The design and operation of a facility for filling hard shell gelatin capsules

Graham C. COLE

Summary

Hard Shell Gelatin Capsules are a very popular and convenient method of administrating drugs to patients for conventional dosages and more sophisticated regimes such as sustained release. The shells can be filled at high speed, they provide ready identification, are easy and pleasant to take by masking bitter tasting drugs and are robust.

There are also advantages in developing a capsule product as opposed to a tablet, for the formulator and the company filling the shells. (1) Many combinations of products can be filled (*Figure 1*). Some processes used to prepare the product can be complex, for example extrusion and spheronisation and it is necessary to consider this multiciplicity in the design and operation of the manufacturing operation.

Current Good Manufacturing Practice (cGMP) and the demands of the regulatory authorities world-wide requires greater care in the design of manufacturing facilities, the selection of materials used in their construction, their layout, the equipment used in the preparation of the materials to be filled and the filling operation itself. This paper will present some ideas and suggestions based on cGMP in three areas:

- the design and layout of the building,
- the evaluation and selection of equipment,
- validation.

The higher standards that are demanded can result in higher costs, however by careful design these costs can be reduced and in many cases eliminated completely.

Validation is an extra cost which must be incorporated into the overheads and whether an outside consultant is used or internal resources are used, it still has to be met. Estimates of cost range from 2-3 percent up to 15 percent of the total installed capital cost of the plant and equipment. The Food & Drug Administration (FDA) (USA) takes the view that if it hasn't been written down then it hasn't been done !

Whether the project is a new grassroot facility or refurbishment of an old building or area, then validation considerations must be taken on board by the design team from day one.

In each section only the production methods, the facility and the equipment required for powder filling operations will be evaluated.

About the author

Graham Cole is a chemical engineer with over 35 years experience in the Pharmaceutical Industry. He has a degree in technology with the Open University, is a Fellow of the Institution of Chemical Engineers of Great Britain and is a Chartered Engineer.

He entered Glaxo Laboratories as a Laboratory Technician in 1955 leaving in 1961 to join Aspro-Nicholas Process Development group where he became Manufacturing Manager. He joined Merck Sharp and Dohme in 1966 where he was responsible for process development, process automation, equipment evaluation and facility design. In particular, he introduced many of Merck's capsule filling processes into facilities in Europe. Latterly he was with Davy McKee (now part of Kvaerner Process), a pharmaceutical engineering contractor and now has his own consultancy which started in 1991. He has published many articles and papers on solid dosage form development and published a book on Pharmaceutical Production Facilities (now in its second edition). He has also contributed to books on Hard Capsules (their development and technology) and Pharmaceutical Coating Technology.

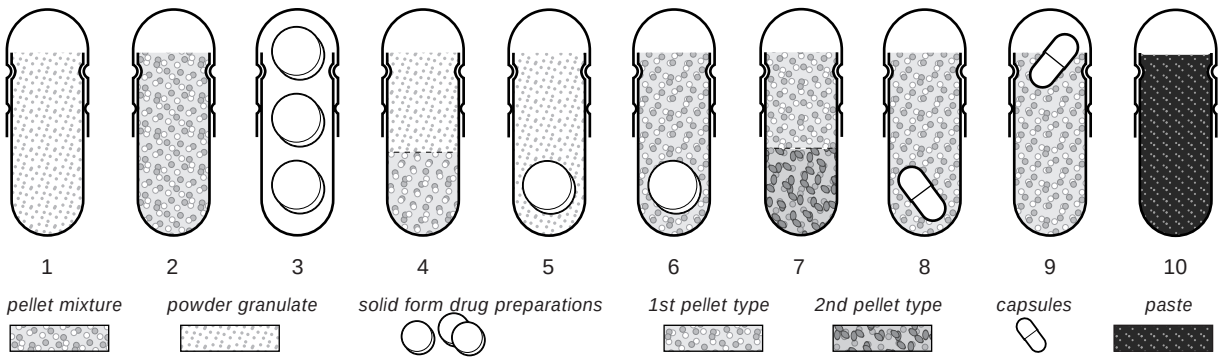

Figure 1. Various combinations of different drug formulations in capsules.

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1.0. Facility design and equipment requirements

There are many different products that can be filled into hard shell capsules, ranging from a single powder substance, through mixtures of powders to pellets and tablets and combinations of any of these. Powder filling only will be considered here and it is assumed that capsules will be available ready printed.

In the development and implimentation of any project there are a number of objectives that must be addressed.

a. What type of products are to be handled? Are they highly potent? Can they cause allergic reactions in the operators? Are they mutagenic? – to name but a few.

Current Good Manufacturing practice suggests there are two overriding considerations that take precedence.

These are:

- total containment of the product within a closed system,
- providing a barrier between the product and the operator i.e. total protection.

b. Are these products beta-lactams eg penicillin?

If this is the case then a separate manufacturing facility must be designed.

c. What quantities and mix of products are required?

There may be relatively small quantities of a number of products required rather than large quantities of individual products. In one case, flexibility of the operation is the main objective requiring a multiplexity of services whereas a single dedicated production line can save on materials handling, personnel, and special conditions (protection from light and oxygen).

Some products require complex processing operations to modify the availability of the drug in the patient. For example pellets provide a mechanism to sustain the release of the drug over long periods. To produce and fill both the active and placebo pellets into capsules requires both good formulation and efficient unit operations. The filling of thixotropic substances may also be an option.

The design and operation of a facility which includes these manufacturing operations is not covered in detail in this paper, but many of the principles are, and it is important to be aware that in the design of any operation changes may occur in the future which should be considered at the conceptual stage.

A five year forecast of what requirements will be needed as there may be new capsule products coming through from Research and Development and some older products may be declining in volume. These factors should be assessed in the design of a new facility, the refurbishment of an existing operation or in selection of new equipment for development and production purposes.

1.1. Process concept

To design the facility requires an understanding of the overall capsule filling process. The building and building services provide the envelope around the process and the process operation must be performed in areas designed to conform to current Good Manufacturing Practices (cGMP). It will also need a Validation Programme.

For any capsule filling operation there are four essential requirements:

- a supply of empty shells,
- a supply of powder,
- the process equipment,
- a building to house the equipment, raw materials and finished product.

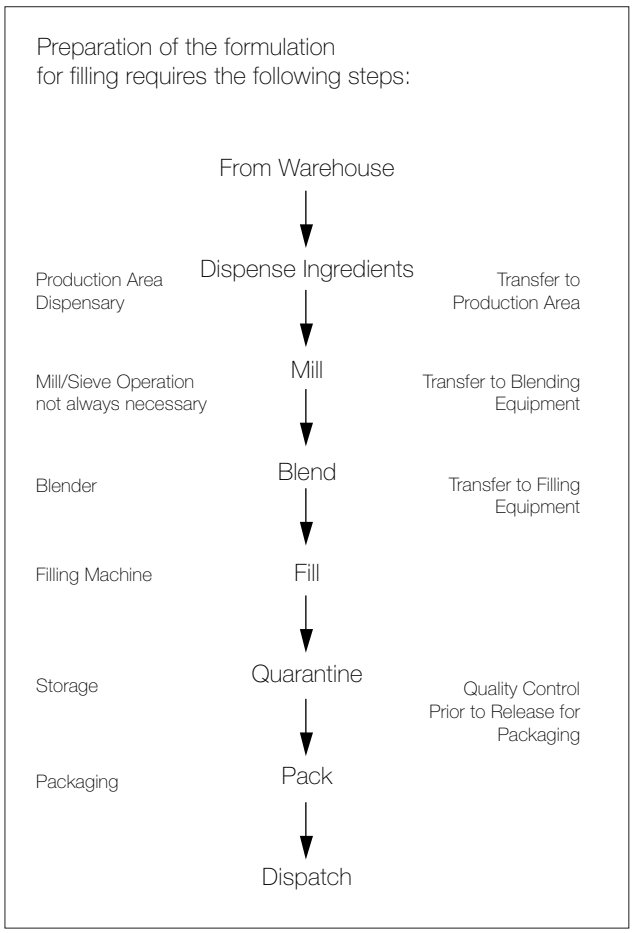

Figure 2. Flow diagram for capsule filling.

The building may be an adjunct to an existing operation and the site will provide ancillary personnel services, the necessary process services (electricity, heating, HVAC etc) and control laboratories. Where this is not the case (eg green field sites) then an allowance must be made for these requirements.

A simple flow diagram is shown in *Figure 2*. All or some of these operations take place whether in a laboratory or on a production scale.

For efficient and accurate operations the following stages must be assessed.

- storage of empty and filled capsules - warehousing,
- raw material dispensing,
- process operations, milling, mixing and filling,
- packaging.

1.2. Warehousing

In all companies the size of the inventory is critical to the efficient operation of any plant. More and more companies are employing Just-in-Time (JIT) concepts to minimise stock levels and ensure that First in First Out (FIFO) principles apply. A typical flow diagram is shown in *Figure 3*.

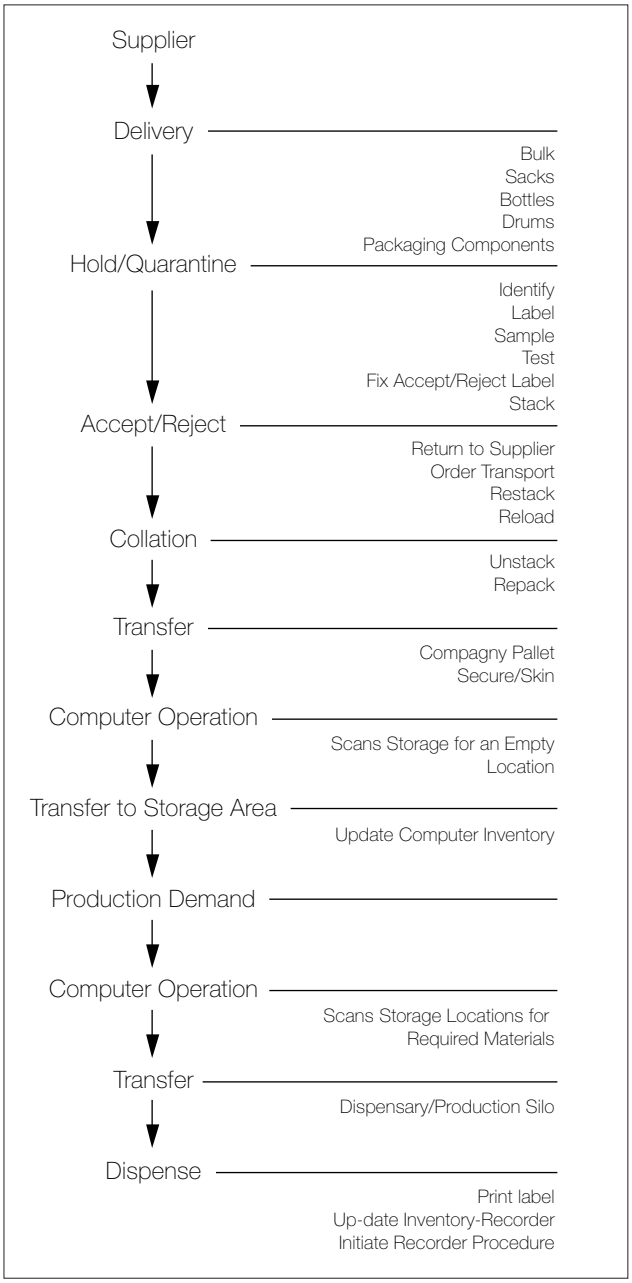

Figure 3. Flow diagram for storage of materials.

Capsules are sensitive to extremes of temperature and humidity which depend on the local environmental conditions. Storage areas should be designed to be environmentally controlled to between 10° C and 30° C and 30 per cent and 70 per cent relative humidity. Providing the capsules are in sealed containers, then damage can only occur if the warehouse has windows which permit sun to shine on the containers, producing localised overheating. Similarly if containers are placed close to a heating source within the plant, then distortion of the shell body and cap will occur. If a machine is operating at 90,000 filled capsules per hour (cph) then one damaged capsule in 10,000 causes a problem on the filling machine or the presorter every six to seven minutes.

