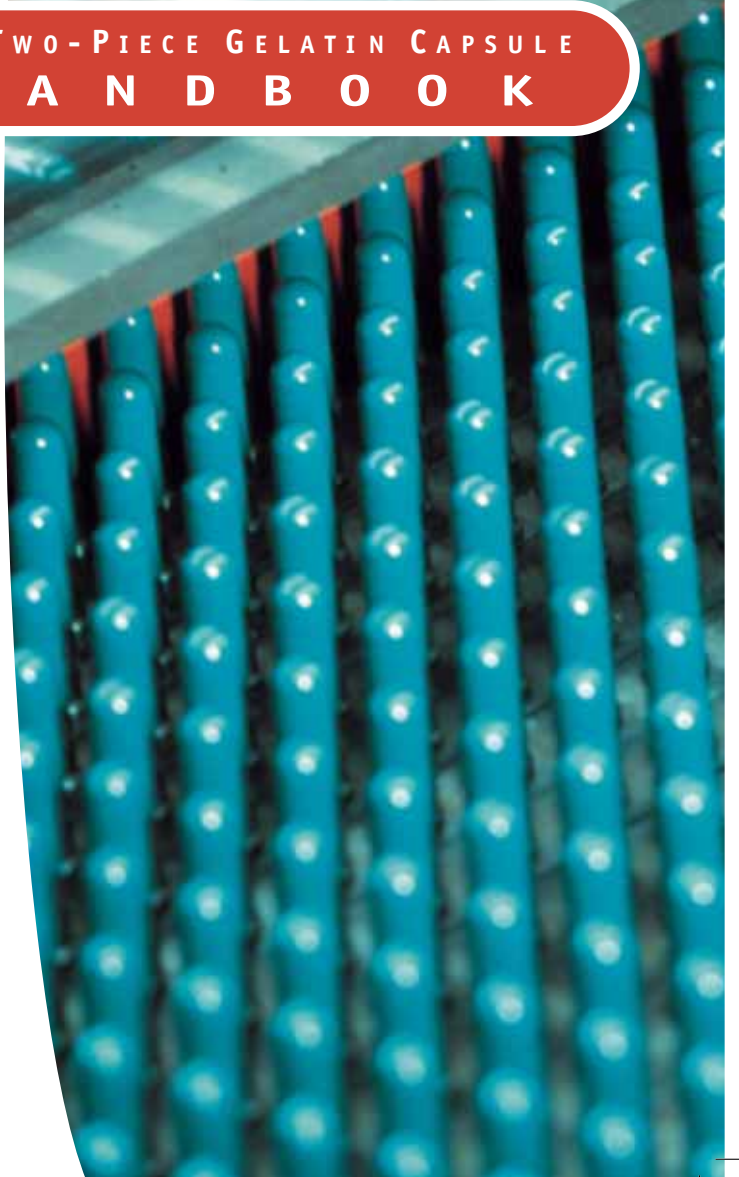


THE TWO-PIECE GELATIN CAPSULE
H A N D B O O K



 **Qualicaps**

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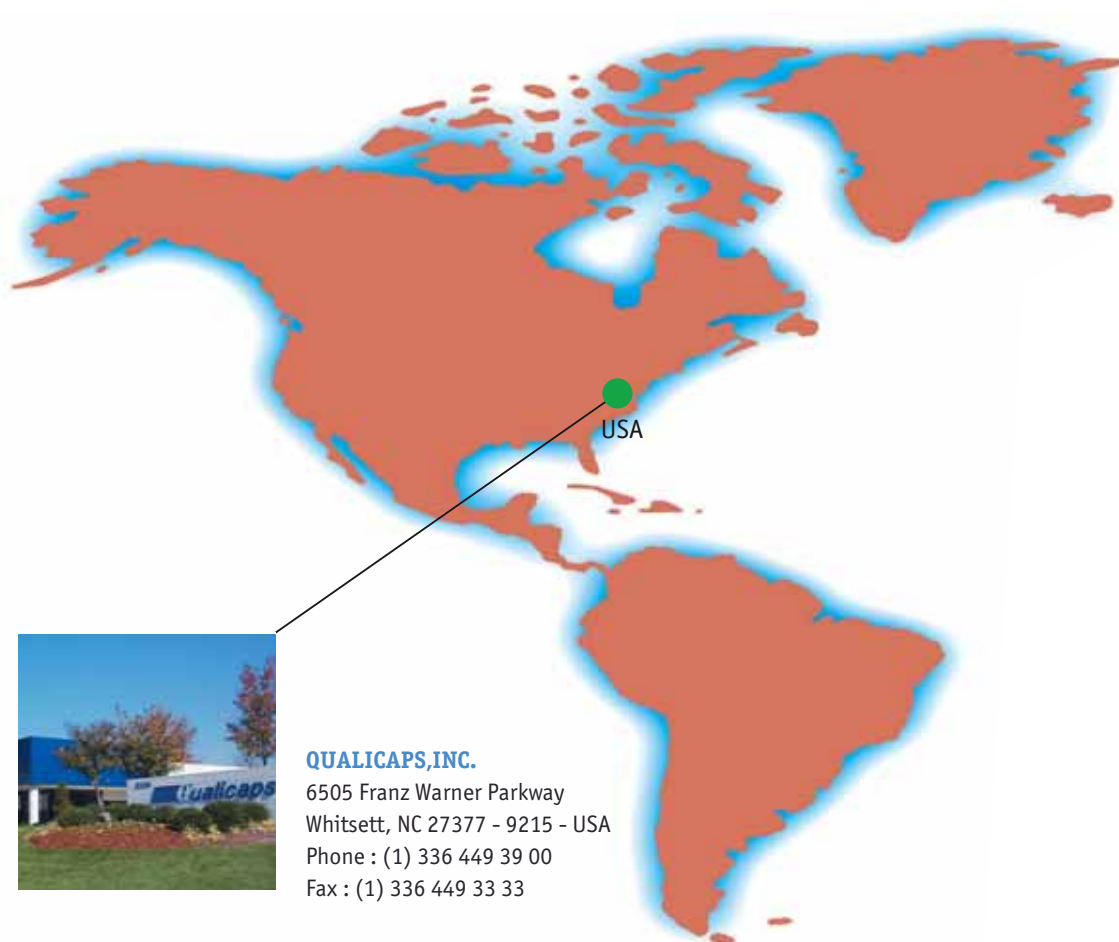
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1. PROFILE OF THE QUALICAPS GROUP

PROFILE OF THE QUALICAPS GROUP

The Qualicaps Group is one of the world's leading supplier of empty Gelatin Two-piece Capsules for the Pharmaceutical and Health & Nutrition industries. Qualicaps' international capsule operation ensures continuous worldwide supply with three manufacturing sites in Japan, USA and Europe.

