsule shell. In the case where there are several colourants mixed in very different proportions, it may be necessary to modify the composition of the mobile phases as described below and the extraction processes.

- **Test Solution:** Take a number of capsules (caps or bodies) sufficient to obtain a final concentration between 0.1 mg/ml and 0.5 mg/ml for each colourant. To this quantity of capsules, preferably cut into small pieces, add 5 ml of a mixture of 10 ml of ammonia (25%), 10 ml of purified water and 60 ml of methanol. Leave in the dark for 30 minutes. Repeat the operation if necessary until the extract solution is almost colourless. Mix the extract solutions and concentrate them.

- **Standard Solution:** Prepare a solution with a concentration between 0.1 mg/ml and 0.5 mg/ml of each colourant using as solvent 5 ml of a mixture of 10 ml of ammonia (25%), 10 ml of purified water and 60 ml of methanol. Protect from light.

- **Chromatographic Systems**

  a) Perform thin layer chromatography using a plate covered with Silica Gel G.

Spot on the plate 2 µl to 10 µl of each solution as a band in a length of 10 mm. Develop the plate for 10 cm using a mixture of 10 ml of ammonia (25%), 10 ml of water, 40 ml of butanol and 40 ml of ethanol. Dry the plate. The spot or spots on the chromatogram obtained with the extraction solution are similar in their position and appearance to the spot or spots from the chromatogram obtained with the standard solution.

b) Perform thin layer chromatography using a plate covered with microcrystalline cellulose for chromatography.

Spot on the plate 2 µl to 10 µl of each solution as a band in a length of 10 mm. Develop the plate for 10 cm - 12 cm using a mixture of 20 ml of water, 25 ml of pyridine and 55 ml of ethyl acetate. Dry the plate. The spot or spots on the chromatogram obtained with the extraction solution are similar in their position and appearance to the spot or spots from the chromatogram obtained with the standard solution.

INTERPRETATION OF RESULTS

Compare it with chromatograms of standard dyes. The dyes are identified by comparing the test and standard spots for their appearance and position.

REFERENCE

Based on European Pharmacopoeia 10th 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 10th Edition, Titanium Dioxide Monograph.

TEST: IDENTIFICATION OF IRON OXIDES

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 all 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 color appears if iron oxides are present.

REFERENCE

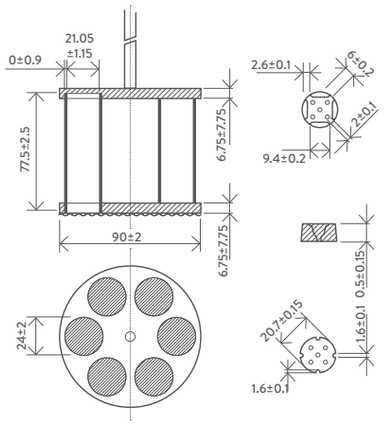
Based on European Pharmacopoeia 10th Edition, Identification Reactions of Ions and Functional Groups, 2.3.1.

TEST: DISINTEGRATION

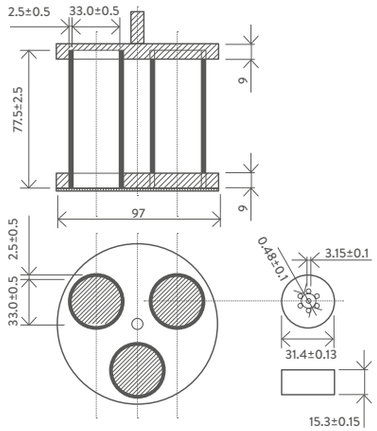
SPECIFICATION Capsule should disintegrate in less than 15 minutes

PROCEDURE

Place one capsule in each of the 3 or 6 tubes of the basket and add a disc to each tube. Operate the apparatus using the specified medium (purified water), maintained at 37 ± 2°C, as the immersion fluid. At the end of the specified time (15 minutes), lift the basket from the fluid and observe the capsules; all of the capsules have disintegrated completely. Depending on the size of capsules; use *Apparatus A* for capsules that are not greater than a length of 18 mm and *Apparatus B* for capsules that are longer.