Capsules are supplied in containers ranging from 50,000 for size 000 to 500,00 for size 5. The warehouse will need to allocate sufficient storage locations with adequate capacity for the number of products produced per month and reserve storage depending on what JIT rules exist. (Each storage location generally will hold four containers and depending on the size of capsule, this represents 20,000 (size 000) to 2,000,000 for size five.

In addition storage space must be available for raw materials and finished stock.

The simplest way of handling all these requirements is by installing a computer controlled Materials Management System. This records incoming goods, allocates location, and notifies internal departments of the arrival of these goods. The status

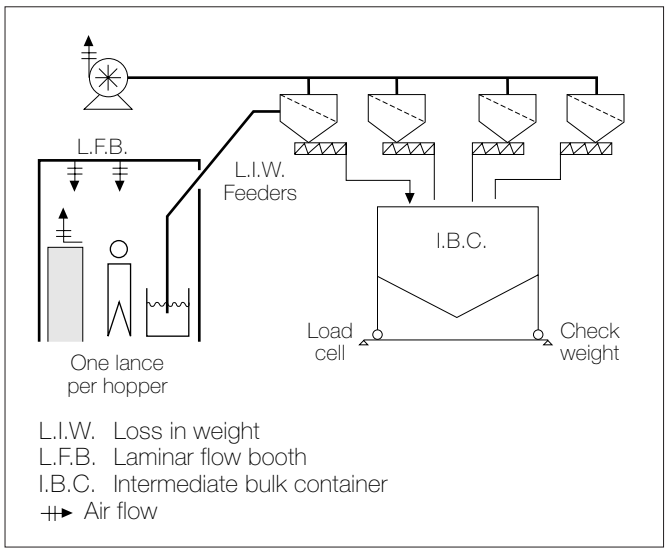

Figure 4. Schematic of a pharmaceutical dispensary.

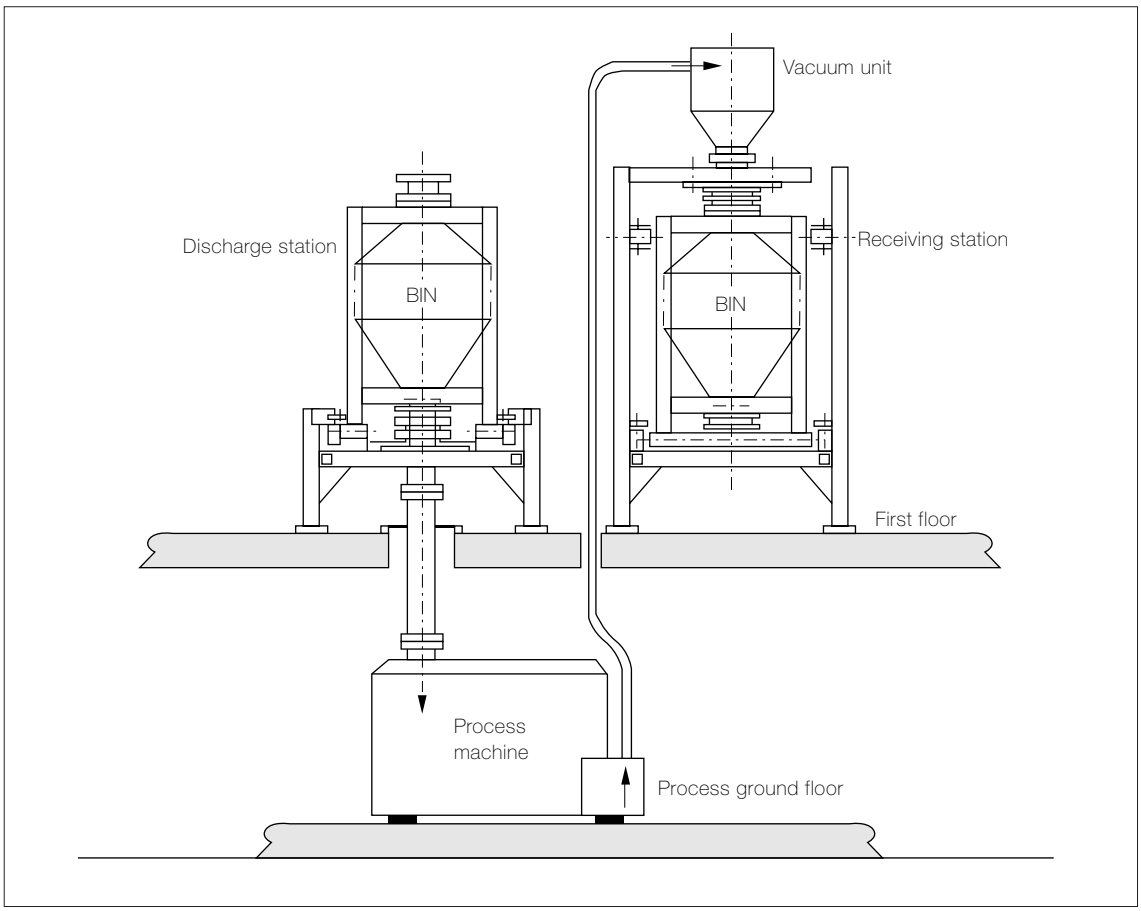

Figure 5. Automated materials handling.

of the material can be controlled using the computer and with limited personnel access the Quality Control Department can provide means of quarantining the materials until they are passed for production use or sale. Bar codes are now widely used to identify products.

1.3. Dispensary

A schematic example is shown in *Figure 4*.

The size and equipment required will depend on the scale of the operation and the nature of the materials being dispensed.

All balances will be selected on the basis of their sensitivity and range of weights required. For example:

Balance 1	0 - 1.0 kg	(sensitivity 0.01 mg)
Balance 2	0-10 kg	(sensitivity 500 mg)
Balance 3	0-50 kg	(sensitivity 1.0 g)

In some cases a floor balance may be installed for larger quantities up to 200 kg. It should be remembered that the cost of balances increases with their sensitivity. These balances will need to be located in cubicles in the dispensary, so that there is no danger of cross-contamination and different products can be weighed out simultaneously. An area should be provided for the short term storage requirements of materials used in large quantities and an adjacent area should be provided for materials used in small quantities ie colours and surfactants.

Each cubicle should be equipped with laminar air flow to ensure maximum protection for the operator, minimise dust contamination of the surrounding area and cross contamination.

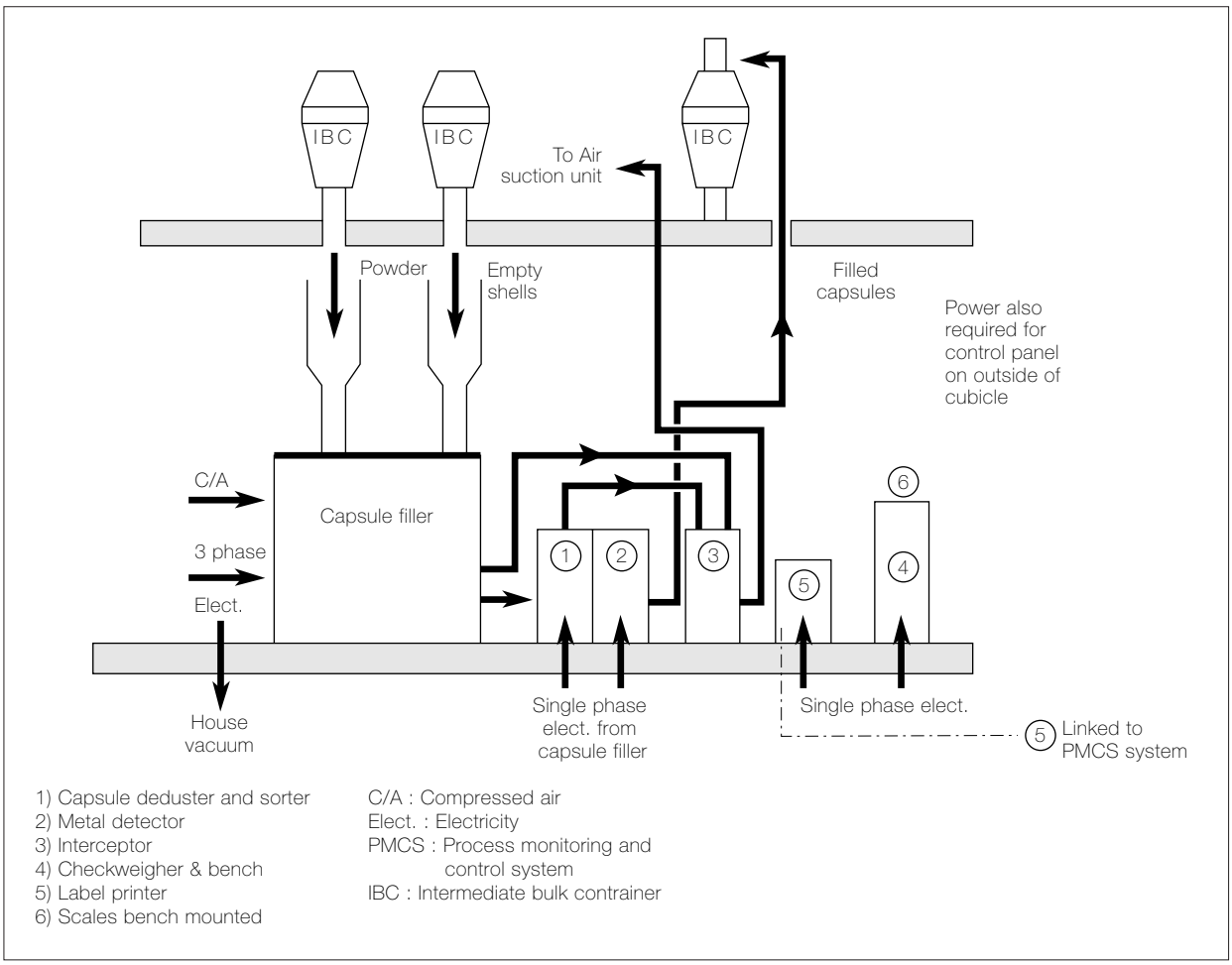

Figure 6. Capsule filling cubicle.

Each dispensary should be equipped with suitable dust masks, air supplied suits, safety showers and eye wash stations, to ensure the maximum safe handling of the materials. A carefully designed Heating, Ventilating and Air Conditioning (HVAC) and dust extraction system is a major requirement.

1.4. Process

The next stage in the material handling procedure is to transfer the batch of raw materials to the production area for preparation of the powder mix ready for capsule filling. Two unit operations may be necessary here. The objective is to produce a homogeneous free flowing powder mix. This may require pretreatment of one or all of the ingredients and it may be necessary to mill or sieve these materials to produce a uniform particle size. The selection of the milling and sieving equipment will depend on the required physical specifications of the material. Some material is supplied in specific size fractions that only necessitates breaking down the agglomerates. On the other hand, some material such as the active, may need to be milled to produce material in a specific size range say, 0-5 µm for optimum therapeutic activity. Here a fluid energy mill will be required.

The layout of the process area will depend on the material handling concept. For simple manual transfer (using Bins and Scoops) each piece of equipment is operated on a stand alone basis. If pneumatic transfer is used for an automatic transfer operation, then the mill can be linked to the blender and the blender to the capsule filler or an intermediate bulk container (IBC) (see *Figure 5*).

