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Review Article

Pilot Plant Scale-Up Technique of Oral Solid Dosage Form In Pharmaceutical Industry

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ABSTRACT

Pilot plant scale-up techniques play a critical role in the pharmaceutical industry by bridging the gap between laboratory-scale formulations and full-scale commercial production. These techniques ensure the successful transition of a product from the research and development phase to large-scale manufacturing while maintaining product quality, efficiency, and compliance with regulatory standards. Key processes in scale-up include evaluating formulation stability, developing manufacturing strategies, optimizing production parameters, and adhering to Good Manufacturing Practices (GMP). The significance of pilot plant studies lies in their ability to identify and address challenges related to equipment compatibility, raw material handling, and process controls, thus enabling cost-effective and time-efficient production. By employing robust methodologies and adhering to regulatory guidelines such as Scale-Up and Post-Approval Changes (SUPAC), pharmaceutical companies can achieve consistent product performance, minimize risks, and ensure market readiness.

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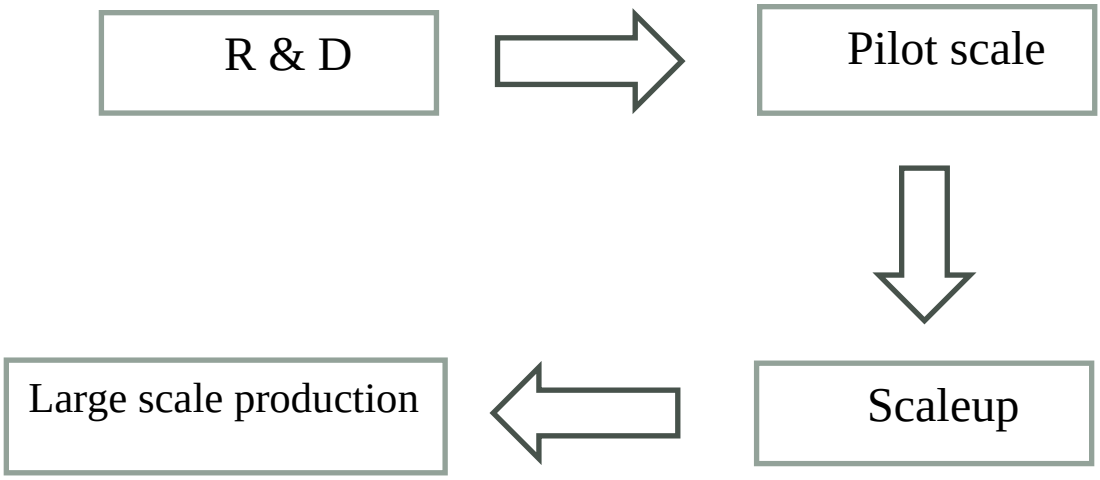
Introduction

Pilot plant is a part of pharmaceutical industry in which a lab scale formula is converted to a feasible product by developing a liable practical method for manufacture. It can also be defined as a technique that involves development of a practical procedure for manufacturing dosage forms that may result into transformation of lab scale process into a viable product. The scale-up is helpful in designing a prototype by utilizing the information obtained from pilot plant model. In this technique, a formula is examined and shifted to a most suitable formulation by developing a reliable and useful manufacturing procedure which affects the organized transition from laboratory to regular processing in a large- scale production facility.

Pilot plant scale up studies is essential in pharmaceutical research for preventing recurrence of long and expensive tests. It is important to collect sufficient information during appropriately designed development and process optimization studies while scaling up the experimental formulation from the laboratory through pilot to the production scale [1, 2].



Why perform pilot plant studies

A pilot plant permit examination of a product and process on an Intermediate scale previous to large amount of money are carry out full scale production. It is generally not possible to predict the effects of many fold increase in scale. It is not viable to design a large complex food processing plant from Laboratory data alone with any degree of success.

A pilot plant can be utilized for

Assessment the result of laboratory studies and making product and process rectifying and development. Manufacture small amount of product for sensory, chemical, microbiological evaluation, limited market testing or supply SAN (Storage Area Network) to potential customers. Regulate sup pliable by products of waste stream requiring treatment before discharge. To supply data can be used in manufacturing a conclusion on whether or not to begin a full scale production process [1-3].

Objectives of scale up

It improves various parameters required in the formulation and development of physically and chemically stable therapeutic dosage forms. It generates strategies for production and process control. It enables handling of raw materials as per their specifications. It determines the steps involved in raw material processing. It develops the master manufacturing formula. It develops pilot plant studies to form an identical examination of the formula to tolerate batch scale. It evaluates, validates, and finalizes the production and process controls. It allows any sort of modification in the process. It properly evaluates and validates the developed product. It modernizes the manufacturing equipment. It ensures physical and mechanical compatibility between the equipment and preparation. It makes the process more economical and less time consuming. It develops modern marketing strategies. It overcomes the problems in small-scale techniques by developing large- scale techniques [4].

Rationale for pilot plant studies

The basis for pilot plant studies are: The process examines a product and its processes on an intermediate scale before utilizing large quantities in full-scale production. It helps predict the effects of a many-fold increase in scale and designs a large, complex food processing plant using only laboratory data.