The Qualicaps Group has a long-standing tradition of producing high quality capsules and filling equipment.



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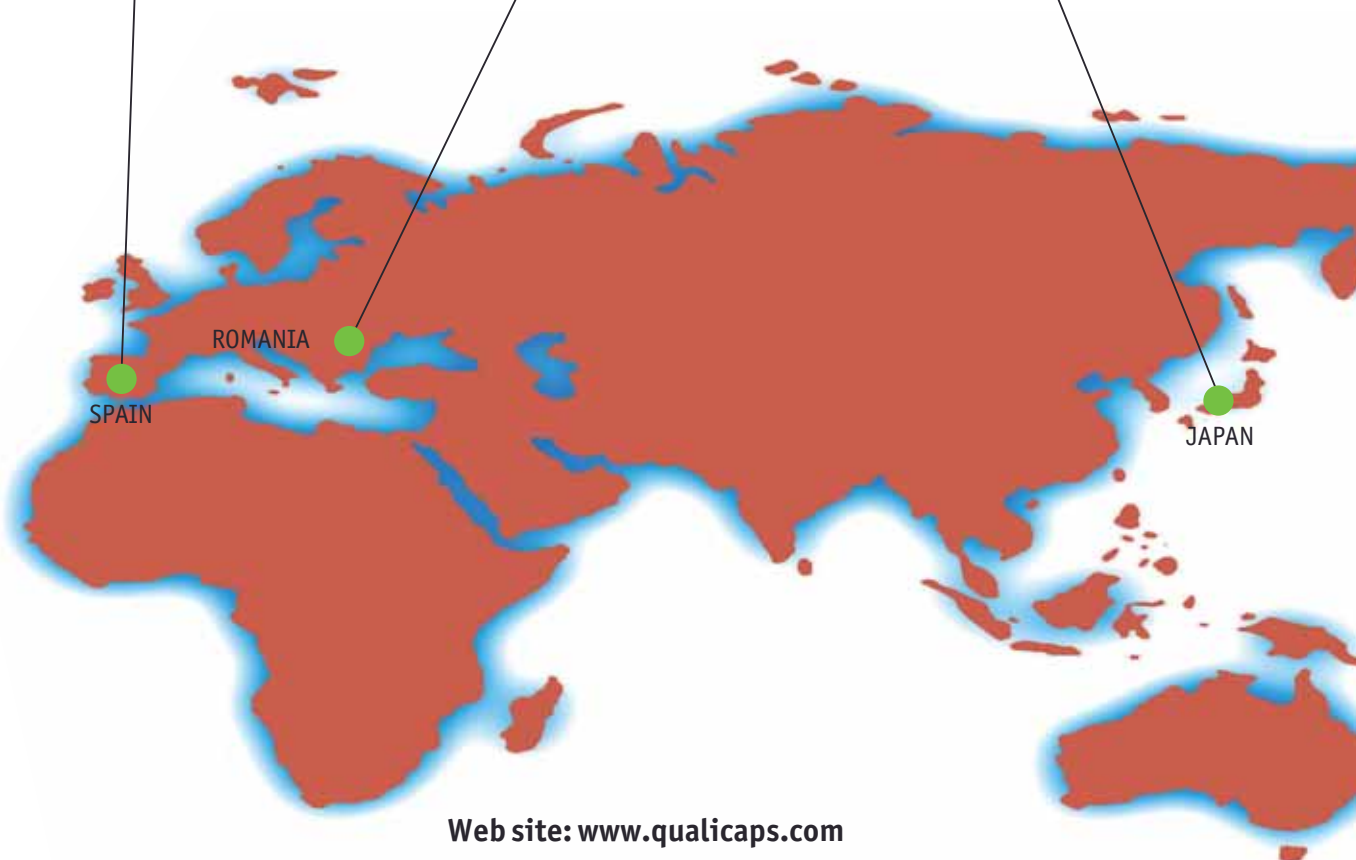
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2. QUALITY SYSTEMS

2.1 In-process Measurement and Control

2.2 Quality Auditing

2.3 Official Accreditations

QUALITY SYSTEMS

Qualicaps Europe S.A.U. and Qualicaps Romania S.R.L. capsules are produced using a continuous manufacturing process. Adherence to the published specifications are assured using Good Manufacturing Practices (GMP).

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

The quality auditing system is designed to maintain specified Acceptable Quality Levels (AQL).

The quality control system ensures that Qualicaps capsule manufacturing complies with current Good Manufacturing Practice (cGMP) and the norms of the International Quality Standard (ISO) organisation.

2.1 IN-PROCESS MEASUREMENT AND CONTROL

Statistical process controls are used during the manufacture of each batch. Capsules are checked during processing by a system of operator self-inspection that consists in taking regular random samples. In-process measurements, including dimensions of cap and body, moisture content and a check for visual quality and colour, are made to ensure conformance to specifications.

2.2 QUALITY AUDITING

The purpose of the quality audit is to provide a final verification that the in-process controls have been effective. Before the release of each batch, a thorough review is made of all process control documents and records to ensure that there was conformance to the in-process control and operator self-inspection procedures during manufacture. The final inspection of a capsule batch is based on the evaluation of a representative sample and includes controls for dimensional uniformity and visual quality attributes. Sampling and acceptance for this final inspection system is based on

the Acceptable Quality Level properties of each plan. Customers can be assured that capsules, which pass these tests, have an extremely high probability of conformance and therefore, an inherently high level of quality.