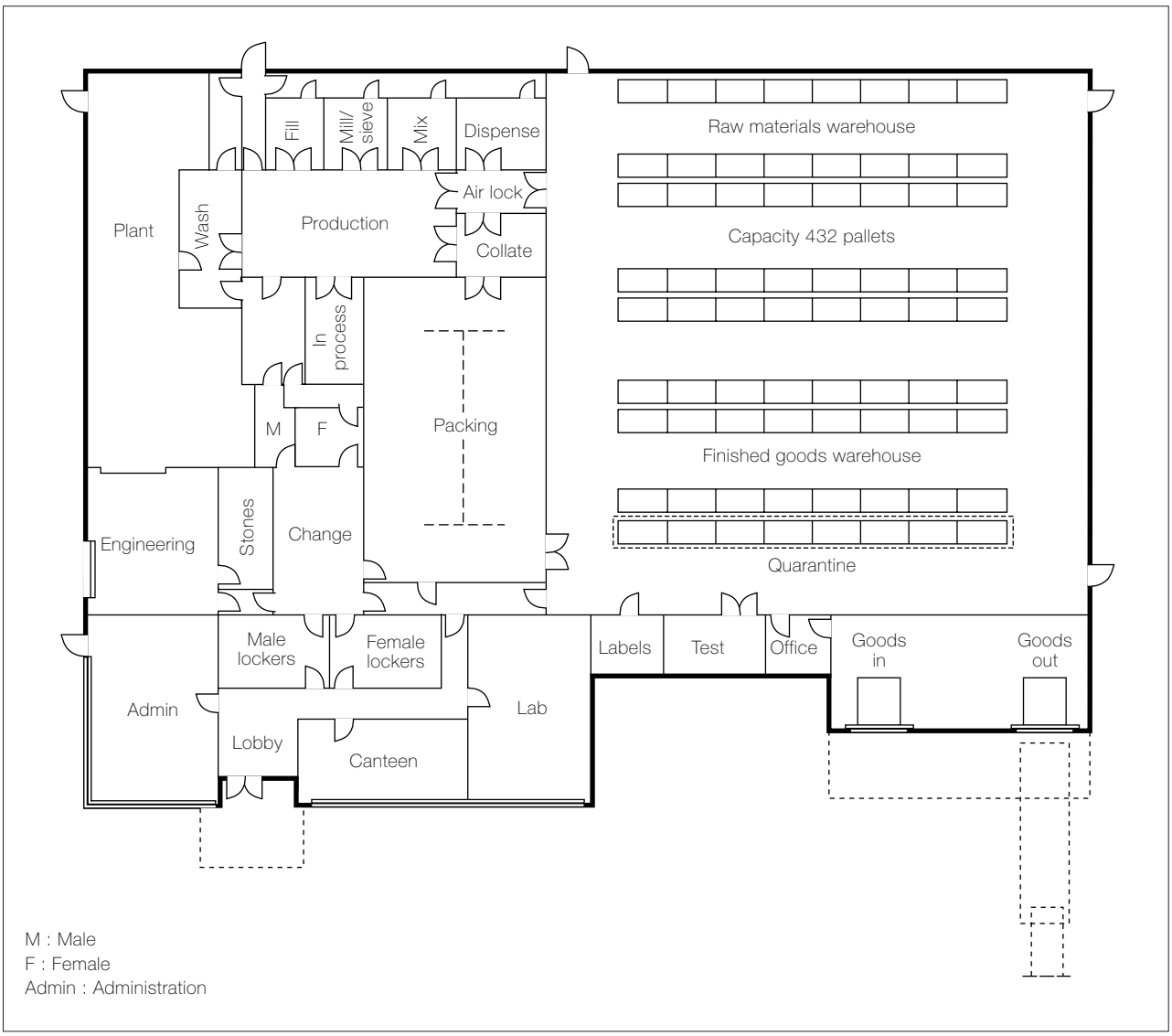

Figure 7. Capsule filling facility layout.

Figure 6 shows a section through an automated feed and receiving system for a capsule filler. This unit is linked to a Process Monitoring and Control System (PMCS). Powder and empty capsules are fed under gravity from an IBC and the filled capsules are transferred back to a third IBC. The interceptor in this concept is designed to remove excess dust from the capsule filling operation and capsule sorting and dedusting operation. For an automated system, filled capsules can be stored in an IBC until released to packaging and the IBC can be positioned above the packaging unit and the filled capsules are then gravity fed into the blister packer or securitainer filling unit.

The objective in all these operations should be to minimise manual transfer and reduce exposure and contact of the product to the operator and the environment.

At this stage it is useful to produce an equipment list and equipment data sheets. In the conceptual stage the designer is mainly concerned with the dimensions, weight, service requirements, links to adjacent equipment and control services. It is also

necessary to have an idea of the amount of manual intervention that will be required. While labour may be very cheap in some parts of the world, automated handling and control is more reliable.

1.5. Layout and design of facility

A typical layout is shown in *Figure 7*.

Process areas require high quality finishes to maintain cGMP standards. Traditionally pharmaceutical secondary manufacturing facilities have been designed on the basis of single rooms or cubicles for each stage of the manufacturing process. Transfer of materials has been accomplished using a large drum or mobile trolley. Today the industry is investing in more automatic transfer systems for material handling in an attempt to reduce costs and improve yields. This results in a more integrated manufacturing unit. Computer Integrated Manufacturing (CIM) is becoming more widely used in the Pharmaceutical Industry to reduce labour costs, improve efficiency and increase yields. It also reduces the size of the building and the high cost areas within that building for each manufacturing operation. The objective is to remove as many of the service functions outside of the process area into a lower grade technical area. This means that process utilities can be serviced without interfering with manufacturing operations Each access door from the maintenance corridor and entrance door to each cubicle from the central production area is fitted with an interlock so that both doors cannot be opened simultaniously. This concept is illustrated in *Figure 8*. A comparison with *Figure 9* shows how the expensive process space has been reduced. *Figure 10* shows a section through this type of facility. *Figures 11* and *12* show the layout of a traditionnal solid dose manufacturing facility and all of these drawings have been shaded to show the grading of each area e.g. light grey, dark grey and black. These gradings refer to the quality of the air required in each area and the quality of the finishes required, Black will require minimum standards and light grey the maximum. *Figures 13, 14* and *15* illustrate the concept required for an automated facility. It is important to note here in comparison with *Figures 11* and *12*, the considerable savings that can be achieved in building costs by reducing the size of the buildings footprint and of the process area. The traffic floor (*Figure 15*) illustrates the pathway for the movement of IBC's for feeding and receiving product from the process equipment on the floor below.

Detailed sections

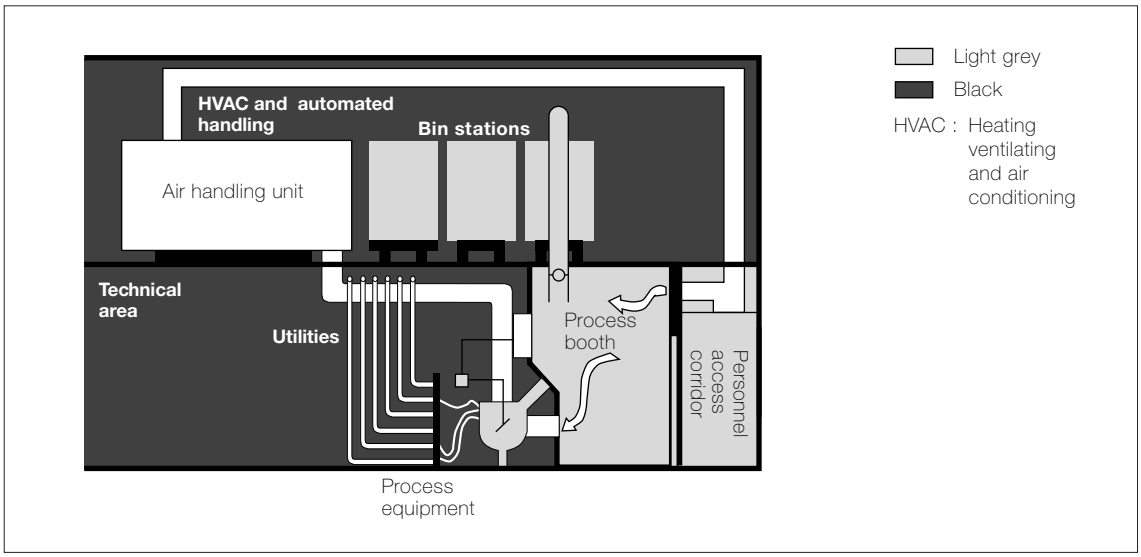

Figure 8. Detailed section through an automated manufacturing facility.

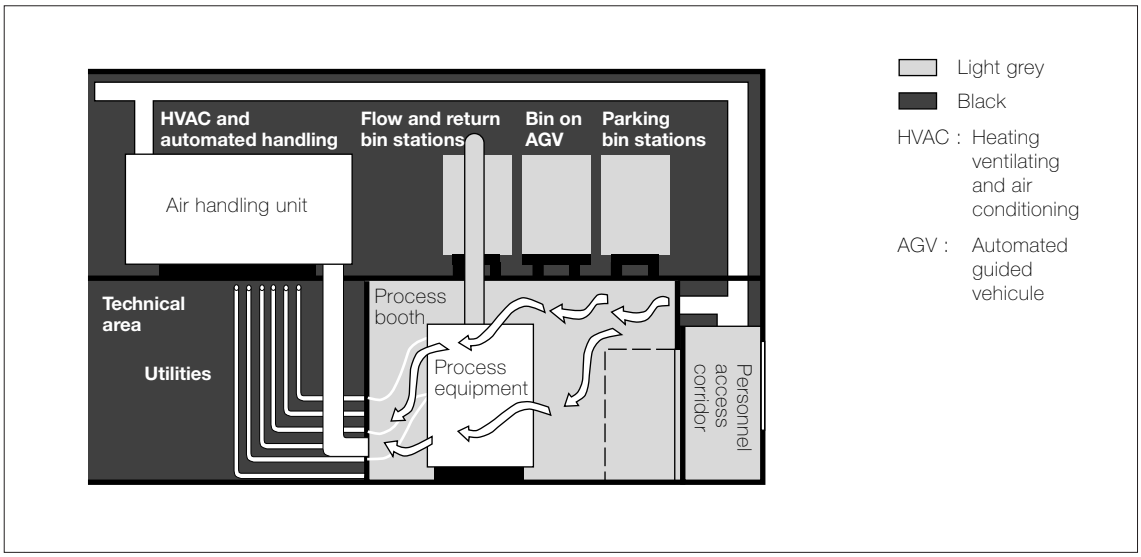

Figure 9. Detailed section (contained equipment) through an automated manufacturing facility.

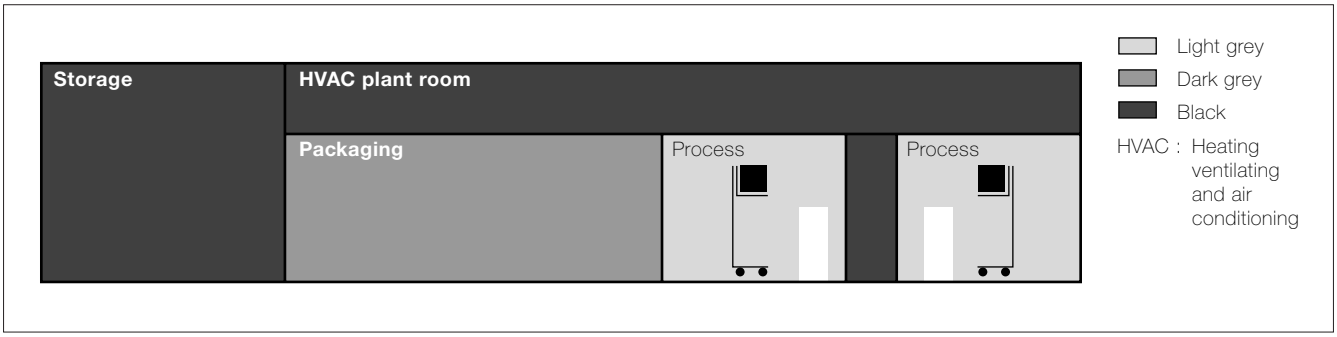

Figure 10. Section through a traditional manufacturing facility.