Significance of pilot plant studies

The following reasons have made the pilot plant studies important: These studies are helpful in standardizing formulations. These

studies are helpful in analyzing different important manufacturing equipment. These studies are helpful in optimizing and controlling production rate these studies provide information on equipment assembly used during the scale up batches equipment assembly used during the scale up batches. These studies identify the specific features of a product required to maintain its quality and helpful in maintaining suitable records and reports to support GMP [5].

Advantages

Members of the production and quality control divisions can quickly observe scale of runs. Supplies of excipients, drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division. Explosion to engineering department personnel is provided for equipment installation, maintenance and repair.

Disadvantages

The frequency of direct inter-connection of the formulator with the production personnel in the manufacturing area will be decrease. Some difficulty in manufacturing will be directed regarding its sown pilot plant procedures [6].

Pilot plant scale up activities

The major activities takes place during scale up in early development phase are;

Technical aspects of process development, Technical aspects of scale up, Organization responsibility Determination of responsibility of technology transfer team, Technology transfer documentation, FDA pre-approval inspection preparation.

Steps Involved [5]

Scale up is the process designing a prototype using the data acquired from the pilot plant model. The steps of scale up represented in below;

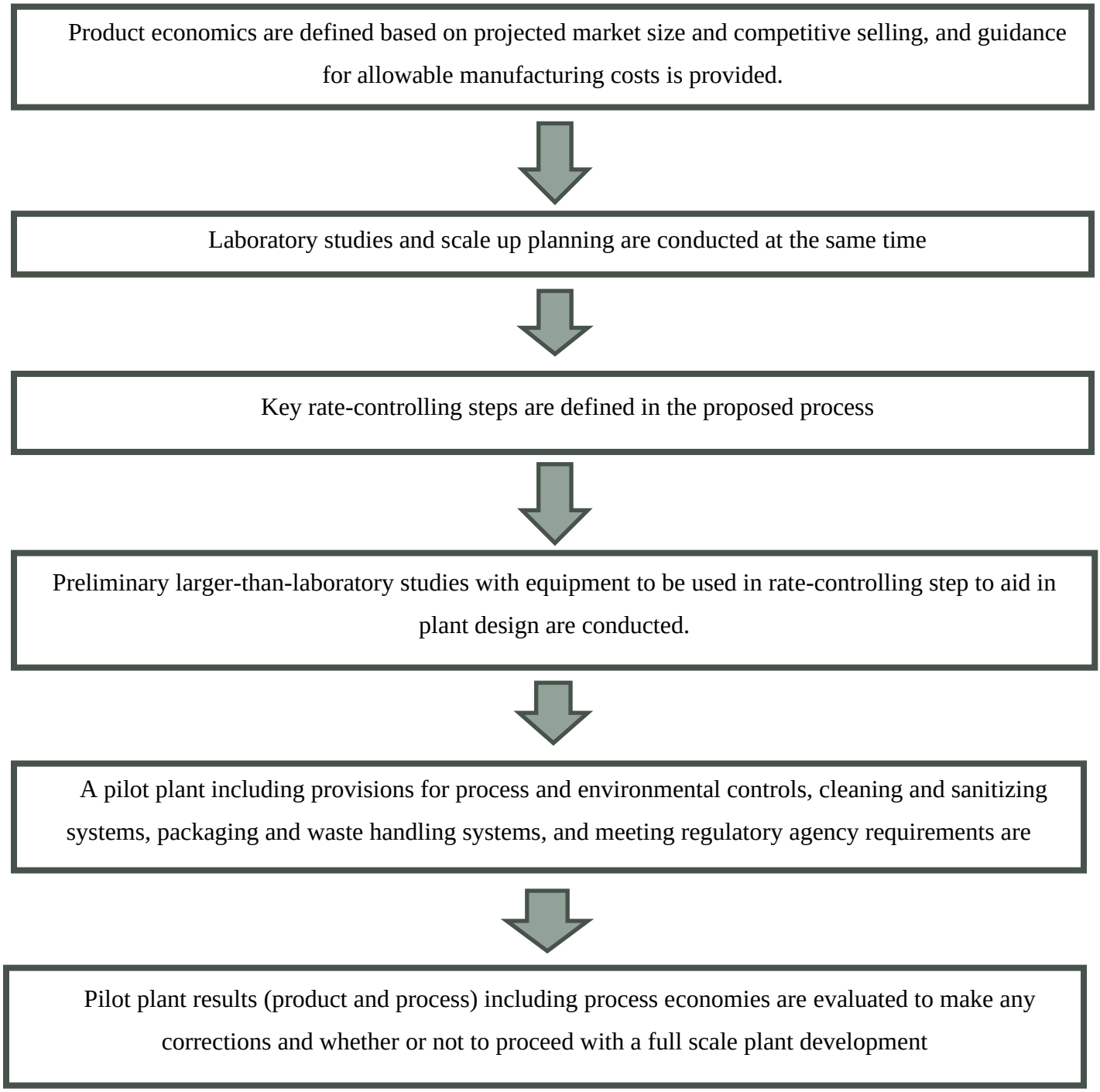


Figure 1: Steps in Scale Up

GENERAL CONSIDERATION FOR PILOT PLANT SCALE UP INTRODUCTION