2.3 OFFICIAL ACCREDITATIONS



ISO 9001:2008 CERTIFICATE



ISO 14001:2004 CERTIFICATE



FDA (FOOD AND DRUG ADMINISTRATION) AUTHORISATION LETTER



QUALICAPS EUROPE, S.A.U.

- DMF 11090 for USA
- DMF 9896 for Canada
- ISO 9001 : 2008
- ISO 14001 : 2004

CERTIFICATE OF GMP COMPLIANCE



ISO 9001:2008 CERTIFICATE



QUALICAPS ROMANIA, SRL

- DMF 21632 for USA
- DMF 2008-109 for Canada
- GMP certification
- ISO 9001 : 2008

3. CAPSULE CHARACTERISTICS

3.1 Posilok® Capsule Design

3.2 Capsule Types

3.3 Capsule Sizes

3.4 Colour Selection

3.5 Capsule Print Types

CAPSULE CHARACTERISTICS

3.1 POSILOK® CAPSULE DESIGN

POSILOK® is the brand name for the capsule locking feature used by Qualicaps. This ensures that the contents are securely contained in the capsules. The feature has also been designed to give an 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 ensure good filling machine performance.

PRE-LOK®

Good 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, ensuring 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 presented to a filling device and dosed with material.

POSILOK®

After filling the two parts of the capsule are rejoined :

- The special design of the capsule locking profile fitted with air vents is to avoid overpressure during rejoining.
- This special desing helps further reduce the risk of reopening and helps to maintain a constant closed joined length, ensuring the optimum filling of all types of products.

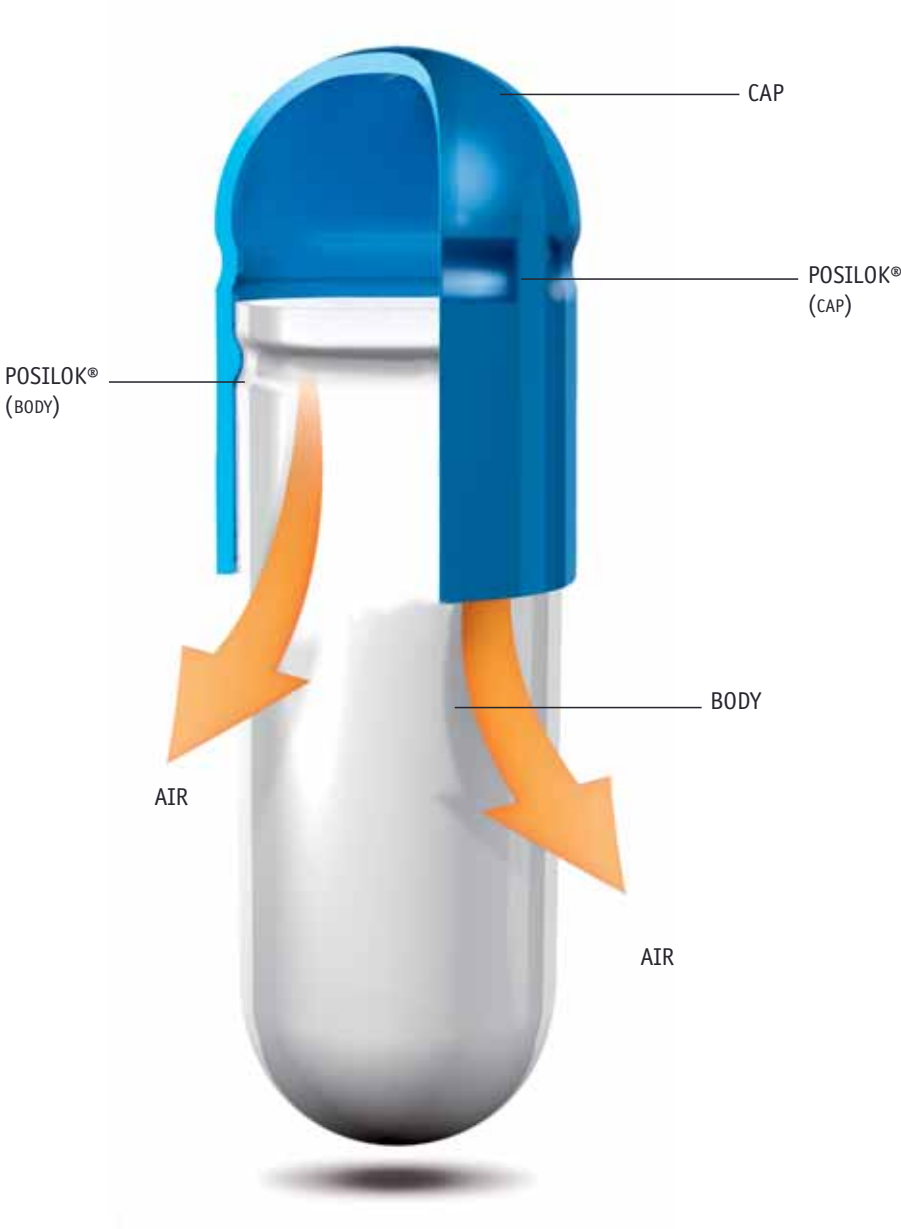
The POSILOK® locking feature enables the filling of different types of formulation such as:

- Powders
- Pellets
- Tablets
- Semi Solid Matrices
- Liquids

For liquid formulations, the HICAPSEAL 40/100 sealing machines, developed by Qualicaps, are available.

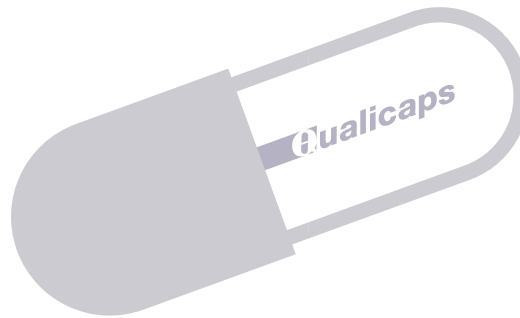
SECURE LOCKING

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 filling into blister packages, minimal product loss during packaging and no separation.