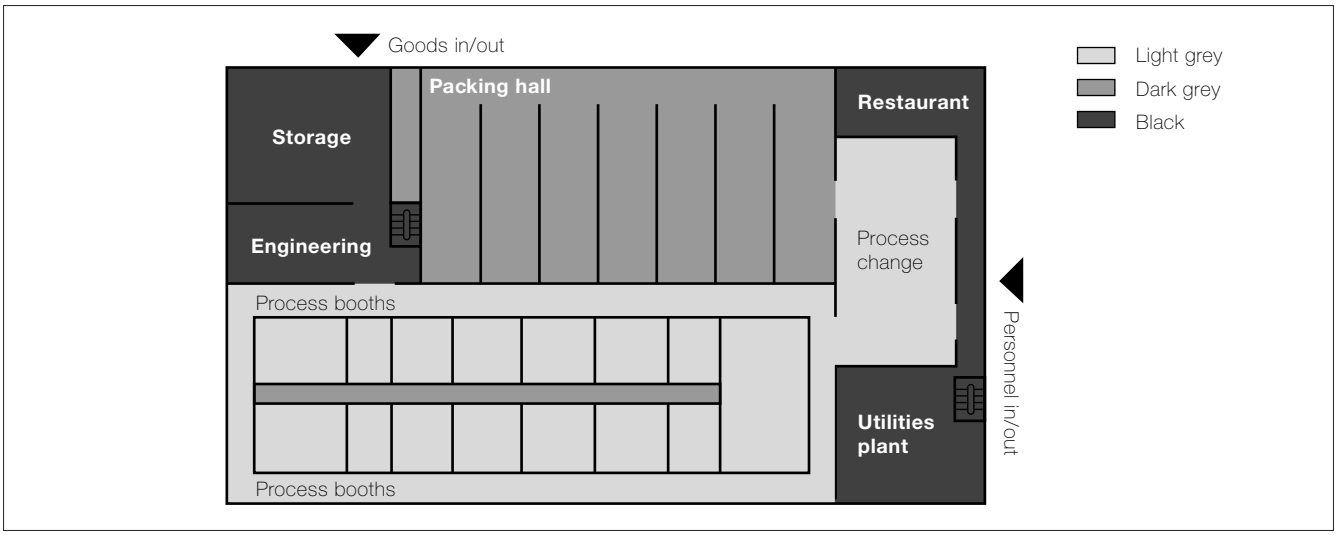

Figure 11. Ground floor layout – Traditional.

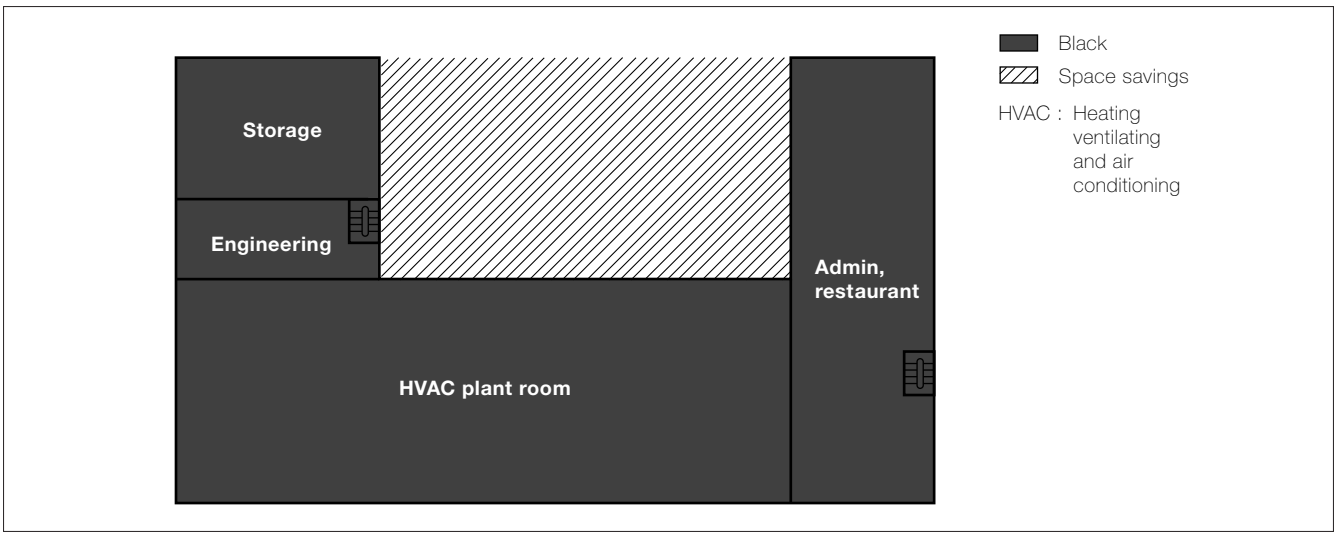

Figure 12. First floor layout - Traditional.

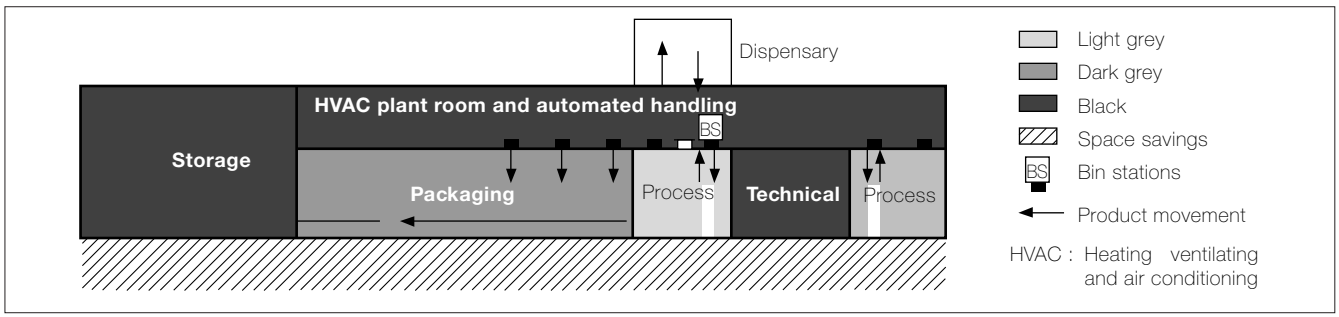

Figure 13. Section through automated and non-automated manufacturing facility showing flow of material.

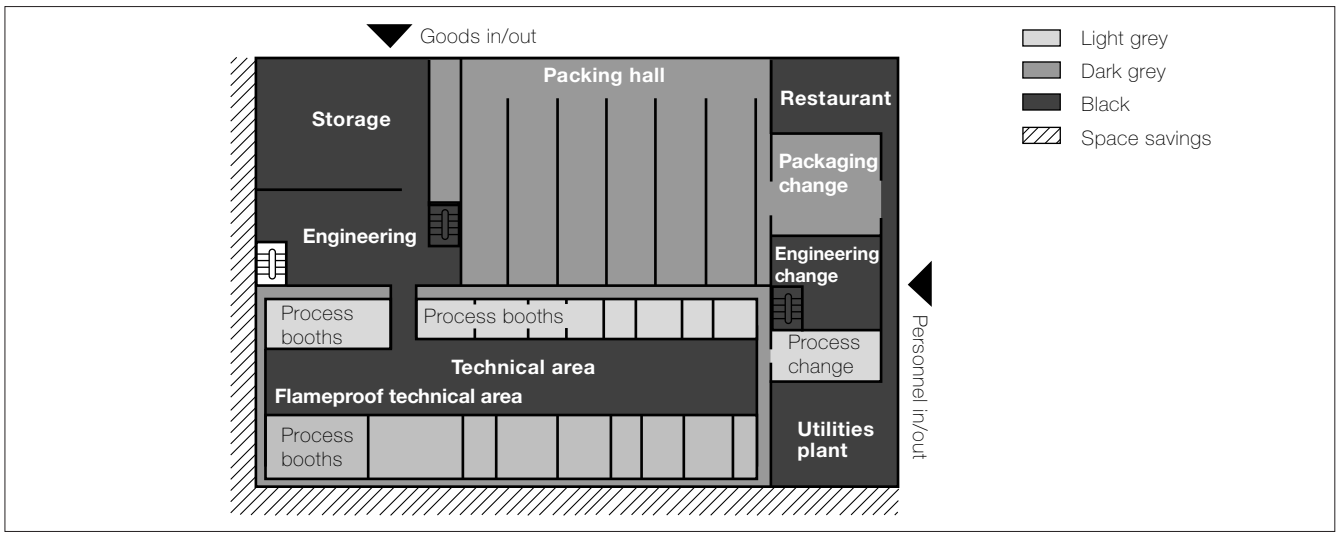

Figure 14. Ground floor layout for an automated facility.

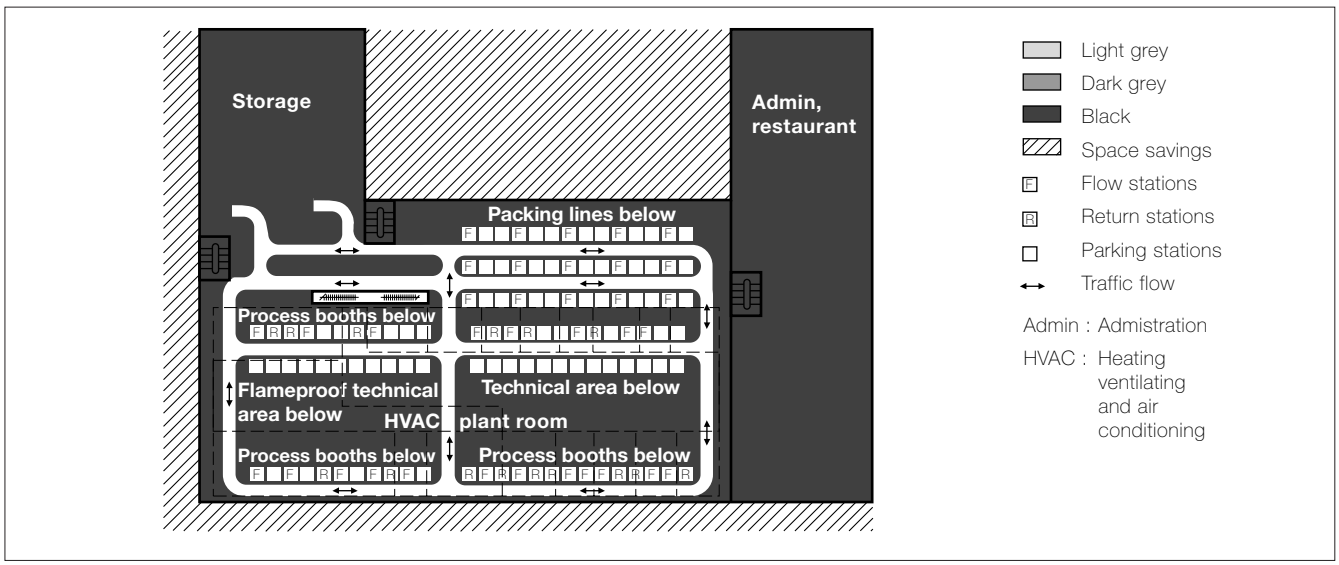

Figure 15. First floor layout for an automated facility.

Table 1. Automatic hard gelatin capsule filling machine (updated October 1999).