Apparatus A
(Dimensions in millimetres)



Apparatus B
(Dimensions in millimetres)

INTERPRETATION OF RESULTS

To pass the test, all the capsules must have disintegrated completely. Disintegration is considered to be achieved when only fragments of shell (capsules) remain on the screen; if a disc has been used, fragments of the shell may adhere to the lower surface of the disc. If 1 or 2 dosage units fail to disintegrate, repeat the test on 12 additional capsules. The requirements of the test are met if not less than 16 of the 18 capsules tested have disintegrated.

REFERENCE

European Pharmacopoeia, 10th Edition, Disintegration of Tablets and Capsules, 2.9.1.

TEST: SULPHATED ASH

SPECIFICATION Not more than 3.0% for transparent capsules and not more than 9.0% for opaque capsules

PROCEDURE

Place 2.0 g of capsules (caps and bodies) in a crucible and add 2 ml of dilute sulphuric acid. Heat at first on a water bath, and then transfer to a muffle furnace and ignite at 600 ± 25°C. Continue the incineration until all black particles have disappeared. Allow the crucible to cool and weigh.

Calculate the sulphated ash as a percentage of the original weight.

INTERPRETATION OF RESULTS

The percentage of sulphated ash is:

- Not more than 3.0% for transparent capsules
- Not more than 9.0% for opaque capsules

REFERENCE

Based on European Pharmacopoeia 10th Edition, Sulphated Ash, 2.4.14.

TEST: ARSENIC

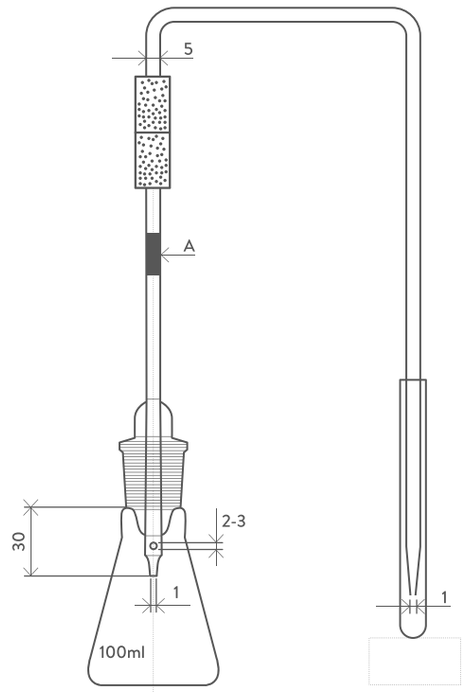
SPECIFICATION Not more than 1 ppm

PROCEDURE

Weight 1 g of product (capsules) into a crucibled and ignited (Calcinate) at about 600°C during 16 hours. Allow to cool (the calcinated residue).

- **Apparatus:** The apparatus consists of a 100 ml conical flask closed with a ground-glass stopper through which passes a glass tube about 200 mm long and about 5 mm in internal diameter. The lower part of the tube tapers to an internal diameter of 1 mm, and about 20 mm from its tip is a lateral orifice 2-3 mm in diameter. When the tube is in position in the stopper, the lateral orifice is at least 3 mm below the lower surface of the stopper. A second glass tube of the same internal diameter is connected to the first tube. The second tube is bent twice at right angles and the free end of the tube tapers to an internal diameter of 1 mm. This end is immersed in a test-tube containing 3.0 ml of silver diethyl-dithiocarbamate solution R. Other suitable equipment may be used. Into the first tube insert 50-60 mg of lead acetate cotton R, loosely packed, or a small plug of cotton and a rolled piece of lead acetate paper R weighing 50-60 mg.

In the conical flask, dissolve the prescribed quantity of the substance (the calcinated residue) to be examined in 25 ml of water R, or in the case of a solution adjust the prescribed volume to 25 ml with water R. Add 15 ml of hydrochloric acid R, 0.1 ml of stannous chloride solution R and 5 ml of potassium iodide solution R, allow to stand for 15 min and introduce 5 g of activated zinc R. Assemble the 2 parts of the apparatus immediately and immerse the flask in a water-bath at a temperature such that a uniform evolution of gas is maintained. Prepare a standard in the same manner, using 1 ml of arsenic standard solution (1 ppm As) R, diluted to 25 ml with water R. If foaming occurs, 1 ml of 2-propanol R may be added to the flask.