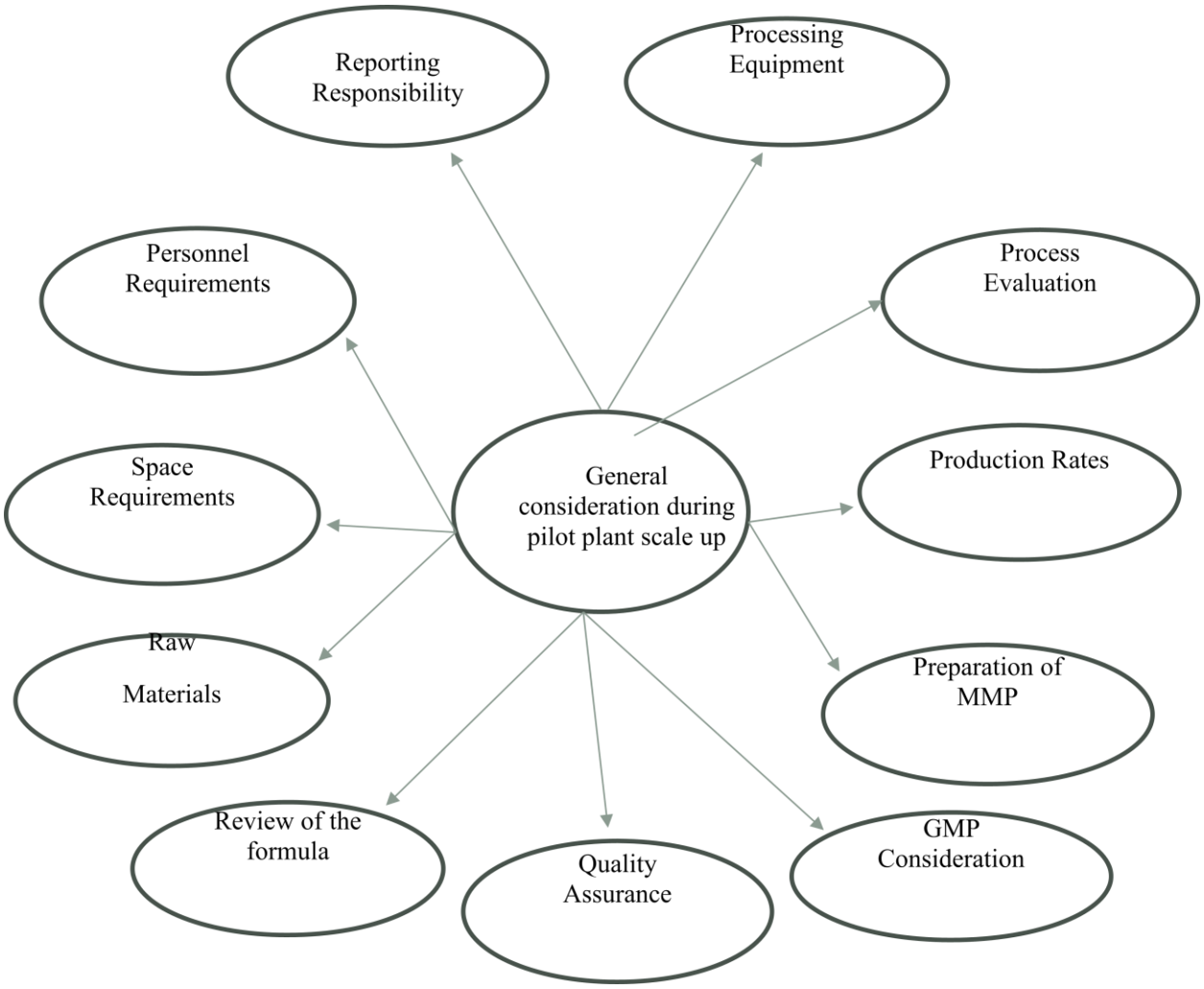


Figure 2: General consideration for pilot plant

Pilot plant studies should involve a close investigation of formula to find its ability to resist batch-scale and process modifications. It suld also involve reviewing a wide variety of significant processing equipment, and evaluating and finalizing availability of raw materials fulfilling the product requirements during the scale up efforts in the pilot plant production and process control. Additionally, proper records and reports should be issued to support GMPs and to deliver historical development of the product formulation, process, equipment training, and conditions. A manufacturer's choice to scale up or scale down a process is based on the economics of the production procedure, i.e., in the material cost,

personnel, equipment related to the procedure, and its regulation.

Reporting responsibility

In reality, the pilot plant function can be a part of the R&D or operation-oriented groups. If it is a part of R&D, there is a need of separate staff and importance is also given on consideration of hierarchy of responsibility to scale-up formulations manufactured by the R&D department and that emerges as the product. On the other hand, the formulator of the product can provide support even after transition into production. The goal of the pilot plant is to assist the transfer of a product from the laboratory to the production, irrespective of the approach adopted by the industry. The pilot plant's efficiency is estimated by the simplicity with which new products or processes are taken into regular production. This can be attained by good management between various departments such as R&D, packaging, processing, engineering, quality assurance, quality control, administration, and marketing.