Continuous Motion Machines

Machine Type	Capsule Sizes	Theoretical Output Per Hour (powder filling)	Dosing Principle (powders)	Pellet Filling	Tablet Filling	Liquid and Paste Filing	Comments
MG 2							
MG COMPACT	000-5	6-48000		Yes	Yes	Yes	Unit for
MG FUTURA	000-5	6-48000		Yes	Yes	Yes	extrusion
G 38/N	00-5	60000		Yes	-	-	of
G 60	00-5	60000		Yes	Yes	-	high solids
G 60/NETT	00-5	60000	Dosator	Yes	Yes	-	content
G 37/N	00-5	100000	and piston	Yes	Yes	-	pastes is
G 100	00-5	100000		Yes	Yes	-	available
G 120/N	00-5	120000		Yes	Yes	-	for G 36, MG
G 120	00-5	120000		Yes	Yes	-	Compact and
G 120/NETT	00-5	120000		Yes	Yes	-	MG Futura.
IMA ZANASI DIVISION							
MATIC 60 E/F	000-5	60000	Dosator	Yes	-	-	-
MATIC 90 E/F	000-5	90000	and piston	Yes	-	-	-
MATIC 120	000-5	120000		Yes	-	-	-

Intermittent Motion Machines

Machine Type	Capsule Sizes	No. of Capsules Per Segment	Theoretical Output Per Hour powder filling)	Dosing Principle (powders)	Pellet Filling	Tablet Filling	Liquid and Paste Filling
ROBERT BOSCH GMBH							
GKF 130	00-5	1	7800		Yes	Yes	Yes
GKF 400 S	00-5	3	24000	Tamping and	Yes	Yes	Yes
GKF 700 S	000-5	5	42000	disc dosing	Yes	Yes	Yes
GKF 2000 S	00-5	18	150000		Yes	Yes	Yes
HARRO HOEFLINGER							
KFM III-I	00-5	1	4800	Tamping and	Yes	Yes	Yes
KFM III	00-5	3	15000	disc dosing	Yes	Yes	Yes
ROMACO MACOFAR							
CD-5	00-5	1	6000		Yes	Yes	-
CD-20	00-5	3	20000	Dosator and	Yes	Yes	-
CD-40	00-5	6	40000	piston	Yes	Yes	-
CD-60	00-5	10	66500		Yes	Yes	-
IMA ZANASI DIVISION							
ZANASI 6 E/F	000-5	1	6000		Yes	Yes	Yes
ZANASI 12 E/F	000-5	2	12000		Yes	Yes	Yes
ZANASI 25 E/F	000-5	4	25000		Yes	Yes	Yes
ZANASI 40 E/F	000-5	6	40000		Yes	Yes	Yes
ZANASI PLUS 8 E/F	000-5	1	8000	Dosator and	Yes	Yes	Yes
ZANASI PLUS 16 E/F	000-5	2	16000	piston	Yes	Yes	Yes
ZANASI PLUS 30 E/F	000-5	4	30000		Yes	Yes	Yes
ZANASI PLUS 48 E/F(*)	000-5	6	48000		Yes	Yes	Yes
ZANASI PLUS 70 E/F	000-5	9	70000		Yes	Yes	Yes
ZANASI PLUS 85 E/F	000-5	11	85000		Yes	Yes	Yes
BONAPACE							
RC 530	000-5	6	34000	Dosator and piston	Yes	Yes	Yes

If a customer buys a PLUS 85 and then needs to work 00 or 000, he can buy the size parts and work with 9 elements (ZANASI PLUS in the 70 configuration)
With the necessary size change parts CONI-SNAP SUPRO™ sizes A - E can be filled an all types of filling machine.
(*) ZANASI PLUS 48 E/F can be later upgraded to ZANASI PLUS 85.

2.0. Evaluation of hard shell gelatin capsule filling equipment

Although improvements in the encapsulation operation have taken longer to achieve than is the case for the tablet making process, the capsule filling machine manufacturers today offer an impressive range of machines with varying degrees of sophistication and automation. See *Table 1*. Even hand filling and semi-automatic machines which rely heavily on the dexterity of the operator, have been improved to comply with current Good Manufacturing Practices, and should be evaluated from this viewpoint.

It is important firstly to recognise that different filling techniques are employed by the various machines on offer. These include:

- the volume fill (*Figure 16*),
- the auger feed system (*Figure 17*),
- the tamping method (*Figure 18*),
- compression filling - intermittant (*Figure 19*),
- compression filling - continuous (*Figure 20*),
- the vacuum filling method (*Figure 21*),
- liquid fill/ thixotropic mixtures (*Figure 22*).

It should also be understood that the physical treatment of the powder and its storage prior to use can effect the overall performance of the capsule filling operation.

Essentially the programme will be divided into two parts; pharmaceutical appraisal and mechanical appraisal. This programme will identify the objectives and answer such questions as:

- what capacity (output) is required,
- is the equipment required for laboratory, process development or production purposes,
- is it proposed to establish a standard range of units from laboratory through process development to production (if this approach is adopted then alternative equipment should be evaluated to ensure a back-up position when or if problems develop with the preferred supplier),
- does the equipment comply with current Good Manufacturing Practice (cGMP),
- what validation problems exist,
- what is the effect of using different types and suppliers of capsules,
- safety aspects.

2.1. Pharmaceutical evaluation

A typical formulation will contain all or some of the following:

- active,
- diluent/disintegrant,
- surfactant,
- flow aid,
- lubricant.

The preparation of the powder formulation is crucial to the performance of the filling equipment, but before the product is tested on the equipment, certain basic information can be derived by using a placebo formulation. No placebo formulation can exhibit the exact characteristics of the formulation containing the active, but by careful formulation design and optimisation many physical parameters of the product can be reproduced. Some examples are given here.

At least three different powder mixtures are needed for a satisfactory evaluation. Suitable formulations are as follows.

Coarse powder (fill-weight 250.0 mg): lactose coarse grade 246.0 mg + colloidal silicon dioxide, 1.5 mg + magnesium stearate, 2.5 mg.

Fine powder I (fill-weight 250.0 mg): lactose fine grade, 246.0 mg + collidal silicon dioxide, 1.5 mg + magnesium stearate, 2.5 mg.

Fine powder II (fill-weight 200.0 mg): lactose fine grade, 160.0 mg + maize starch, 38.0 mg + magnesium stearate, 2.0 mg.

A Coarse Powder is defined as having a particle size fraction of between 5 µm and 250 µm with 75 % by weight of over 100 µm and fine powder between 5 µm and 100 µm with 75 % by weight below 50 µm.

The examples given of fill weight will depend on the capsule size required, the total quantity of powder required, the type and output of the equipment under test. The method of preparation, storage material handling and conditions under which the tests take place must be standardised as much as possible. Powder such as lactose and magnesium stearate should be taken from the same original batch to minimise batch to batch variation. The important physical parameters that need to be standardised are:

- Flow,
- Bulk density (both apparent and tapped),
- Powder cohesion.

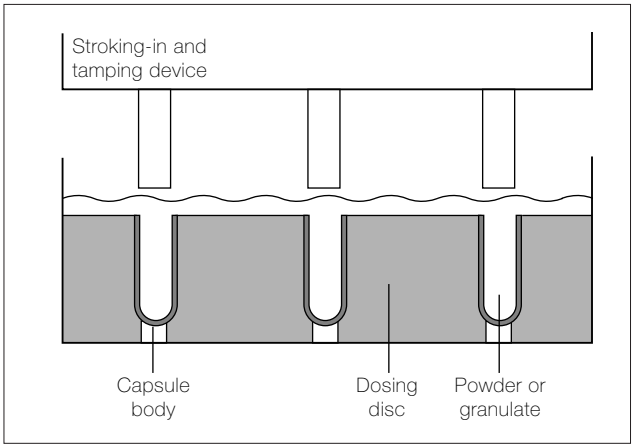

Figure 16. The volume fill.

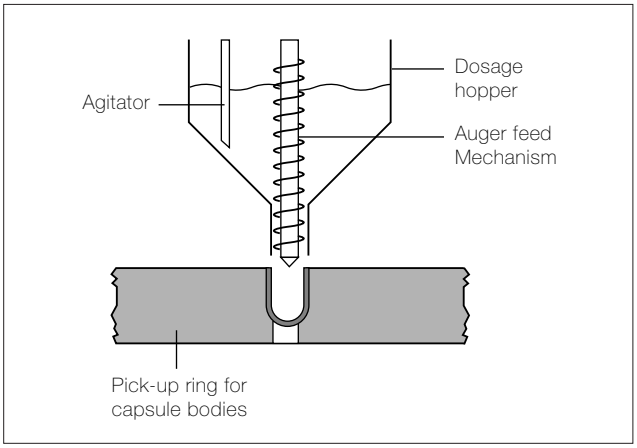

Figure 17. The auger fill feed system.

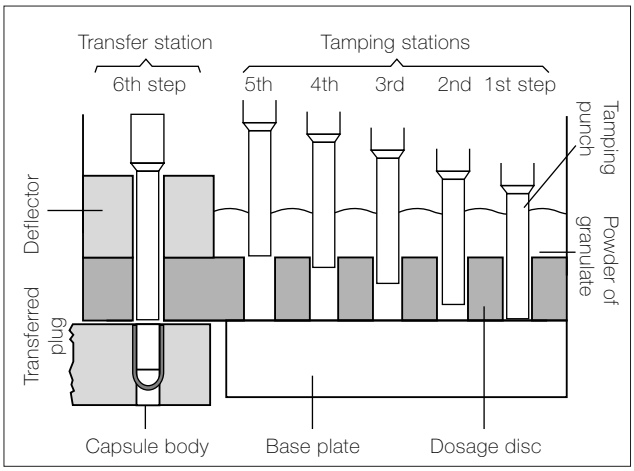

Figure 18. The tamping method.

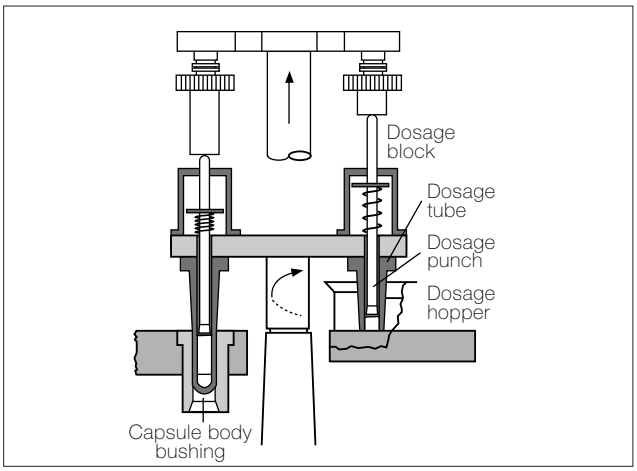

Figure 19. Compression filling - intermittent.

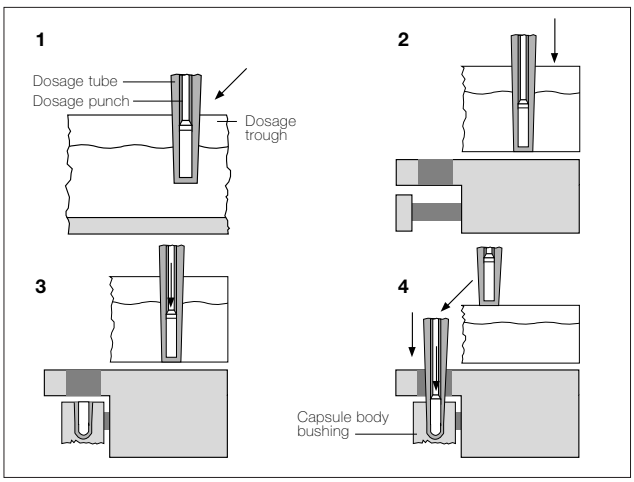

Figure 20. Compression filling - continuous.