3.2 CAPSULE TYPES

The standard Qualicaps capsule is the POSILOK® Two-piece Gelatin Capsule with its positive mechanical lock made by indentations in the cap and body. The vented cap indentation allows air to escape when the capsule is closed on high speed filling machines. The capsule has also a PRE-LOK® feature to prevent separation of the empty cap and body prior to filling.



Other types of capsules are also available and described in this document:

PEG/Gelatin Capsule: This is a Two-piece Gelatin Capsule with Polyethylene Glycol that was specially developed to reduce the brittleness of the gelatin capsule film when exposed to hygroscopic formulations.

3.3 CAPSULE SIZES

Qualicaps capsules are available in sizes ranging from size 00 to 4.



Notes: - Other sizes may be available.
- Not in scale.

3.4 COLOUR SELECTION

Qualicaps manufactures capsules to customer colour specifications and can match existing formulations or colour appearances. Both transparent and opaque capsule colours are available.

The CAPSULECTOR, showing a representative sample of available capsule colours, has been specially developed to assist customers in the choice of colour combinations. It can be obtained from your Qualicaps representative.



3.5 CAPSULE PRINT TYPES

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

Four types of printing are available :

- **AXIAL-PRINT:** Axial printing 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. Your company name or logo can be twice as big with MAGNI-PRINT.
- **ROTOPRINT:** Rectified radial printing, almost 360° coverage gives the maximum printable area and legibility. Single ink colour.
- **ROTOCOLOR:** Rectified radial printing combines almost 360° coverage with different colours of ink on cap and body. The print choice that provides the greatest opportunities for creating an effective product identity.

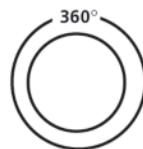
AXIAL-PRINT



MAGNI-PRINT



ROTOPRINT



ROTOCOLOR



* 360° printing may not be achieved for all logos.

Qualicaps Technical Service can assist customers with the design of their printing. Qualicaps produces artwork in the actual size that will appear on the capsule once the design has been selected.

Capsule Imprint

Qualicaps offers the perfect opportunity for product identification with capsules imprinted with information such as company name, product brand, dosage information or product identification code.

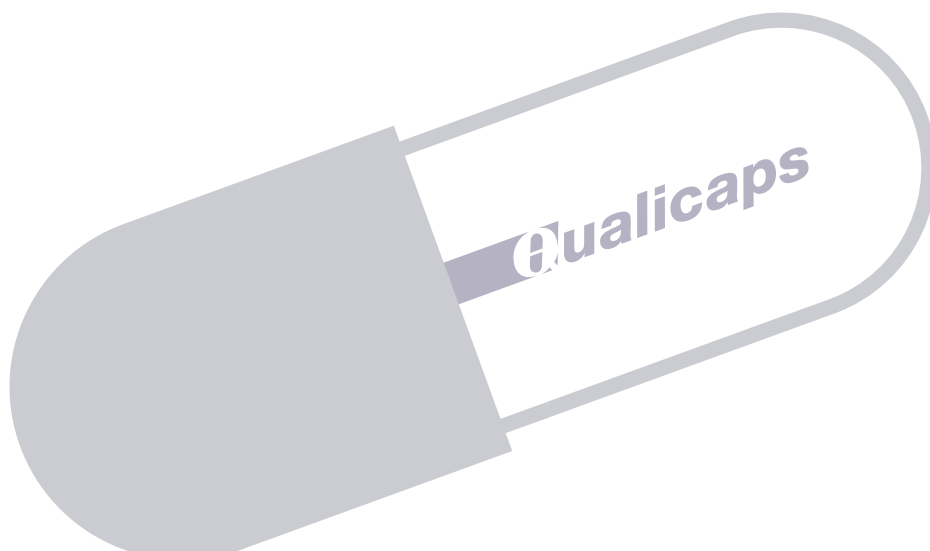
Qualicaps' imprinting options include:

- Axial (or linear) print with a single ink colour.
- Rotoprint radial printing with a single ink colour for maximum printable area and legibility.
- Rotocolor radial printing with a two-colour ink option for maximum printable area and legibility.

Qualicaps can assist customers with information regarding print feasibility of selected logos and print capabilities.

Print ink

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



4. CAPSULE SPECIFICATIONS

4.1 Raw Materials Specifications

4.2 Posilok® Capsule Specifications

4.3 Visual Quality

4.4 Print Quality

4.5 Chemical and Microbiological Specifications

CAPSULE SPECIFICATIONS

Qualicaps follows the latest editions of the European Pharmacopoeia and the USP/USNF for the raw materials specifications. On request, Qualicaps has the capability of using raw materials that meet Japanese legislation.

4.1 RAW MATERIALS SPECIFICATIONS

● Gelatin

The gelatin used is in compliance with the European Pharmacopoeia and the United States National Formulary.

The gelatin is supplied exclusively by member companies of the Gelatin Manufacturers of Europe (GME) Association and complies with the latest EMEA 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 EU Directives and when required with the requirements of the FDA.

The Qualicaps recommended list of colourants for pharmaceutical use, which takes into account regulatory needs and stability characteristics, is shown in the table.

Name	EEC No.	USA	C.I. No.
Sunset Yellow	E 110	FD&C Yellow No.6	15985
Allura Red	E 129	FD&C Red No.40	16035
Brilliant Blue	E 133	FD&C Blue No.1	42090
Titanium Dioxide	E 171	Titanium Dioxide	77891
Iron Oxide Black	E 172	Iron Oxide Black	77493
Iron Oxide Red	E 172	Iron Oxide Red	77491
Iron Oxide Yellow	E 172	Iron Oxide Yellow	77492

Some of above listed colourants are allowed for food supplement use under specific conditions.

● Purified water

The water used by Qualicaps is in compliance with the requirements of the European Pharmacopoeia, USP and JP.

● Additives

Sodium Lauryl Sulphate used as a wetting agent complies with the European Pharmacopoeia and USP/NF.