Personnel Requirements

A pilot plant organization needs a team of personnel, each having a good theoretical and practical knowledge of pharmacy, good communication skills and designing ability to merge new processes with the existing facility. The team is also bound to define equipment specifications and the physical association of process operations for complying with regulatory standards. Additionally, for successful scale up, the manufacturing personnel should be trained on process requirements and GMPs to provide an effective transition into commercial production within a short time period. Experience of formulation process and equipment in the production environment is also important. Pilot plant personnel should know the objective of the formulator and also recognize the view point of production personnel. Due to these reasons, pilot plant organizations include scientists having experience in both areas [5-7].

Space requirements [8]

Administration and information process

Sufficient office and desk space should be provided for both scientist and technician. The space should be close to the working area.

Physical testing area

This area should issue permanent bench top for regularly used physical testing equipment.

Standard equipment floor space

Equipment used should be made movable where ever possible so that after use it can

be stored in the small store room. Space for cleaning of equipment should be also provided.

Storage area

It should have two areas; Approved area and unapproved area, different areas should supply the storage of in-process material finished bulk products from the pilot plant and materials from the experimental scale up Batches made in the production. Storage area for the packaging material should also be provided.

Raw Materials

The pilot plant operation approves and authenticates the active and excipient raw materials used in formulating pharmaceutical products. The raw materials used for small scale formulation trials may not be appropriate for large volume shipments of materials used in a large manufacturing scale. The active ingredients used in a laboratory scale should also fulfill the increasing demands of the product when subjected to scale up. There may be changes in particle size, shape, or morphology, and these changes result in various handling properties or differences in density, solubility rate, static charges, flow properties, etc., of the active/inert ingredients as the batch size increases.

Review of the Formula

A review of every formulation aspect should be done during the scale up process. The use and role of every ingredient in the final product manufacturing on small scale laboratory equipment should be known. Then, the outcomes of scale up using equipment should be determined on a large scale, which may have undergone different types of stresses [8].

Processing equipment

Equipment should be inexpensive, simplest and systematic equipment is used. The size of the equipment should be such that the experiment trials run should be applicable to production sized batches. If the equipment is too small the process developed will not scale up- if equipment is too big then the wastage of the expensive active ingredients.

Process Evaluation [9]

Process evaluation Parameters:

(i) Order of mixing of components.

(ii) Mixing speed.

(iii) Mixing time.

(iv) Rate of addition of granulating agents, solvents, solutions of the drug, etc.

(v) Heating and cooling rates.

(vi) Filters size (liquids).

(vii) Screen size (solids).

(viii) Drying temperature and drying time.

Production rates

While estimating the production rates and the type/sizes of production equipment to be used in the production, the current and future market demands of a product should be kept in mind. The equipment size should be proportional utilization. The selection of equipment and process to be used depends on to it the loss of product in equipment during manufacturing, time needed for cleaning equipment between batches, and the number of batches required for testing [10].

Preparation of Master Manufacturing Procedure [7-8]

The master process records are made for the optimized formulation, in which the manufacturing directions, chemical weigh sheet and in-process and finished product specifications are recorded. The processing steps should be accurate and written in a style which uses language and terms well known to the operators. For writing the manufacturing Procedures, sufficient input should come from the operators or from someone having knowledge and experience in the modern weighing and processing areas. The batch record steps should include specification for mixing time, addition rates, mixing speed, temperature, heating and cooling rates. The record should also bear proper ranges. The batch process record should follow the master process record instructions. The manufacturing process and quality control data should be reviewed annually and if required, some revalidation studies should be performed to make sure that alterations have not ensued. The accurate time, speed, and temperature used in batch process should be recorded. These can be monitored and recorded using suitable controller recorders. GMPs, periodic revalidation, and monitoring of finished product test results through control charts are required for maintaining constant product quality.

Good Manufacturing Practice (GMP) Considerations [11]

The following list includes items which should be a part of GMP for scale up of a new product or process introduction:

i. Equipment qualification
ii. Process validation
iii. Regularly scheduled preventative maintenance
iv. Regular review and revalidation of the process
v. Relevant written standard operating procedures
vi. Use of technically qualified personnel

vii. Adequate facilities for personnel training
viii. A well-defined technology transfer system
ix. Validated cleaning procedures, and a systematic arrangement of equipment for easy material flow and prevention of cross contamination.

Transfer of Analytical Methods to Quality Assurance

The analytical test procedures developed in research during scale up of a new product should be moved to the quality assurance department. The staff of this department should assess the process to ensure that proper analytical instrumentation is present and personnel are trained to do the assigned activities. Research personnel should analyses the assay method and the data acquired during the validation studies for confirming that the analytical procedures have not been changed in a way that may alter the reliability and accuracy of the tests.