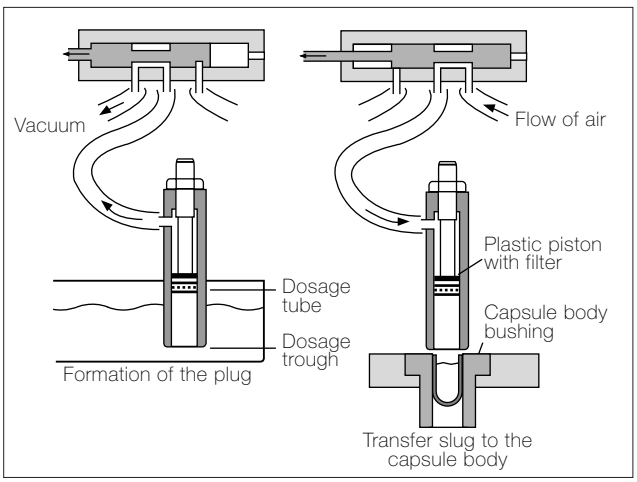

Figure 21. The vacuum filling method.

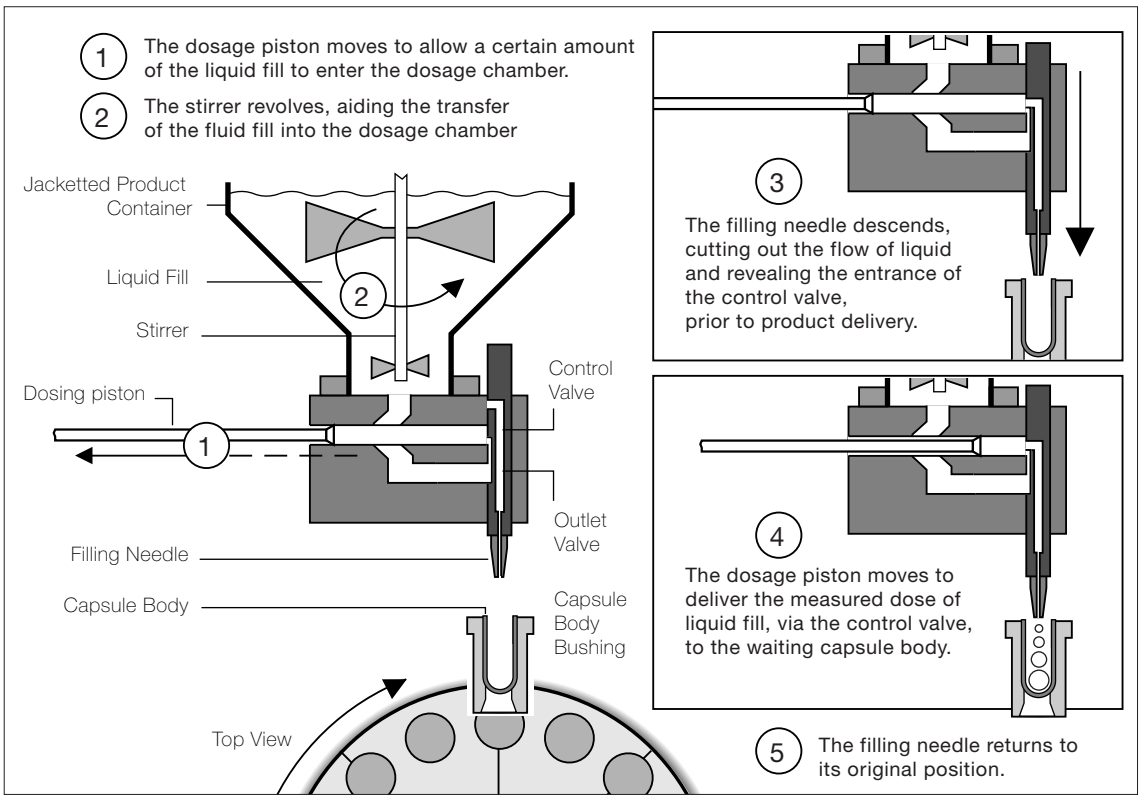

Figure 22. Liquid / Semi-Solid Dosage Method

Their relative importance will depend on the equipment under test, for example flow and bulk density will be critical on machines such as the Parke Davis Model 8 which depend on volume fill and all three on high speed equipment such as the MG2 G37 N.

It is not proposed to detail test methods here, but measurements of flow using the angle of repose, flow out of hoppers, measurement of cohesion using shear cells and bulk density are described in Chapter 8 of Hard Capsules (2).

The number of empty shells required (again they should be all from the same batch) will depend on the filling rate of the equipment under test and the length of time it is proposed to operate. For production trials it is proposed that the number of shells required will be in the order of 500,000 Coni-Snap capsules, 500,000 of an alternative capsule and say 200 kg of the selected placebo formulation.

The initial tests should be conducted to derive basic pharmaceutical and mechanical data such as optimium filling speeds and change over times from one size to another eg size 1 to size 3.

Once it is decided to perform a full scale trial, then these trials should be divided into a number of phases which subject the machine to both ideal and non-ideal operating conditions. A log should be maintained to record faults that develop and the time taken to clear. From this time event log (an example is shown in *Table 2*) a general indication of the machines performance can be derived, for example operating output against theoretical output, the number of faults that occur and the time taken to clear them. Comparison can also be made for change over times from one size to another and cleaning requirements.

Test procedure

To carry out the test, set up the machine with each type of powder in turn and run under ideal conditions, applying the following criteria for the appraisal of the machine.

1. Uniformity of weight between individual capsules.

2. Uniformity of weight between groups of capsules.
3. Uniformity of closure of capsules.
4. General appearance of capsules and need for cleaning.
5. Need for polishing capsules.
6. Proportion of rejects.
7. Time spent clearing operating faults.
8. Output of capsules.
9. In-process control of fill-weights.
10. Maintain a time event log.

The machine should then be run under non-ideal conditions.

1. Hopper: allow the powder to fall to a low level in the hopper, and check the weight variation of the filled capsules.
2. Examine the effects of changing the temperature and, if possible, the humidity.
3. Vary the speed of the machine over as wide a range as is possible.
4. Estimate the amount of dust produced, the smooth running or vibration of the machine, and examine for overheating.
5. List any modifications that are required.
6. Consider the noise level near the machine, the extent to which moving parts are protected and how easy it is to load the machine with empty capsules and material for filling.

If the equipment is fitted with an automatic weight control system, then Phase I should be repeated to check the performance of this system. Only checks on the weight of capsules are required, but a time event log should be kept.

The most fundamental of all these tests is checking the weight of the filled capsule. For manually operated hand fillers this is relatively simple and checks can be in line with an appropriate monograph in the USP, BP or EP pharmacopoeias (or other pharmacopoeia depending on the country of origin) or the company's own corporate specifications. Determination of elementary statistics such as mean weight, standard deviation and coefficient of variation can be used to evaluate the samples. Where the equipment under evaluation has a high output then the experimental plan is more complex and there are other variables which will apply. Raw materials will vary within their defined specifications particularly regarding their physical characteristics such as particle size, surface area, particle shape

Placebo Material - Formula 1

Start time	Action	Remarks	Sample Number
11.10	Start	Relative Humidity 45-50 cer cent, at 21 C.	
11.13		Tachometer reading 158,000 c.p.h.	1
11.14	Stop	Unopened reject capsules three per minute	
11.15	Start	Unopened reject capsules five per minute	
11.19	Stop	Blocked empty capsule feed tube	
11.19	Start		
11.20			2
11.28	Stop	Blocked empty capsule feed tube	
11.19		Start	
11.30			3
11.33	Stop	Broken capsule in upper bush	
11.34	Start and	Powder flowing from hopper due to an electrical fault	
	Stop	Low capsule fill weight	
11.36	Start	Correct capsule fill weight	
11.40			4
11.50			5
11.59	Stop	Blocked empty capsule feed tube	
12.02	Start		

Table 2. Example of an event-time Log.

etc. This results in some variation in powder flow and bulk density and may adversely affect the filling characteristics of that batch of product. The following experimental plan is designed to evaluate a high speed filler operating at 90,000 capsules per hour with a fill weight (excluding capsule) of 250 mg.

a. Define location and environment controls available eg temperature and relative humidity.
b. Define quantity of capsules to be filled.
c. Select formulation and define manufacturing process. (This process must be performed under controlled conditions of temperature and humidity.)
d. Measure physical parameters such as bulk density, flow, particle size, moisture content and chemical tests on product containing actives.
e. Select type of capsules to be used.
f. Define the sampling plan. The machine will operate theoretically for 5 hours where the

powder has a batch size of 125 kg. The simplest method is to collect say 50 filled capsules every 15 minutes and check weigh 20 as required by most pharmacopoeias. (Better to collect too many at this stage than find a shortage during testing. This permits other tests to be performed eg assay, dissolution, content uniformity where active product is being filled).

Where two machines from different manufacturers are being compared then the above plan can be followed but with a change in the batch size of product. The batch size should be doubled to say 250 kg and after manufacture it can be divided in two parts and 125 kg used on each machine. This will then eliminate any batch to batch variation in raw materials and in the manufacturing process. Samples collected during manufacture can be compared to each other and against a known standard.

2.2. Mechanical evaluation

Simple machines are generally the best to operate and maintain. Capsule filling requires an operation that will separate a container, fill it with powder or an alternative, close it and eject it from the machine without damage resulting in a pharmaceutically elegant product. All automatic equipment manufactured by the leading companies (see Table I) can achieve this result, however, certain products perform better on some types of machines than others. It is not always possible to define the scientific basis for this and it is best to test the product on a number of different types to determine the best performance. Mechanically continuous operating equipment is simpler to maintain than intermittent but many companies favour intermittent equipment from a pharmaceutical viewpoint.

One of the main areas of mechanical concern for a capsule filling operation is how quickly and easily a size change may be completed and the machine cleaned ready for the manufacture of a different product. In addition the main emphasis during evaluation must be on the following areas:

a. Lubrication systems.
b. Access for maintenance.
c. Noise level.
d. Mechanical and electrical documentation.
e. Materials of construction and in particular the standards of finish for the product contact surfaces.
f. Maintenance required.
g. Instrumentation systems (automatic weight and pressure control).
h. Equipment specifications.
i. Ease of cleaning.
j. Safety. (How well is the operator protected from moving parts and what interlocks are provided.)
k. Services required.
l. Cost of basic unit, spares, change parts and their availability.
m. Dimensions (footprint and height clearance required) and weight.

All of these items need to be evaluated in the overall appraisal.

2.3. cGMP and validation

No equipment evaluation is complete without an assessment of GMP and Validation requirements.

Validation is expensive and the documentation supplied for the equipment should be examined for details on:

- materials of construction of product contact parts,
- maintenance schedules,
- operating manual,
- diagnostic fault analysis,
- calibration of instruments.

316L (low carbon content) stainless steel is the most commonly used material where products are in contact and is readily acceptable to regulatory agencies as the material of choice. Painted surfaces are now being replaced universally by stainless steel cladding and this improves both the appearance and the cleaning operation.

All automatic equipment requires the use of vacuum to separate the shells into body and cap and the effectiveness of this system should be tested to ensure consistent performance. Dust extraction is required also and an assessment of the way in which the filters are installed, how easily they can be changed and their cost should be determined as part of the engineering/GMP evaluation.

Companies that supply excellent equipment are not always so efficient in providing simple but detailed operating instructions for the machine. It must

be borne in mind that a standard operating procedure (S.O.P.) will be required and assimulating badly written or poorly translated documentation can be lengthy, and expensive.

Calibration of instruments must be addressed to ensure that they are easily maintained in their operating range and it is important to differentiate between critical and convenience instruments. Critical instruments must be calibrated in their operating range against known traceable standards for validation. Examples would be the vacuum gauge for measuring the vacuum required to separate the capsules into their component parts and the gauge for measuring the pressure required for producing a plug on compression filling equipment. Critical instruments are defined as those likely to effect the quality of the finished product for example the hardness of the plug may adversely effect drug dissolution. Convenience instruments are those required to provide data for production operations and management purposes e.g. a capsule counter fitted to a capsule filler. (if the capsule counter is fitted to a package unit for counting capsules into bottles or sercuritainers then it becomes a critical instrument).