Apparatus for the limit test for arsenic (Method A)
(Dimensions in millimeters)

INTERPRETATION OF RESULTS

After at least 2 h, the color obtained in the test-tube with the test solution is not more intense than that obtained with the standard.

Suitability test. The color obtained in the test-tube with the standard is at least as intensely colored as 3 ml of a mixture of 3.0 ml of yellow primary solution, 0.6 ml of red primary solution and 11.40 ml of a solution of hydrochloric acid R (10 g/L HCl).

REFERENCE

Based on European Pharmacopoeia 10th Edition, Arsenic, 2.4.2 method A

TEST: HEAVY METALS

SPECIFICATION Not more than 30 ppm

PROCEDURE I

Compare the colour of a sample of the test solution with a standard solution and a blank test solution. Each sample is prepared using the procedure described below. After two minutes, any brown colour produced in the test solution should not be more intense than that produced by treating the standard solution in the same manner.

- **Test Solution:**
  - Preparation: Weigh 2 g of capsules in a crucible and ignite at 600°C for 16 hours. Add to the ashes 2 ml of 6 M hydrochloric acid solution, and evaporate on a steam bath. Add 10 ml of purified water and a few drops of hydrochloric acid, and neutralise with ammonia using pH indicator strips to verify the value. (The pH must be between 3 and 4.) Filter the solution, add water to the filtrate to obtain a final volume of 25 ml, and adjust the pH using pH indicator strips to verify the value. (The pH must be between 3 and 4.) Wash the residue with 10 ml of water, add to the filtrate and adjust the final volume to 40 ml with water.
  - Colour test: To a 50 ml Nessler tube, add 12 ml of this solution add 2 ml of acetate buffer solution (pH 3.5)* and 1.2 ml of thioacetamide test solution** and mix.

- **Standard Solution:**
  - Preparation: Take 6 ml of the Standard lead solution (10 ppm)*** and dilute to 25 ml with purified water. Adjust the pH to between 3 and 4 with acetic acid 1 M or 6 M ammonia solution using pH indicator strips to verify the value. Add purified water to obtain a final volume of 40 ml and mix.
  - Colour test: To a 50 ml Nessler tube, add 10 ml of this solution, 2 ml of the test solution, 2 ml of acetate buffer solution (pH 3.5) and 1.2 ml of the thioacetamide test solution and mix.

- **Blank Test Solution:**
  - Preparation & Colour test: To a 50 ml Nessler tube, add 2 ml of the test solution, 10 ml of purified water, 2 ml of acetate buffer solution* (pH 3.5) and 1.2 ml of the thioacetamide test solution** and mix.

The test is invalid unless the standard solution does not show a slight brown colour compared to the blank solution.

PROCEDURE II

Proceed in the same way than under Procedure I, but replacing the 1.2 ml of thioacetamide test solution by 0.1 ml of sodium sulphide solution****. Prepare additionally a Monitor solution from the quantity of the substance to be examined prescribed for the test, to which the volume of lead standard solution prescribed for preparation of the reference solution has been added. The test is invalid if the Monitor solution is not at least as intense has been added as the standard solution.

INTERPRETATION OF RESULTS

Any brown colour produced in the test solution is not more intense than that produced in the standard solution after allowing them to stand for at least two minutes.

Notes * Acetate buffer solution (pH 3.5): Dissolve 250 g of ammonium acetate in 250 ml of purified water and add 380 ml of hydrochloric acid (26% approx.) Adjust the pH to 3.5 with 7% hydrochloric acid or 10% ammonia solution. Dilute until 1000 ml with purified water.

** Thioacetamide test solution: To 0.2 ml of thioacetamide solution (40 g/l), add 1 ml of a mixture of 5 ml of purified water, 15 ml of 1 M sodium hydroxide and 20 ml of glycerol (85%). Heat in the water-bath for 20 seconds. Prepare immediately before use.