PILOT PLANT SCALE UP CONSIDERATIONS FOR SOLIDS

In scaling up the production of solid dosage forms (like tablets and capsules) from experimental laboratory batch sizes to medium- and large-scale production, every operation step should be considered suitably. A method using the same type of equipment produces different results when the equipment size and the material quantity are changed considerably.

There are certain considerations for the pilot plant scale up of solid dosage forms like, to make sure that the recently formulated tablets manufactured by the product development personnel are efficiently, economically, and regularly reproducible on a production scale and design and building of the pharmaceutical pilot plant for tablet manufacture should include all the necessary features to assist maintenance and cleanliness etc.

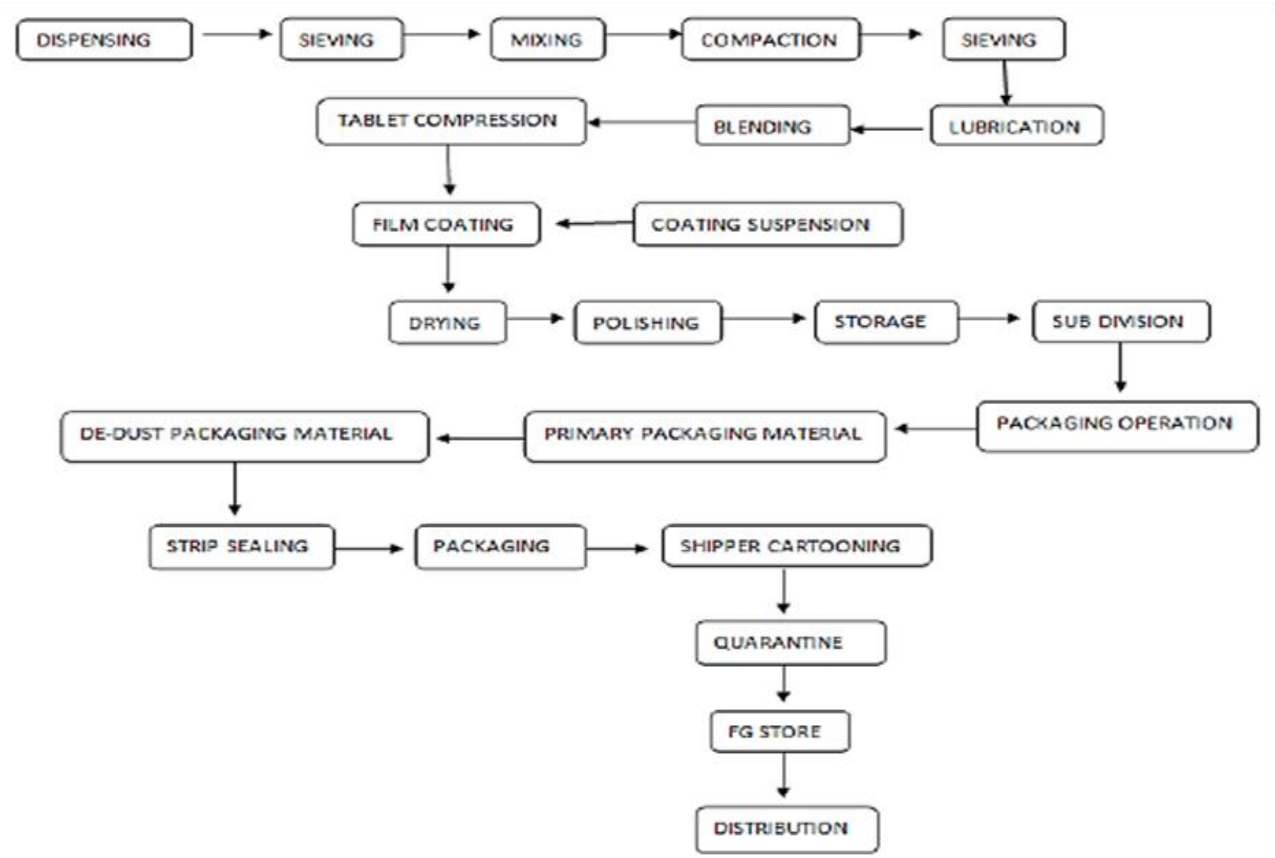


Figure 3: Layout Design

Stages of production of tablets [12-15]

1) Material handling system
2) Dry blending
3) Granulation
4) Drying
5) Reduction of practice size
6) Blending
7) Dry compaction
8) Direct Compression
9) Slugging

Material handling system

In the laboratory, materials are simply dipped of emerged by hand but in intermediate or large scale operations, managing of this substances frequently become important. If a gadget is used to switch substances for more than one product steps have to be taken to stop cross – contamination. Any material managing machine should supply the accurate amount of the ingredient to the system. The more advanced methods of handling materials are vacuum loading systems, metering pumps, screw feed gadget. The sorts of the system selected depend on the nature of materials. Ex- Density, static change [16].

Dry Blending or Mixing [16-17]

The dry blending process utilizes a binary cohesive powder mixture containing particles of two different sizes; the finer particles stick to the surface of the coarse particles. This mixture is also known as interactive mixture.