2.4. Summary

In capsule filling equipment evaluation one of the most important aspects is to define the experimental plan. It may be that some preliminary test work is required to determine what are the most critical operations on a particular machine. This can be achieved using placebo material before proceeding to the plan proper. It should be remembered that faults do not always show up on high speed equipment until it has been operating for several hours and reaches steady state operating temperature.

Placebo formulations do not necessarily behave as products containing active formulations and a final trial will be necessary using the actual product. The size of this trial will depend on cost and whether the material used can be sold. In this case the trials are best conducted in registered premises to ensure all cGMP requirements are met.

It is also worth discussing with other users their particular preferences and experiences. (Many manufacturing companies will discuss their use and its performance of various types of equipment).

The following check list may be useful in developing an experimental plan.

1. Define objectives:

a. Comparison of new equipment against existing (same supplier).

b. Higher output required.

c. Comparison of various equipment available.

d. New product requires capsule filling.

2. Define formulations to be used:

a. Placebo - what physical characteristics required.

b. Product containing actives.

c. Capsule type(s).

3. Define tests:

a. On powder.

b. On filled capsules.

4. Define location:

a. In-house.

b. At equipment suppliers.

c. Other.

5. Define personnel expertise requirements for tests:

a. Formulation pharmacist.

b. Quality control.

c. Engineering support.

d. Others.

6. Validation/cGMP input requirements

7. Cost:

a. Manhours.

b. Materials:

- placebo
- product
- capsules

c. Other:

- transport
- total cost of test programme.

3.0. Validation of hard gelatin capsule filling equipment and ancillary services

Validation is a Quality Assurance procedure and this concept has been developed by the Pharmaceutical Industry to ensure that the manufacture of medical products and devices are produced using

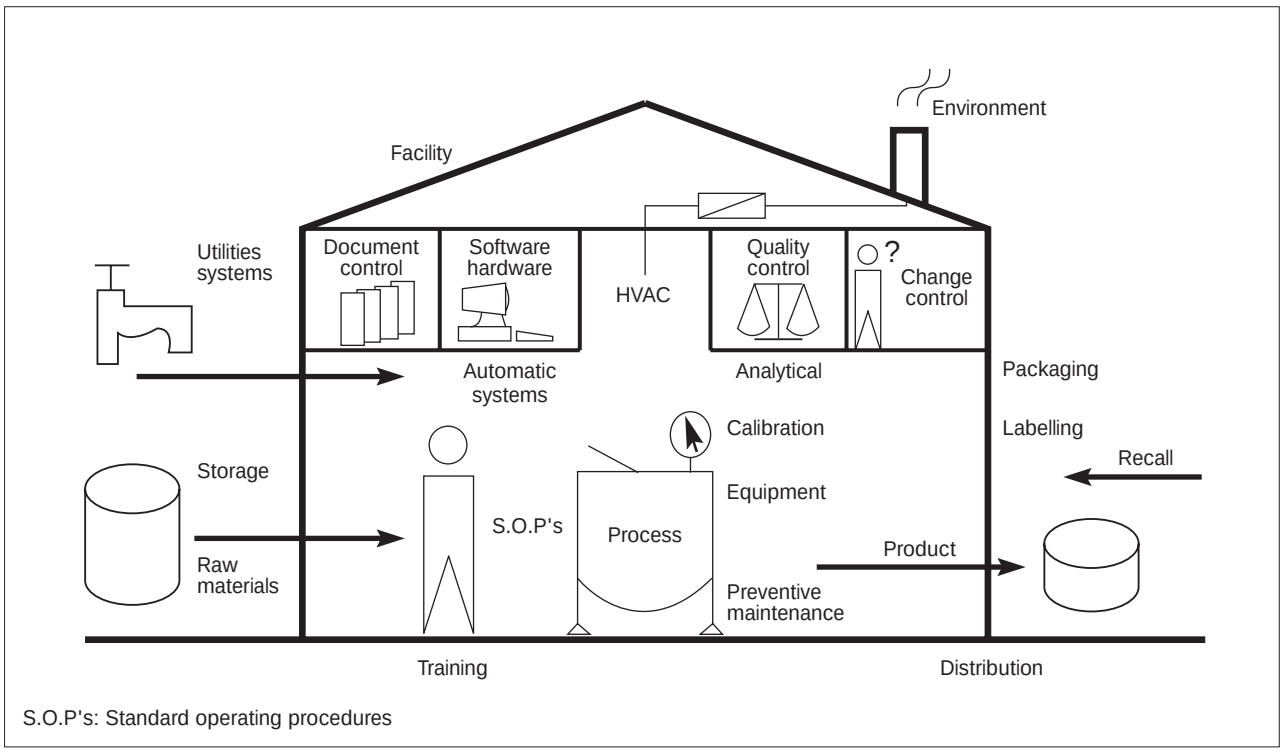

Figure 23. The elements of validation

standards which are approved by national and local regulatory authorities.

The Food and Drug Administration (FDA) in the USA are generally considered to enforce the highest standards and here we will use their requirements as the benchmark.

In the United States or in the country where a company is manufacturing pharmaceutical products for potential sale to the USA, then a FDA inspection is mandatory and the inspector will wish to see the validation documentation. It should be emphasized that validation is a total concept. This is represented in *Figure 23*.

It is not only concerned with equipment and the process, but also the facility, personnel, training, maintenance, automated systems, documentation, and analytical procedures.

There are many definitions of validation, but the one that is universally recognised is:

"Establishing documented evidence that a system does what it purports to do". (Loftus - 1977) and used by the Industry ever since.

However, a more comprehensive definition sums up the ideas of Validation as:

"In today's Pharmaceutical Industry, whether you are thinking about a computer system, a water treatment system or a manufacturing process validation means nothing more than well-organised, well-documented, common sense."

Ken Chapman, Pfizer, 1985

Validation has also been defined as the activity performed to demonstrate that a given utility, system, process, or piece of equipment does what it purports to do. The primary means of accomplishing this end is the scientific study designed to specifically determine whether the entity under scrutiny does in fact:

- Meet or exceeds the specifications of its design.
- Is properly built, shipped, received, stored, installed, operated and maintained.
- Is suitable for its intended application.
- Is in accordance with principles established and generally accepted by the pharmaceutical scientific community.

- Conforms to basic cGMP design criteria.
- Will satisfy the concerns of regulatory bodies.
- Is capable of consistently producing a product that is fit for use.
- Will meet the goals established for productivity, safety, and quality.

This scientific study is generally detailed in a validation protocol. A well designed validation protocol properly supported by senior management will accrue considerable benefit to its sponsor. Not only will regulatory obligations be fulfilled, but also processes will be optimized, productivity improved, and downtime reduced. In short, a validation programme with a sound scientific base and proper experimental design is simply good business if taken seriously and executed conscientiously. The strategy can be documented in what is known as a Master Plan.

The purpose of the Validation Master Plan is to convey to the FDA and other regulatory bodies, understanding of a company's responsibilities concerning the validation and certification of the facility along with plans to discharge that responsibility. It will also serve as a guide to those administering and performing validation activities and as a road map to successful project completion. The Master Plan may be used as an instrument to define areas of responsibility and accountability to validation team members, and it contains all the programmes necessary to certify the validation of the facility system and processes.

By integrating the pharmaceutical and engineering disciplines, the Validation Master Plan describes the facility and outlines a set of activities tailored to that facility providing a cost effective validation programme that not only minimizes regulatory exposure but is delivered within the prescribed time constraints.

The life cycle concept of validation is a recurring theme throughout the Master Plan. Paramount is the establishment of the infrastructure to ensure that the facility is supported by sufficient documentation throughout its conceptual and functional lifetime. This lifetime includes project inception, design, engineering, construction through testing, certification, maintenance, revalication, and change control.

For a capsule filling operation, we will only consider process utilities and the facility, in addition to the capsule filling equipment required to manufacture and fill a powder into hard gelatin capsules. Essentially, we are concerned with product contact either directly or indirectly.

Figure 24 shows how for this project's life cycle the documentation interacts with the Validation documentation. Some of these activities are self-explanatory but others such as user requirement require further exploration.

The user requirement should be prepared by the "user" to formally document each of the requirements of the "system" to be validated in terms of the final process requirement. Specifically it relates to quantity, quality, compatibility, performance, the environment and finishes in terms of:

- materials of construction
- cleanability requirements
- maintenance requirements
- operator interface requirements
- performance criteria
- critical parameters
- operating ranges of critical parameters
- essential design criteria
- requirements of computer systems
- training and documentation requirements

and should make reference to all relevant in-house standards and regulatory documents.

The Master Plan is used to define the boundary limits and provide a "bible" for all members of the validation team to ensure that they all sing from the same "hymn book".

In most companies a validation team or "task force" is assembled under the QA/QC Manager (designated the Validation Manager) and drawn from appropriate departments e.g.

- Analytical Department.
- Production Department.
- Maintenance/Engineering/Electrical.
- Process Development/Formulation.
- Personnel/Training.

Each department will be able to contribute their expertise to the Validation Programme.

So what needs to be validated?

We need to define the limits objectively as validation is a costly procedure.

- Facility

  The rooms in which the raw materials and product are stored, manufactured, filled and dispatched.

- Process Utilities

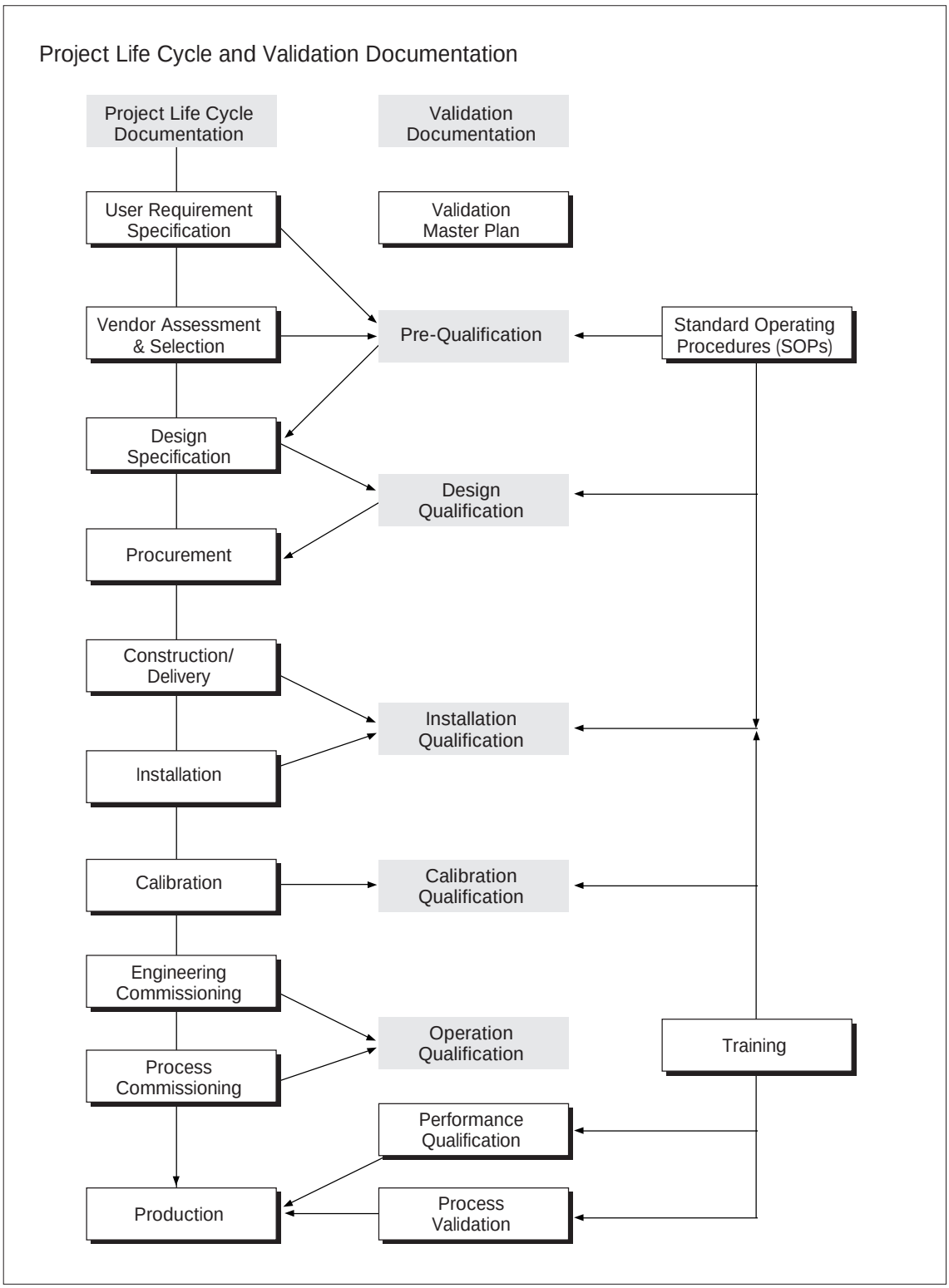

Figure 24. Project life cycle and validation documentation.