The Polyethylene Glycol used by Qualicaps is in compliance with the European Pharmacopoeia (Material only used for the manufacture of PEG/Gelatin 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 solvents used are covered by a guidance document, CPMP/ICH/283/95, issued by EMEA, which sets limits for the amounts that may remain in a finished product. The amounts of residual solvents that remain in the ink applied to a capsule comply with these limits by an order of magnitude. A certificate confirming this can be issued on request.

4.2 POSILOK[®] CAPSULE DIMENSIONS

Standard Size	00	0E	0	
Weight	Target weight (mg)	126	106	98
	Average weight limits (mg)	116-136	98-115	90-106
Capacity	Fill material powder (ml)	0.93	0.77	0.69
	Fill material liquid (ml)	0.84	0.69	0.62
	Total internal capsule volume (ml)	1.16	0.90	0.81
Outside diameter	Cap diameter (mm)	8.56	7.66	7.66
	Body diameter (mm)	8.21	7.36	7.36
	Tolerance (mm)	± 0.04	± 0.04	± 0.04
Length	Cap length (mm)	11.7	12.0	10.9
	Body length (mm)	20.4	20.9	18.6
	Tolerance (mm)	± 0.3	± 0.3	± 0.3
Closed joined length	Closed joined length (mm)	23.5	24.0	21.8
	Tolerance (mm)	± 0.3	± 0.3	± 0.3

The above specifications also apply to Qualicaps[®] PEG/Gelatin capsules.

● **Weight:** Capsules are manufactured by a dipping process. The weight of the individual capsules varies about a target value. Customers should determine tare weights for filling by testing samples from in-house batches. The average weights above are determined from the gross weight of samples of 100 capsules at the standard moisture content of 13.0 % to 16.0 % w/w. These values are not applicable to individual capsules.

● **Capacity:** Two-piece capsules can be filled with a range of materials with different physical properties: powders, granules, pellets and liquids. 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.

1E	1	2	3	4
83	76	63	50	40
76-90	70-82	58-68	46-54	37-43
0.56	0.50	0.37	0.28	0.21
0.50	0.45	0.33	0.25	0.19
0.64	0.59	0.45	0.33	0.25
6.95	6.95	6.38	5.85	5.34
6.65	6.65	6.08	5.60	5.07
± 0.04	± 0.04	± 0.04	± 0.04	± 0.04
10.6	9.7	8.9	7.9	7.2
18.4	16.7	15.3	13.5	12.4
± 0.3	± 0.3	± 0.3	± 0.3	± 0.3
21.2	19.5	17.8	15.8	14.5
± 0.3	± 0.3	± 0.3	± 0.3	± 0.3

● **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 filling machine conditions. This dimension should never be considered as an approval/rejection criteria.

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

● **Closed joined length*:** This value is given as a filling machine set-up recommendation and not as an approval/rejection criteria 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 length shorter, then the cap or body may be damaged and the locking mechanism may fail, if longer, they will come apart. We recommend that this value is given to packaging equipment manufacturers prior to making a decision on blister pocket specifications.

(*) Other sizes such as 2 regular, 2 elongated and 5 can be delivered under customer request.

4.3 VISUAL QUALITY

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

The visual quality of a capsule batch is determined using statistical sampling plans defined in Military Standard MIL-STD 105E.

The specifications are derived from the Military Standard MIL-STD 105E and assessed on a combined sample taken through the batch from $\sqrt{N} + 1$ cartons (N, is the total number of cartons in the controlled batch).

● AQL definitions and values

Acceptable Quality Level (AQL)

AQL as defined in MIL-STD-105E is the maximum percent defective that for the purpose of sampling inspection can be considered satisfactory as a process average.



Visual Quality Specifications	Capsule defect classification	AQL
	Major A	0.010 %
	Major B	0.040 %
	Minor	0.25 %

● Definition of visual defects

Visual defects are classified according to the following definitions:

Major A: Affects the performance of a capsule as a package for the final product or could contribute to a major filling problem.

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

HOLE	An irregular opening in the cap or body
SPLIT	A split in the film starting from the cap or body edge
CRACKED	A cap or body with many splits
UNCUT CAP/BODY	An untrimmed cap or body
FAILURE TO SEPARATE	Cap and body may not be separated properly
TRIMMING	A piece or the whole trimmed end of a cap or body inside a closed capsule
DOUBLE DIP	Extra thick cap due to being dipped twice
SHORT CAP	Cap length is 1 mm less than specified length
SHORT BODY	Body length is 0.4 mm less than specified length
JOINED IN LOCK	Capsule is in locked position
DOUBLE CAP	A capsule with an additional cap covering the body end
UNJOINED	A single cap or body
THIN SPOT (CAP SHOULDER)	A thin area in the cap shoulder which may rupture when the capsule is filled
MASHED	A mechanically damaged capsule that has been squashed flat
LONG CAP/BODY	Length of cap or body is 1 mm more than specified length
PINCHED	Cap or body is damaged in collets. Pinches > 3 mm are classified as a Major A defect
TELESCOPE	A closed capsule with a protruding piece of either cap or body produced by a double split