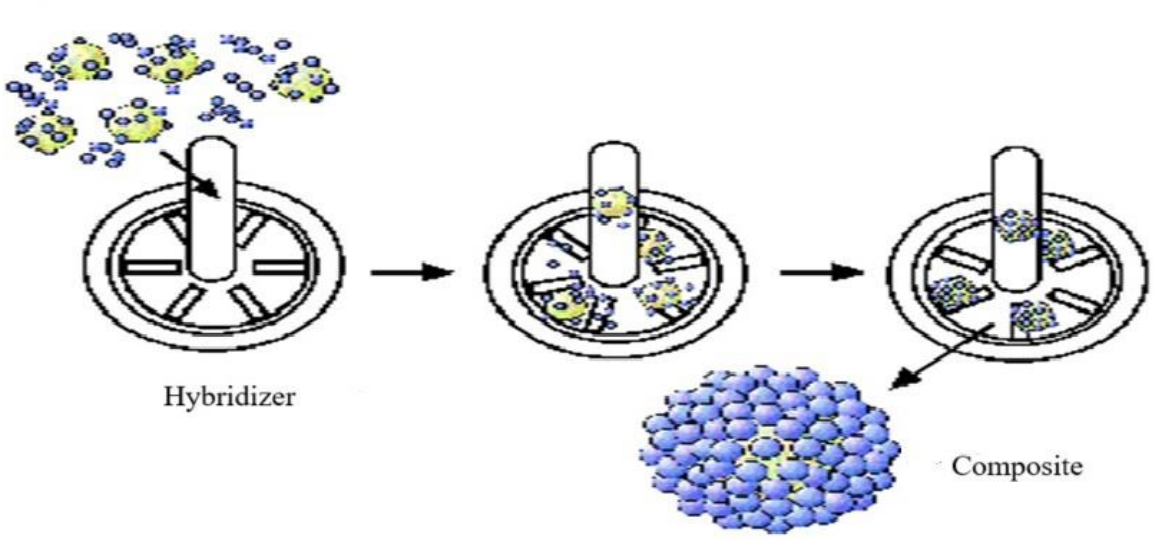


Figure 4: Dry blending method

The agglomerates of fine and coarse powders break down when the fine and coarse particles are blended. During blending, the particles interact and collide with each other, thus, generating an electric charge. This process is irreversible, i.e., the fine and coarse particles do not return to their agglomerate states. New agglomerates, containing finer particles that stick to the coarse particles' surface, are produced as a result of blending. However during the first step, the coating particles stick randomly on the core particles' surface. Processes like screening and/or milling are performed initially to make blending more dependable and reproducible [17].

Problems Associated with Improper Blending

- Flow problem through the equipment,
- Non-reproducible compression, and
- No content uniformity.

Equipment Required for Blending [18]

- V-blender,
- Double cone blender,
- Ribbon blender,
- Slant cone blender,
- Bin blender, and

- Orbiting screw blender's vertical and horizontal high intensity mixers.

Parameters to be considered for improving the Blending Process

- Blending time,
- Blender loading, and
- Blender size.

Granulation [19-21]

The process of granulation involves agglomeration of smaller particles into larger ones, in which the original particles can still be recognized. Pharmaceutical granulation involves enhancing the surface area and dissolution of API by rapidly breaking down the agglomerates. Granulation process is a form of particle designing.

Functions of Granulation Process

- It facilitates uniform drug distribution throughout the product.
- It increases material density.
- It improves flow rates and rate uniformity.
- It aids in metering or volumetric dispensing of drugs.
- It reduces dust production.
- It enhances product appearance.

Types of Granulation Methods

1) Wet granulation method, and
2) Dry granulation method

Table 1: Drying technique for granulation

Granulation Techniques	Drying Techniques
Wet granulation method	Tray or fluid bed dryer
	Vacuum / gas stripping/microwave
	Spray dryer
	Extrusion /spheronisation/pelletisation
Dry granulation method	Direct compression
	Slugging mill
	Roller compactor

Different processes involved in granulation mechanism are wetting, nucleation, coalescence (or growth), consolidation, and attrition (or breakage). Spray rate (or fluid distribution) and feed formulation properties affect the initial wetting of feed powder and the existing granules by the binding fluid.

Table 2: Different parameters and methods for characterization of granules

Parameters	Methods
Particle morphology	Optical microscopy
Particle size distribution	Sieve analysis and laser light scattering
Nature	Powder x ray diffraction
Thermal analysis	DSC, TGA, DTA
Identification	Near infrared spectroscopy
Surface area	Gas adsorption
Granule porosity	Mercury intrusion method
Granule strength	Development of a formulation
Granule flowability and density	Mechanical method, hopper method , density apparatus

Drying

The most familiar conventional method of drying a granulation is still the circulating warm air oven that is heated by means of either steam or power. Drying instances at particular temperature and air flows quotes must be established for every product and for every precise oven load. Fluidized bed dryers are and attractive opportunity to the circulating hot air oven. The essential issue considered as part of scale up fluidized bed dryer is premier loads, charge of air flow, intent air temperature or humidity [21].