Typically compressed air, heating, ventilating and air conditioning, (HVAC), vacuum systems, dust extraction and collection, purified water and effluent treatment system.

- Manufacturing equipment

Mixers, mills, capsule fillers, capsule sorting and cleaning equipment, metal detectors, packaging equipment.

- Control systems

Those devices which record various process operations such as the weight of raw materials used and automatic weight control systems.

- Process validation

Each unit operation requires a validation test programme. A typical process block flow diagram is shown in *Figure 2*. The balances required in the dispensary are considered part of the calibration programme. If pneumatic transfer is used, then this part of the process must be linked in a protocol to an item of processing equipment.

Table 3 provides a basis for determining the number of protocols that need to be produced. It is not an exhaustive list and neither is it a minimal list, but indicative of what has to be produced.

Many companies have a Performance Protocol completed before Process or Product Validation is completed. This specifically tests the equipment and systems within the operation required by the product.

	INSTALLATION QUALIFICATION	OPERATIONAL QUALIFICATION	PROCESS VALIDATION
FACILITY (PROCESS ROOMS)	x	–	–
PROCESS UTILITIES			
HVAC	x	x	x
Compressed Air	x	x	x
Purified Water	x	x	x
Vacuum	x	x	x
Dust Extraction	x	x	–
Effluent Treatment	x	x	–
EQUIPMENT			
Blender	x	x	–
Mill	x	x	–
Sieve	x	x	–
Capsule selector	x	x	–
Capsule filler	x	x	–
Capsule cleduster	x	x	–
Metal detector	x	x	–
Capsule inspection unit	x	x	–
Capsule counter/filler (containers)	x	x	–
Capsule blister packer	x	x	–
SYSTEMS			
Material handling system	x	x	–
Automatic weight control	x	x	x
PROCESS			
Mixing	–	–	x
Milling/sieving	–	–	x
Capsule filling	–	–	x

Table 3. Protocols required.

3.1. Scope of documentation

It is not proposed to detail here all the validation documentation required. For a more comprehensive study other references should be consulted, such as the book on the Design of Pharmaceutical Production Facilities (3) FDA Code of Federal Regulations section 21 (4). The Rules Governing Medicinal Products in the European Community (5) and the GMP Regulations of Japan (6).

The outlines for the requirements of the Master Plan, Installation Qualification (IQ), Operational Qualification (OQ), and Process Validation (PV) are defined below and should be compiled as "stand alone" documents.

3.1.1. Master plan

The Master Plan should contain the following sections and can be used as an internal document to show the visiting inspector and to be used as a reference source for all members of the validation team. For example, the table of contents may contain the following:

1. Approval page
2. Introduction
3. Scope
4. Glossary of terms
5. Preliminary drawings/facility design
6. Raw material qualification
7. Process description(s)
8. Rooms and room classifications
9. Description of utilities
10. Description of process equipment
11. Automated systems
12. Equipment history files
13. Construction documentation
14. Description of required protocols
15. List of standard operating procedures
16. Required document matrices
17. Validation schedule/construction schedule/ integrated schedule

18. Protocol outlines/summaries
19. Environmental monitoring programme
20. Analytical testing procedures
21. Calibration programme
22. Training programme
23. Preventive maintenance programme
24. Change control programme
25. Document control programme
26. Manpower requirements
27. Key personnel
28. Protocol examples
29. Standard operating procedures (SOP) examples
30. Appendix

3.1.2. Installation Qualification protocol

An Installation Qualification protocol (IQ) contains the documented plans and details of procedures which are intended to verify specific static attributes of a facility, utility system, or process equipment. The Installation Qualification (IQ) when executed is also a documented verification that all key aspects of the installation adhere to the approved design intentions and that the manufacturer's recommendations have been implemented.

3.1.3. Operation Qualification protocol

An Operation Qualification protocol (OQ) contains the plan and details of procedures to verify specific dynamic attributes of a utility system, or the process equipment, throughout its operating range including worst case conditions. The Operation Qualification, when executed, is documented verification that the system or subsystem performs as intended throughout all anticipated operating ranges.

3.1.4. Protocol preparation

Capsule filling equipment will require two protocols, an IQ and an OQ. An outline of the content of each page of each protocol is given here. The IQ will detail specific specifications of a capsule filler; for example the approval page may require the participation of each or some of the following functional areas:

	Name	Signature	Date
Manufacturing	…		…
Engineering	…		…
Quality assurance	…		…
R & D	…		…
Safety	…		…
Site manager	…		…
Regulatory affairs	…		…
Validation Manager	…		…

The following pages or sections will be required:

Equipment use

- Specification,
- Materials of construction for product contact surfaces,
- Inspection check list,
- Installation check list,
- Any relevant drawings eg section through dosator and filling hopper,
- Manufacturers certification,
- Calibration review,
- Standard operating procedure (SOP),
- Cleaning procedure,
- Training required,
- Supporting utilities,
- Summary and certification.

Appendix: Here any relevant documents should be referenced eg, purchase order, manuals supplied for maintenance.

Similarly an OQ document will be compiled as follows:

- Approval page (as for IQ),
- Use,
- Instrument list:
  - Critical,
  - Convenience,
- Calibration procedure,
- Test procedures,
- Acceptance criteria summary,
- Summary of test results and certification.

Appendix - reference documents.

Process utilities

IQ and OQ protocols must be produced for each of the services that will be required by the capsule

filling equipment. Usually these are; compressed air, vacuum, HVAC, and dust extraction. The supply of electricity is usually covered in the protocol for the facility and detailed on a Room Data Sheet.

3.1.5. Process Validation protocol

The Process Validation protocol (PV) is a documented plan and details procedures to verify specific capabilities of process equipment and systems through the use of simulation materials such as the use of a nutrient broth in the validation of an aseptic filling process, or the use of a placebo formulation in a capsule filling process. However, three batches of the product material must be manufactured and sold to comply with the regulatory validation requirements.

It is not proposed to detail this protocol as this needs to be treated separately. However, it must be remembered that each unit operation of the process must be validated. For example a series of experiments must be conducted to demonstrate that under the stated conditions a homogenous mixture is produced for each batch of product manufactured.

3.2. Validation protocol for a MG2 G37N capsule filler

3.2.1. Objective:

The validation of this capsule filler requires the development of Installation and Operation Qualification documents. For the Installation Qualification document the following actions are required.

1. A detailed specification must be written which highlights all those parts of the machine that are in product contact.

Generally these parts will be constructed using 316L stainless steel. (This does not mean that all other materials are unacceptable, but the regulatory authorities have more knowledge of the use of this material than any other and demonstrating its acceptability will be simplified eg less expensive).

This information can be abstracted from the manufacturers' literature, drawings and other relevant manuals, plus certificates of analysis of the materials used.

2. There are two operating systems of a capsule filler that need to be assessed. These are the capsule powder system, and handling of the empty capsule shell.

Each part can be broken down as follows

Capsule Handling System (Sectional drawings are useful)

- empty capsule feed hopper
- feed tube
- rectification unit
- transfer system
- separation system (all parts that handle the cap and capsule body)
- unification system
- ejection system

Powder Handling System

- bulk powder hopper
- powder feed system to dosing hopper
- powder filling system (if a compression filler is being used then each individual dosator must be specified eg piston and cylinder)
- the powder dosing or filling hopper

Where stirring devices or augers are used to ensure homogenity and improve flow, then these parts must have a detailed specification for the validation document.

3.2.2. Instruments

All critical instruments (those that effect product quality) should be listed and calibrated against a known standard eg:

a. vacuum gauge

b. pressure control (hardness of the plug)

c. fill weight

d. machine speed

3.2.3. Utilities

Those utilities which are used in the machines operation such as

- compressed air,
- vacuum,
- dust extraction,
- HVAC system of room (control of temperature and humidity),

will each require IQ and OQ documentation. In addition the quality of the compressed air will need to be tested for colony forming units (CFU) hydrocarbon content, particulates and moisture using a validated analytical method and ensuring that the air meets the specification of the relevant pharmacopoeia (USP, BP, EP, etc.).

3.2.4. Filling control system

There is a move in many countries (Europe, USA and Japan) for more automation in the operation of capsule filling equipment. Where these process control and monitoring systems are in place, then a separate section is required for their installation and operational validation. Computer Validation is a complex subject and needs to be considered at the onset of the project.

It should be remembered that in addition to the capsule filler, its services and the room in which it is located, any ancillary equipment used to handle the empty capsules, powder and filled capsules must be treated identically. This would include:

- an empty capsule sorter,
- conveyor of empty shells to filling machine,
- bulk storage system for powder and feed conveyor to filler,
- filled capsule deduster and sorter.

Having established the installation specifications and produced a document which identifies all the validation requirements, then this can be used to verify that the installation is in accordance with regulatory requirements, the corporate standards and equipment manufacturers' specification, as certified by the Validation Specialist and Manager.

3.2.5. Operational Qualification (OQ)

This document is developed in a similar way to the IQ, but here the objective is to check that all the dynamic attributes of the capsule filler conform to the required specifications as detailed in the IQ.

- the machine operates within the desired range of output,
- all the critical instruments operate in their calibrated ranges and the traceable standard against which they have been calibrated is identified,
- all the relevant documents are in place, such as SOP's and planned maintenance schedules,
- what tests are required, who can perform them and a record of the results when they have been conducted,
- a summary of the calibration schedule on an in-house programme for monitoring the quality of the process utilities eg compressed air.

3.3. Summary

The cost of validation is considerable. In the USA it has been estimated that it can add as much as 15 per cent to the installed capital cost of the project. However, validation correctly performed and executed can save the company large sums in ensuring consistent production, minimised down time and an avoidance of recalled products from the market place. In addition it reduces the cost of in-process control and provides quality assurance for all products.

The following actions need to be conducted by the validation team.

1. Collect relevant data
- operating manuals,
- drawings (piping and instrumentation drawings (P & ID's)),
- calibration documents,
- SOP's,
- maintenance schedules,
- pest control procedures,
- quality control procedures,
- training records.

2. Prepare documentation:
- assimilate relevant data,
- define boundary limits,
- define equipment requirements,
- define format,
- define responsibility,
- define test instruments requirements.

3. Test procedures:
- complete test.

4. Certification.

4.0. Conclusion

In this paper some concepts have been discussed which provide a framework for the design, layout and operation of a capsule filling manufacturing facility to ensure compliance with International GMP requirements and to reduce costs.

There are many possible layout combinations that meet this criteria and these requirements have to be assessed depending on the size of the operation, the equipment and the personnel available.

The use of manual operations are being phased out in many countries and it is not primarily because of costs, but additionally because a properly designed and validated automated system will provide a greater degree of quality assurance.

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