

50 STEPS FOR SUCCESS IN MANUFACTURING EMPTY HARD GELATIN CAPSULES FOR PHARMACEUTICAL USE

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This article is solely written to guide, educate and train regulatory community at large.

This article is based self experience of 25 years of the author

1.0 Introduction:

The empty hard gelatin capsules are very sensitive packaging material for the drug products. The sourcing of the same requires great skills and vigilance. The followings are the most critical parameters which need to be checked before placing order:

1. What is the source of gelatin? Is it GMP Compliant or Not?
2. If Halal, Kosher, TSE and BSE certificates are available?
3. If the quality control/ quality assurance facilities are adequate
4. If all the sizes and all types of printing facility available?
5. If inspection, packaging, storage and transportation of the product is adequate to retain the quality of the capsules
6. If the product available readily

This article is written to guide Empty Hard gelatin capsule manufacturers the products meeting all compendia requirements and the specific requirements of the buyers.

Check Points:

A	Check Gelatin Source
1	Check if E Gelatin confirming to USP,B.P. or E.P Grade
2	Check it Gelatin confirming to BSE, TSE and FMD is used
3	Check it the supplier has filed DMF Type III with US FDA
4	Check if Halal and Kosher Certification is available for gelatin
4	Check if by chance Commercial Grade, Industrial Grade or Food Grade gelatin has been employed for capsule manufacturing. Such products are not allowed for Empty hard gelatin capsules
6	Check if the Gelatin source is well reputed:

	Rousselot (www.rousselot.com) ,Bcagelatin (www.bbcagroup.com) Narmada gelatin (India)
7	Check if Colors and Pigments are from : Colorcon , Kris , Hombitan
8	Ensure Halal Certification for Raw gelatin is available (Explanation: Gelatin shall be obtained "lawful" or "permitted" animals hide. Following sources and practices are prohibited for sourcing gelatin Swine/pork and its by-products, Animals improperly slaughtered or dead before slaughtering Animals killed in the name of anyone other than ALLAH (God),Alcohol and intoxicants ,Carnivorous animals, birds of prey and land animals without external ears ,Blood and blood by-products)
9	Ensure Kosher Certification for Gelatin available: (Explanation: This certification is less stringent than Halal. It only prohibits the gelatin made from skin of swine. All other sources are permitted. It does not require killing the animals in the name of Allah. This certificate is required mainly by Jews
10	The gelatin shall be good enough to make the surface of the capsule smooth , evenness of the thickness and smooth incision
B	Check Quality Control Facility is up-to-date
11	Well equipped QC Laboratory
12	Intelligent disintegration tester
13	Gas chromatograph
14	Microware digestion device
15	Atomic absorption
16	Graphite oven,
17	Chlorohydrins and Ethylene oxide detector
18	Fast Measure Moisture Meter
19	Glass Constant temperature water bath
20	UV Spectrophotometer
21	Dedicated Micro Lab
22	Dedicated Physiochemical testing Wet lab
23	Special facility for testing Packaging Materials
D	Check if Quality Assurance Facility is up-to-date
24	The total manufacturing process from receiving raw materials to packaging is strictly controlled by our Q.A department at every step. With the help of most advanced analyzer, measuring apparatus and bloom strength testing machine
25	These capsules are manufactured under controlled continuous production environments under strict GMP guidelines laid down by World Health Organization.
26	Samples are regularly tested for physical defect, length, dome, double, wall thickness, moisture content, color shades, weight variation and other relevant parameters.
27	We have extremely well documented Quality Assurance programs and such rigorous control at every stage of production and packing enables us to deliver Zero Defect capsules to our customers
28	A very efficient and high capacity Genset shall be available to ensure uninterrupted supply of electricity for processing and storage of Capsule.