*** Standard lead solution (10 ppm): Prepare a 1000 ppm stock solution in a glass flask by dissolving 159.8 mg of lead nitrate in 50 ml of purified water. Add 1 ml of nitric acid and adjust the final volume to 100 ml with purified water. The expiry date of this stock solution is less than 6 months. Dilute 100 times in two steps to get a 10 ppm concentration.

**** Sodium sulphide solution: Dissolve 5 g of sodium sulphide in a mixture of 10 ml of purified water and 30 ml of glycerol (98.0% - 101.0%).

The test is invalid unless the standard solution does not show a slight brown colour compared to the blank solution.

In case of using sodium sulphide solution, the test is not valid if the monitor solution is not at least as intense as the standard solution.

REFERENCE

Based on European Pharmacopoeia, 10th Edition, Heavy Metals, 2.4.8 (Method A).

TEST: ELEMENTAL IMPURITIES

SPECIFICATION ICH Q3D Guideline for Elemental Impurities. Permitted Oral Concentrations of Elemental Impurities Option 1.

- Class 1 elements: cadmium, lead, arsenic and mercury: limits of 0.5, 0.5, 1.5 and 3.0 ppm, respectively.
- Class 2A elements: vanadium, cobalt and nickel: limits of 10, 5 and 20 ppm, respectively.
- Class 3 elements: lithium, antimony, barium, molybdenum, copper, tin and chromium: limits of 55, 120, 140, 300, 300, 600 and 1100 ppm, respectively.

PROCEDURE

- Equipment: ICP-MS with a closed vessel microwave digestor.
- Digestion reagents: HNO_3/HCl/H_2O_2/ultrapure water.
- Sample preparation: Weigh with accuracy, approximately 0.40g of sample into the digestion vessel. Add 2 ml of HNO_3 (65%), 0.5 ml of HCl (32%), 1 ml of H_2O_2 (30%) and 7 ml of ultrapure water. Perform the digestion process increasing temperature to 210°C for 60 min, and then held at the same temperature for 40 minutes. After cooling, transfer quantitatively to a 25 ml volumetric flask and dilute with 1% v/v HNO_3. (Note: A white precipitate can be observed if titanium dioxide is present in the capsule sample. Then perform sample centrifugation at 3750 rpm for 20 min. Use supernatant for the analysis).
- Calibration: Calibration is performed by using an ICP-MS multi-element standard. Signals obtained for some of the elements are recalculated using the appropriate equations in order to correct the possible spectral interferences.
- Analysis: Place blank, standard and capsule samples in the autosampler and analyze using the IPC-MS equipment.

INTERPRETATION OF RESULTS

The content of elemental impurities must be less than the stated specifications.

REFERENCE

Based on European Pharmacopoeia 10th Edition, Determination of Elemental Impurities, 2.4.20.

TEST: LUBRICANT CONTENT

SPECIFICATION Not more than 0.5%

PROCEDURE

To a flask, add 1.0 g of capsules, separated into caps and bodies, add 30 ml of methylene chloride and shake for 5 minutes. Transfer this extract to a tared flask. Repeat the treatment with a further 30 ml of methylene chloride and transfer this to the same flask. Evaporate the extracts and reweigh the flask. Calculate the weight of residue as a percentage of the sample weight.

INTERPRETATION OF RESULTS

The residue is not more than 0.5%.

REFERENCE

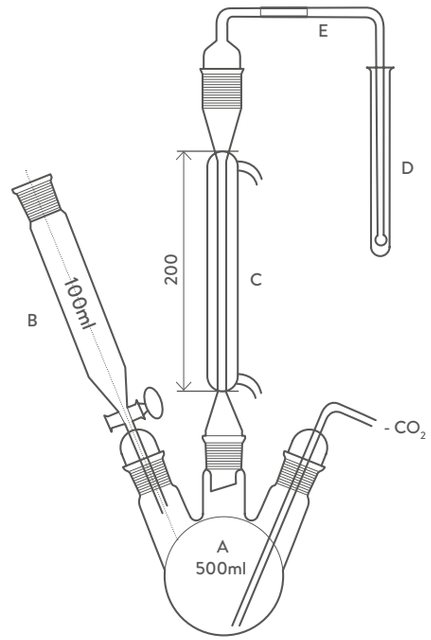
French Pharmacopoeia 10th Edition, Monograph for empty gelatin capsules (1986).