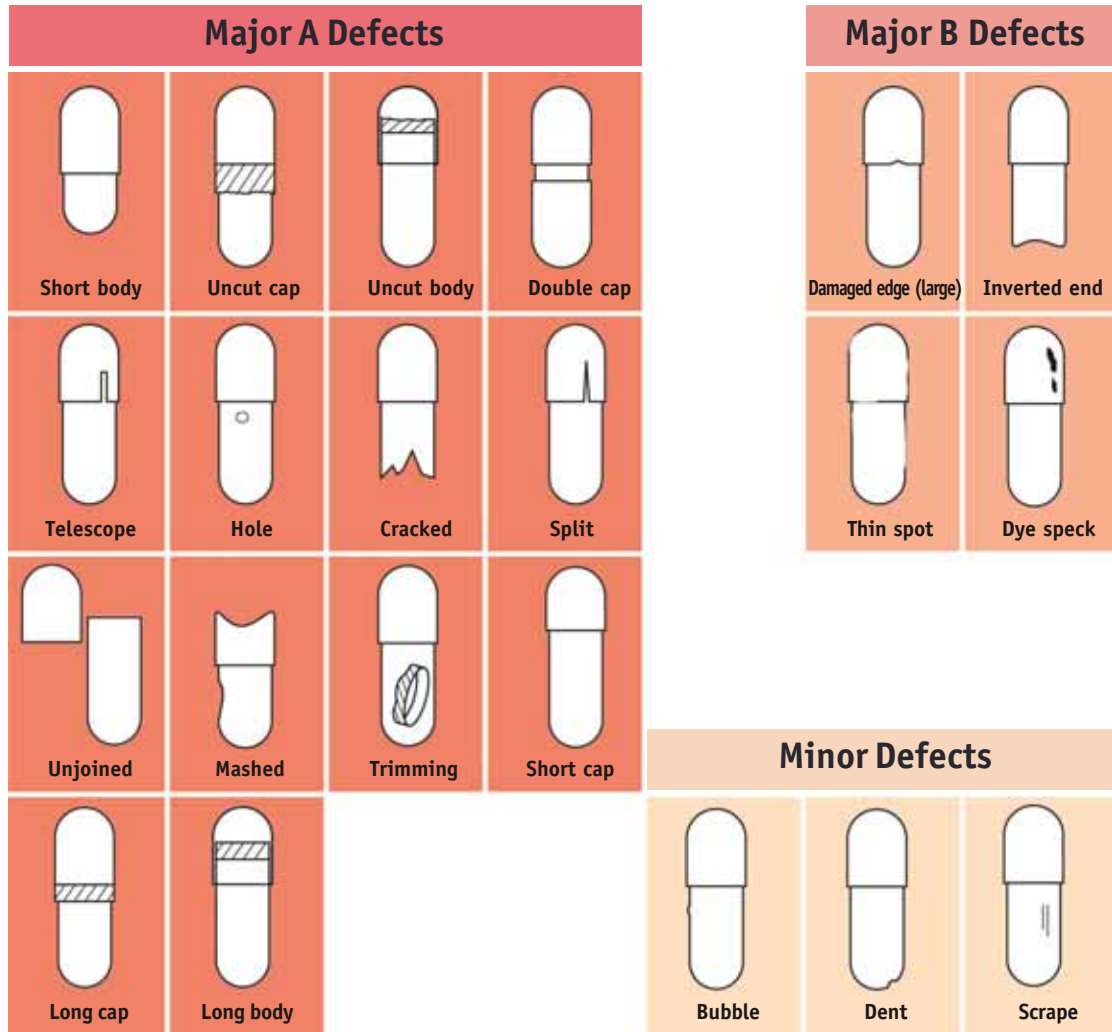
MAJOR B

LONG JOINED	Capsule not closed sufficiently to engage the prelock
DYE SPECK	A coloured spot of pigment aggregate different from the colour of cap or body
INVERTED END	A cap or body with the end pushed inwards
GREASE	Mould release aid spots on the inside of capsule
DAMAGED EDGE-LARGE	The edge of the cap is roughly trimmed. The imperfection is v shaped and > 1 mm into the specified length
SMALL PINCHED	Cap or body is damaged in collets. Pinches < 3 mm are classified as a Major B defect.
TURNED EDGE	Folded over edge on body cut line
THIN SPOT	A thin area in the cap or body wall which may rupture when the capsule is filled

MINOR

SCRAPE	A scratch mark on the surface of a cap or body
CRIMP	Cap or body is damaged in collets outside of the capsule > 3 mm
GREASE LIGHT	Small marks of grease
DENT	A depression formed in the end of cap or body. The dent is less than half of the diameter of the capsule part
DAMAGED EDGE SMALL	The edge of the cap is roughly trimmed. The imperfection is V shaped and < 1 mm into the specified length
BUBBLE	An air bubble in the cap or body wall which has a diameter greater than 0.4 mm
STARRED END	Multiple small imperfections located at the ends of the cap or body
CHIPS, TAILS, STRING	Small fragments of gelatine still attached or free within the capsule from different colour than cap or body
BLACK SPECK	A non contaminant black spot
DYE SPECK	A small pigment aggregate from the components of the cap or body

● Visual defects diagrams



4.4 PRINT QUALITY

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

The Print Quality of a capsule batch is determined using statistical sampling plans defined in the Military Standard MIL-STD-105E.

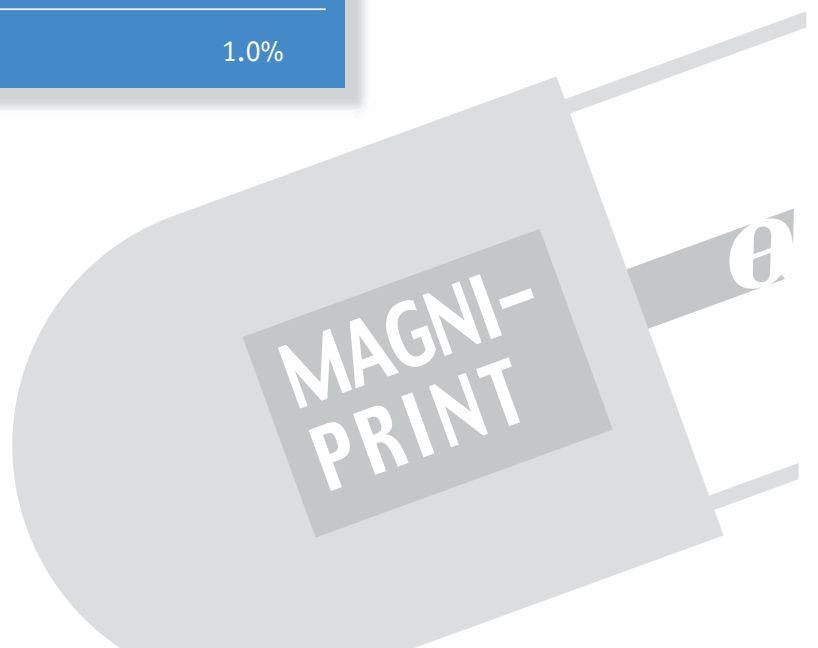
The specifications are derived from the Military Standard MIL-STD-105E and assessed on a combined sample taken through the batch from $\sqrt{N} + 1$ cartons (N, is the total number of cartons in the controlled batch).