29	Quality built into the process from vendor site to buyer site. WE audit all our vendors and ensure safe delivery to all our buyers site
30	All manufacturing processes and quality management procedures are qualified and validated in compliance with cGMP and other international standards.
31	Also all batch records on the capsule products, not to speak of the records on the raw materials and Excipients, are produced and managed through SAP-R/3, and they can be tracked anytime anywhere within the plant.
32	Strict process monitoring and Quality inspection
33	Strict control on viscosity of the gelatin solution
34	Uniformity in capsule colors
35	Precise printing on capsules.
36	Strict control on humidity and temperature
C	Check Detailed and all requisite Specifications for Finished products is in place
37	Pesticide Residues Shall be absent
38	Gelatin used for capsules shall be preservative free
39	Viscosity $\geq 60 \text{mm}^2/\text{s}$
40	Arsenic $\leq 1 \text{ppm}$
41	Ash for transparent capsules $\leq 2.0\%$
42	Ash for translucent capsules $\leq 3.0\% \sim 4.0\%$
43	Ash for opaque capsules $\leq 5.0\%$
44	Degree Of Tightness $\leq 2/10$
45	Brittle $\leq 15/50$
46	Disintegration $\leq 10 \text{min}$
47	Heavy Metals $\leq 50 \text{ppm}$
48	Chlorohydrins shall be absent
49	Loss On Drying 12.5% ~ 17.5%
50	Suitable for Dry Powder/Granules filling
51	Trachoma Does not allowed
52	Uniform color and glossy.
53	Separated incisions not allowed
54	Significant deformation not allowed
55	Bubbles more than 0.3mm in diameter not allowed, diameter 0.1mm~0.3mm<1pcs
56	Plug hack not allowed
57	Clear wrinkle not allowed
58	Oil dirt not allowed
59	Bursting Strength Suitable
60	Lose tight degree Suitable
61	Clear shrunken and thin head not allow.
62	Black spots more than 0.3mm in diameter not allowed, diameter 0.1mm~0.3mm<1pcs.
63	There shall be no intra batch and batch to batch variation in color of the capsules
64	The incision is very smooth to prevent the small medicinal powder leaking out of the depart

E	Check if the following Quality Certifications are available
65	US DMF / CEP filed for Capsules
66	BSE & TSE Free and FMD Free Certification
67	Ethylene oxide free
68	Halal certification
69	Kosher Certificate
70	Shelf Life certification of 5 Years
71	100 % Derivation from Skin Certification
72	INVIMA certified
73	Preservatives Free Gelatin Certification
74	Pesticide Free Gelatin and other raw materials
75	ISO9001:2000 Certificate
76	GMO Free Raw materials
77	Dust Free Class 100,000 Environment
78	Humidity and Temperature certification for Storage
79	Good Packaging and Storage Certificate
80	cGMP Compliance Certificate
81	COA for Gelatin
82	COA for Other Ingredients as per EP/BP/USP
83	9 CFR 94.18 (a) Compliance certificate
84	Product Release For sale by QA
85	No Conviction Certificate issued by FDA for Exports
86	COPP (Certificate of Pharmaceutical products) issued by State FDA (for Exports)
87	Free Sale Certificate
88	Certificate for Food colors used for Printing and type of printing (linear, circular, spiral, oriented, Non-oriented etc)
G	Check if the Packaging System is robust
89	PE bag/ Aluminum foil bag+ Styrofoam board lined in carton Cartons may be locked type and separated type Custom packaging Services also available The packaging shall be suitable for heat and cold shocks.
H	Check that Storage for Gelatin capsules are appropriate
90	Temperature: between 15° C to 25° C Humidity: between 35% and 65%
91	Be sure not to place heavy loads on top of the capsules Store carefully to prevent distortion of the product (delicate)Keep them away from direct contact with sunlight, hot water and high temperatures
92	They are stored in a well-sealed original package; Cartons are stored on pallets (right side up) in a well protected area
93	The finished capsules are stored at 22°C (Range 15 to 25 C) and 50% (Range 35 to 60 %) relative humidity.
94	Heat sources such as space heaters or sunlight through windows are avoided. It is ensured that steam pipe or incandescent electric lamps. if any is at least one

	meter away from steam pipes or
F	Check if any of the following Advanced Features are incorporated:
95	Facility to choose a wide range of colors
96	Facility for precise control of temperature and humidity using DATA AIRE control
97	SMSR (Single machine Single Room) Concept,
	Moisture Content during Production and Storage using DAHU (Dedicated AHU System)
98	The hard gelatin capsules are processed in Pharmaceutical Companies for filling drugs. The capsules must ensure smoother filling, higher filling rate and low rejections
99	Linear printing, Circular printing or Customized as per need. Printing ink produced by British Colorcon

Summary: Manufacturing empty hard gelatin capsules is not easy. The capsules are very delicate products. Both science and art is involved in capsule manufacturing. It is advised the product shall be sourced from cGMP Compliant and well managed manufacturers.

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