Reduction of Particle Size

Particle size indicates the product quality and performance. It also affects the other properties associated with particulate materials. The flow rate of larger and spherical particles is more than that of the smaller or high aspect ratio particles. Dissolution of smaller particles occurs more rapidly (forming suspensions of higher viscosities) than that of the larger particles. Therefore, control and measurement of the particle size distribution of several products is necessary [22].

Problems Produced by Improper Particle Size

- ✓ Weight variation of tablets occurs because of inadequate filling of the die cavity due to large-sized particles.
- ✓ Weight variation of tablets may also occur due to flow ability problems of very fine particles.
- ✓ Chances of mottling increases if the colored granules are coarser.
- ✓ Capping may occur as a result of augmented press speed.

Equipment Involved in Particle Size Reduction

1. Oscillating granulator (for not too hard oversize granulation),
2. Hammer mill,
3. Mechanical sieving device, and
4. Screening device.

Blender

Blending in solid dose manufacturing has two objectives that are to achieve blend uniformity and to distribute the lubricant. Type of blending system often differs from that the usage of in laboratory scale. In any blending operation, each segregation and combining arise concurrently are a feature of particle length, form, hardness, an density and of the dynamics of the mixing motion. Particle abrasion is more possibly to arise when excessive share mixers with spiral screws or blades are used. When a low does energetic component is to be mixed it could be sandwiched between two partitions of directly compressible excipients to avoid loss to the surface of the blender [23].

Dry compaction

Granulation by dry compaction can also be accomplished via passing powders among rollers that compact the material at pressure of up to 10 heaps per linear inch. Materials of very low density require curler compaction to achieve a bulk density sufficient to permit encapsulation or compression. One of the pleasant examples of this technique is the densification of aluminum hydroxide. Pilot plant personnel must decide whether the final drug combination or the active ingredient could be extra efficiently processed on this manner than via conventional processing so that you can produce a granulation with the desired tablet or encapsulation properties [24].

Direct Compression

This process involves direct compression of powder mixture of API and other excipients into tablets. Compression of granules on a high speed tablet press is a crucial test performed to ensure proper tablet formulation and granulation process. Compression features of a formulation are evaluated by keeping the press speed equal to that to be used in normal production during lengthy trial runs. High speed tablet compression is determined by the capacity of the press to interact with the granules. Uniform filling of smaller tablets utilizing a high press speed is more difficult. Induced die feed systems are necessary for high speed machines. These machines are provided with variable speed capabilities and a variety of feed paddles to achieve optimal feed for every step of granulation [25].

Slugging

Also known as dry granulation, pre compression or double compression. This is accomplished on a tablet press designed for slugging. This operates at pressures of approximately 15 tans, compared with a normal tablet press, which operates at stress of 4 tans or less. Slugs-range in diameter from 1 inch. For the extra without difficulty slugged material, to a few or 4 inch in diameter for materials which are greater hard to compressand require more stress per unit location to yields satisfactory compact. If too much satisfactory powder is generated at some point of the million go operation the fabric should be screened and fines recycled via the slugging operation [26].

Tablet coating

Sugar coating, which is done in traditional coating pans, has changed significantly due to recent advancements in coating technology, including the use of aqueous film coating. A unique formulation of the tablet core and coating solution may be required for tablet cores made of naturally hydrophobic materials when film coating with an aqueous system. In a small lab coating pan, a film coating solution might have been discovered to function well with a specific tablet, but it might be completely inappropriate for use on a large production scale [27-30].

CAPSULES

Capsules are defined as unit solid dosage forms of medicaments available as small containers (shells) made of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word capsula, meaning a small container. There are mainly two types of capsule which are hard gelatin capsule and soft gelatin capsule. Hard gelatin capsules are made up of two separate parts called body and cap where soft gelatin capsules are hermetically sealed one piece capsule which cannot be separated. The manufacturing of hard gelatin capsule are produced in two steps where shell is manufactured by one type of machine and then filling is done by another machine but soft are manufactured in one step.

The manufacturing process of hard gelatin capsule is shell composition-gelatin which is used for shell composition it is produced from the collagen by hydrolysis or by extraction process. Generally they are two types of gelatin, which are differentiated by isoelectric point and by nature of viscosity and film forming capacity. To produce optimize shell the combination of pork skin and bone gelatin is often used. Here the

coloring agent is used for color the drug, opaquing agent such as titanium dioxide is preferred for protection against light. Preservatives such as paraben are often used [31].

Steps in capsule production

i. Mixing of ingredient
ii. Granulation and lubrication
iii. Making of capsules
iv. Filling of capsules
v. Uniformity testing
vi. Packing and labelling

Manufacturing of Hard gelatin capsules

Shell composition [32-33]

Gelatin

Prepared by the hydrolysis of collagen, gelatin in its chemical and physical properties depends upon the source of the collagen and extraction. There are two basic types of gelatin: Type-A and Type-B. The two types can be differentiated by their isoelectric points (7.0-9.0 for Type A and 4.8-5.0 for Type B) and by their viscosity and film-forming characteristics. Combination of born skin and bone gelatin are often used to optimize shell characteristic. The physicochemical properties of gelatin of most interest to shell manufactures are the bloom strength and viscosity.