● AQL definitions and values

Acceptable Quality Level (AQL)

AQL as defined in MIL-STD-105E is the maximum percent defective that for the purpose of sampling inspection can be considered satisfactory as a process average.

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



● 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:

Print illegible or prevents 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 (ILLEGIBLE PRINT)	MINOR
Unprinted	Ink Line/Spot	Ink Line/Spot
Incorrect logo	Misplaced Legend (off-register)	Misplaced Legend (off-register)
	Multiple Legends	Multiple Legends
	Partial Legend	Partial Legend
	Smudged Legend	Smudged Legend

Qualicaps

● Print defect descriptions and diagrams

MAJOR A : UNPRINTED



The entire legend is missing.

MAJOR B / MINOR : INK LINE / SPOT

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



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



An ink line or spot greater than 1 mm is a Minor defect.

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

The legends are not centred correctly about the cap cut edge of a closed capsule.





A capsule with a legend or legends having missing characters, which would result in misidentification, is a Major B defect.





A capsule with a legend with a part of a letter or logo missing, which is still identifiable, is a Minor defect.

MAJOR B / MINOR : MULTIPLE LEGENDS

	Legend printed more than once on the same capsule. Major B defect if the legend is illegible.
	Minor defect if the legend is still legible.



MAJOR B / MINOR : PARTIAL LEGEND

Part of the legend is missing.

	Major B defect when at least half of the legend is missing and it is illegible.
	Minor defect when parts of the legend are missing and it is still legible.

MAJOR B / MINOR : SMUDGED LEGEND

The legend is smudged or smeared.

	Major B defect when the legend is illegible.
	Minor defect when the legend is still legible.

4.5 CHEMICAL AND MICROBIOLOGICAL SPECIFICATIONS

● Chemical specifications

Items	Specification
Identification of Gelatin	Meets test
Odour	Meets test
Moisture Content/Loss on Drying (LOD)	13.0 - 16.0 %
Identification of Organic Colourants	Meets test
Identification of Titanium Dioxide	Meets test
Identification of Iron Oxides	Meets test
Disintegration	Less than 15 min
Sulphated Ash	< 3.0 % for transparent capsules < 9.0 % for opaque capsules
Arsenic	< 1 ppm
Heavy Metal	< 30 ppm
Lubricant Content	< 0.5 %
Sulphur Dioxide	< 0.1 %
Identification of Sodium Lauryl Sulphate	Meets test

● Microbiological specifications

Items	Specification
Total Aerobic Microbial Count	10^3 cfu/g
<i>Salmonella</i>	Absence in 10 g
<i>Escherichia coli</i>	Absence in 1 g
<i>Staphylococcus aureus</i>	Absence in 1 g
<i>Pseudomonas aeruginosa</i>	Absence in 1 g
Total Yeast & Mould Count	10^2 cfu/g
Bile-Tolerant Gram-Negative Bacteria	Absence in 1 g

5. CAPSULE TECHNICAL INFORMATION

5.1 Packaging

5.2 Storage

5.3 Capsule Filling

CAPSULE TECHNICAL INFORMATION

5.1 PACKAGING

● Cartons

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

1. An inner liner made of a laminate of pharmaceutical-grade materials : polyester / polyethylene/ aluminium foil. This is heat-sealed after the capsules have been packed into it to give a container with minimal moisture transfer properties.
2. A cuboid cardboard carton of standard dimensions. This protects the inner liner during transportation.

Capsule size	Capsules per carton in 000's	Net Weight (kg*)	Gross Weight (kg*)
00	75	8.5 - 10.5	10.5 - 12.5
0E	75	7.0 - 9.0	9.0 - 11.0
0	100	9.0 - 11.0	11.0 - 13.0
1E	120	9.0 - 11.0	11.0 - 13.0
1	135	9.5 - 11.0	11.5 - 13.0
2	175	10.0 - 12.0	12.0 - 14.0
3	225	10.5 - 12.0	12.5 - 14.0
4	300	11.0 - 13.0	13.0 - 15.0

Cartons for sizes 00-4: 60 cm long x 40 cm wide x 75 cm high

* weights are given to the nearest 0.5 kg



● Pallets

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

The standard pallet assembly consists of four or six 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.

● Special protection

For shipments to countries which have extreme climatic conditions, a special protection is used instead of the wrapping used normally.

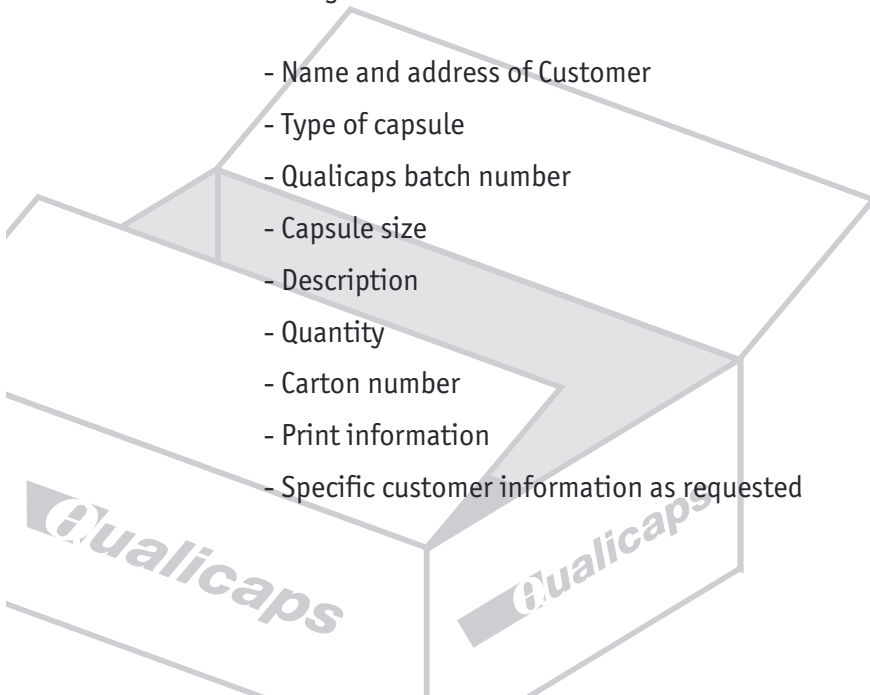
This protection, called a TROP-PACK, consists of an outer cardboard cover combined with expanded polystyrene sheets placed between the cardboard cartons and the cover.