TEST: SULPHUR DIOXIDE

SPECIFICATION Not more than 0.1%

PROCEDURE

Add to the flask (A) 10 g of capsules and then 150 ml of water. Pass through the apparatus a current of carbon dioxide for 15 minutes at a rate of 100 ml per minute. Into the tube (D) add 10 ml of dilute hydrogen peroxide solution, neutralised with 0.1 M sodium hydroxide solution, using a 0.1% w/v solution of bromophenol blue in 20% v/v ethanol. Add to the reservoir (B) 80 ml of dilute hydrochloric acid and heat to boil for 1 hour under reflux. Open the tap of the reservoir (B), stop the flow of carbon dioxide, the heating and the condenser (C). Transfer the contents of the tube with a little water into a 200 ml wide-necked conical flask. Heat on a water bath for 15 minutes and allow to cool. Add 0.1 ml of 0.1% w/v bromophenol blue solution in 20% v/v ethanol. Titrate using 0.1 M sodium hydroxide solution until the colour changes from yellow to blue violet.



(Dimensions in millimetres)

Calculate the amount of sulphur dioxide (%) using the equation:

$$\frac{0.032 \times V_{NaOH} \times F_{NaOH} \times 100}{\text{g sample}}$$

INTERPRETATION OF RESULTS

The concentration of sulphur dioxide is not more than 0.1%.

REFERENCE

French Pharmacopoeia 10th Edition, Monograph for empty gelatin capsules (1986).

TEST: IDENTIFICATION OF SODIUM LAURYL SULPHATE

SPECIFICATION Must be positive

PROCEDURE

Into a test tube, weigh 3 g of capsules and add 6 ml of purified water. Heat on a water bath at 65°C to dissolve the sample. Take 1 ml of this solution and add 9 ml of purified water. Add 0.1 ml of 0.1% methylene blue solution, 2 ml of sulphuric acid and 2 ml of methylene chloride, and shake.

INTERPRETATION OF RESULTS

An intense blue colour develops in the methylene chloride layer if sodium lauryl sulphate is present.

REFERENCE

Based on European Pharmacopoeia, 10th Edition, Monograph for sodium lauryl sulphate (Identification Part B).

5.3 Test Methods for Microbiotical Specifications

TEST: TOTAL AEROBIC MICROBIAL COUNT (TAMC)

SPECIFICATION 10^3 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 not more than 45°C. Prepare at least two such Petri dishes using the same dilution and incubate at 30°C - 35°C for 3 - 5 days. Select the plates corresponding to a given dilution and showing the highest number of colonies less than 250. Take the arithmetic mean of the plates and calculate the number of colonies per gram of product.

INTERPRETATION OF RESULTS

The prescribed limit to be interpreted is as follows:
10^3 CFU - maximum limit of acceptance: 2000 CFU

REFERENCE

European Pharmacopoeia, 10th Edition, Microbial examination of non-sterile products (Total viable aerobic count), 2.6.12. Harmonized Method.

TEST: ESCHERICHIA COLI

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. Shake the container, transfer 1 ml to 100 ml of MacConkey broth and incubate at 42°C - 44°C for 24 - 48 hours. Subculture on plates of MacConkey agar and incubate at 30°C - 35°C for 18 - 72 hours.

INTERPRETATION OF RESULTS

Growth of colonies indicates the possible presence of E. coli. This is confirmed by identification tests. The product complies with the test if no colonies are present or if the identification tests are negative.

REFERENCE

European Pharmacopoeia, 10th Edition, Microbial examination of non-sterile products, 2.6.13. Harmonized Method.

TEST: TOTAL YEAST AND MOULD COUNT (TYMC)

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 Sabouraud-dextrose agar at not more than 45°C. Prepare at least two such Petri dishes using the same dilution and incubate at 20°C - 25°C for 5 - 7 days. Select the plates corresponding to a given dilution and showing the highest number of colonies less than 50. Take the arithmetic mean of the plates and 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, 10th Edition, Microbial examination of non-sterile products, 2.6.12., Harmonized Method.

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