This provides a barrier to avoid damage caused by temperature fluctuations and physical damage during transit.

● Identification

Each carton and/or pallet is identified with a Qualicaps label containing the following data :

- Name and address of Customer
- Type of capsule
- Qualicaps batch number
- Capsule size
- Description
- Quantity
- Carton number
- Print information
- Specific customer information as requested



5.2 STORAGE

It is essential to read and understand the following information in order to ensure that Qualicaps Two-piece Gelatin Capsules maintain their quality during the period between manufacture and filling.

● Moisture content

Qualicaps Two-piece Gelatin Capsules are manufactured with a moisture content between 13.0 and 16.0 %^{w/w} and should be maintained at this level for optimum filling performance.

Capsule dimensions are directly related to the moisture content. Certain elementary precautions are required to prevent undue moisture gain or loss. The moisture content varies in relationship to the relative humidity of the air to which they are exposed. If the moisture content rises significantly, the capsules will swell and may become soft and sticky. If the moisture content falls too low, the capsules will shrink and may become brittle. Either way, there will be some deterioration in the capsule properties and difficulties may occur during filling.

● Transportation

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

For supplies to countries that have extreme climatic conditions, capsules are further protected by Qualicaps TROP-PACK packaging. This is designed to protect the capsules from the sudden temperature changes and adverse conditions during transportation. Pallets should not be left standing in the open or exposed to direct sunlight during transit.

● Warehousing

The ideal condition for the storage of capsules is at a temperature between 15°C and 30°C. Capsules stored correctly in Qualicaps packaging will give the optimum performance in production. Care should be taken to maintain them at an even temperature. Any relatively even temperature between 5°C and 35°C could be used provided that it does not fluctuate too rapidly. Storage near heat sources in warehouses should be avoided, e. g. radiators, heaters or sunlight shining through windows. These will cause localised heating and moisture migration within the capsules with corresponding dimensional changes that will result in poor performance on the filling machine.

● Capsule shelf life

Qualicaps Capsules stored correctly in our packaging will have a satisfactory 3 year shelf-life. The temperature of the environment should not exceed the recommended limits to avoid water migration inside the vapour-proof liners leading to possible capsule wall distortions.

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

Qualicaps packaging is designed to maintain the quality of the empty capsule between manufacturing and filling. If the recommendations given in this section are followed, you will achieve the benefits that the Two-piece Gelatin Capsule gives to the user.

● Incoming quality control and sampling

The integrity of the packaging is important in order to maintain 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 recommended that when taking a sample the minimum size cut in the liner is made. It should be reclosed in the best manner possible, preferably by heat sealing, which maintains 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 close the cut.

5.3 CAPSULE FILLING

● Filling area condition

The moisture content of capsules is directly related to the relative humidity of air to which they are exposed. Capsules are removed from their packaging and exposed during the filling process. Particular care needs to be taken to ensure their optimum performance especially with high speed filling machines.

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% w/w. Capsules can be filled outside these conditions if sufficient care is taken.

The 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 sited in a controlled area but the conditioning 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

Qualicaps capsules are manufactured with the greatest care to ensure optimum running on the 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 recommended that the bores in the bushes on the filling machine should be checked to ensure that they are within the machine manufacturer's specifications (check these with the machine manufacturer or your Qualicaps technical coordinator).

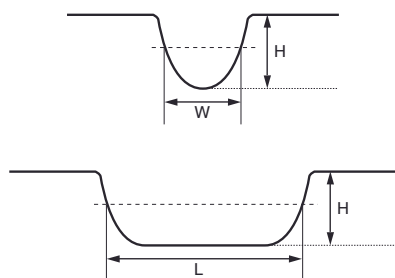
Care should be taken to reclose the capsules to the correct closed joined length after filling. If the capsules are overclosed, faults will be caused due to distortion of the shells with the possibility of cracking or splitting and possible reopening. If the capsules are underclosed, due to poor machine settings or if they are over filled with product, they will come apart causing problems during packaging.

● Blister packaging

The chart below gives the recommended minimum dimensions for the die roll cavities for the 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.

Minimum Die Roll Cavity Dimensions (mm)

	H	L	W
00	9.10	25.0	9.80
0E	8.20	25.1	8.90
0	8.10	22.8	8.80
1E	7.50	22.2	8.20
1	7.40	20.5	8.10
2	6.90	18.8	7.60
3	6.30	16.8	7.00
4	5.80	15.5	6.50
5	5.40	12.4	6.10



- 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)

6. ADDITIONAL INFORMATION

6.1 Other Products

6.1 OTHER PRODUCTS

Qualicaps Group provides QUALI-V® cellulose capsules with a low moisture content, an outstanding dissolution profile and improved mechanical properties. In addition, Qualicaps Group develops and supplies a full range of equipment for the pharmaceutical industry.

- 1 *Capsule Filling Machines for Laboratories.*
- 2 *Capsule Filling Machines for Powders, Granules, Tablets and Liquids.*
- 3 *Hard Capsule Sealing Machines.*
- 4 *Weight Inspection Machines for Capsules and Tablets.*
- 5 *Visual Inspection Machines for Capsules and Tablets.*
- 6 *Tablet Imprinting Machines.*



1 **LIQFIL Super 5**



2 LIQFIL Super 40



2 LIQFIL Super 80/150



3 HICAPSEAL 40/100



4 CWI 40/90/150



5 CES 50/100/150



6 IS 500

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