Colorants

Various soluble synthetic dyes ("coal tar dyes") and insoluble pigments are used**.** Not only play a role in identifying the product, but also may improve patient compliance. For example, white for analgesia; lavender for hallucinogenic effects; orange or yellow for stimulants and antidepressants.

Opaquing Agents

Titanium dioxide may be included to render the shell opaque**.** Opaque capsules may be employed to provide protection against light or to conceal the contents.

Preservatives

When preservatives are employed, parabens are often selected.

Shell manufacture [34]

Dipping

Pairs of stainless steel pins are dipped into the dipping solution to simultaneously form the caps and bodies**.** Pins are at ambient temperature; whereas the dipping solution is maintained at a temperature of about 50°C in a heated, jacketed dipping pan**.** The length of time to cast the film has been reported to be about 12 seconds.

Rotation

After dipping, pins are elevated and rotated 2-1/2 times until they are facing upward**.** This rotation helps to distribute the gelatin

over the pins uniformly and to avoid the formation of a bead at the capsule ends.

Drying

The racks of gelatin-coated pins then pass into a series of four drying ovens**.** Drying is mainly done by dehumidification**.** A temperature elevation of only a few degrees is permissible to prevent film melting**.** Under-drying will leave the films too sticky for subsequent operation.

Stripping

A series of bronze jaws strip the cap and body portions of the capsules from the pins.

Trimming

The stripped cap and body portions are delivered to collects in which they are firmly held. As the collects rotate, knives are brought against the shells to trim them to the required length.

Joining

The cap and body portions are aligned concentrically in channels, and the two portions are slowly pushed together.

Sorting

The moisture content of the capsules as they come from the machine will be in the range of 15-18% w/w. During sorting, the capsules passing on a lighted moving conveyor are examined visually by inspectors. Defects are generally classified according to their nature and potential to cause problems in use.

Sizes and Shapes

For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 to 5. The largest size normally acceptable to patients is No. 0.Three larger sizes are available for veterinary use: 10, 11, and 12, having capacities of about 30, 15, and 7.5 grams, respectively.

Sealing

Capsules are sealed and somewhat reshaped in the Etaseal process. This thermal welding process forms an indented ring around the waist of the capsule where the cap overlaps the body.

Storage

Finished capsules normally contain an equilibrium moisture content of 13-16%. It is important to maintain a relative humidity of 40-60% when handling and storing capsules.

Composition of the Shell

Similar to hard gelatin shells, the basic component of a soft gelatin shell is gelatin; however, the shell has been plasticized. The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3-1.0 for a very hard shell to 1.0-1.8 for a very soft shell. Up to 5% sugar may be included to give a "chewable"

quality to the shell. The residual shell moisture content of finished capsules will be in the range of 6-10%.

Manufacturing of Soft Gelatin Capsule

Soft gelatin capsules-plasticizer

It is made up of a soft shell that is elastic and pliable. Commonly used plasticizers are glycol, sorbitol, and propylene glycol-400. There should be minimal interaction between the liquid fill material and the soft gel shell. The presence of water is 30%-40% of the wet formulation, and its presence is important during gel preparation (Augsburger LL, 1990). The colorants, which may be natural or synthetic, are used for desired shell color. An opacifier is also added to prepare an opaque shell; a commonly used opacifier is titanium dioxide. The preservative, used to prevent the growth of microbes, is typically present in a concentration range of 0.2%; commonly used preservatives include methyl paraben and propyl paraben. Flavoring agents used to mask bitter taste commonly include ethyl vanillin, essential oil, and sucrose.

Formulation [35]

Formulation for soft gelatin capsules involves liquid rather than powder technology. Materials are generally formulated to produce the smallest possible capsule consistent with maximum fill. The liquids used are limited to those that do not adversely affect the gelatin walls. The pH of the lipid can be between 2.5 and 7.5.Emulsions cannot be filled because water will be released, which would affect the shell. The types of vehicles used in soft gelatin capsules fall into two main groups:

1. Water-immiscible, volatile or semi-volatile liquids, such as vegetable oils, mineral oils, medium-chain triglycerides, and acetylated glycerides.
2. Water-miscible, nonvolatile liquids, such as low molecular weight polyethylene glycols (PEG), which have come into use more recently due to their ability to mix with water readily and accelerate the dissolution of dissolved or suspended drugs.

All liquids used for filling must flow by gravity at a temperature of 35°C or less. The sealing temperature of gelatin films is 37-40°C.

Manufacturing Process [36]

Plate Process

Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets. Applying vacuum to draw the sheet into the die pockets. Filling the pockets with liquid or paste. Folding the lower half of the gelatin sheet back over the filled pockets. Inserting the "sandwich"

under a die press where the capsules are formed and cut out.

Rotary Die Process

In this process, the die cavities are machined into the outer surface of two rollers. The die pockets on the left-hand roller form the left side of the capsule, and the die pockets on the right-hand roller form the right side of the capsule. Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism. As the die rolls rotate, the convergence of the matching dies pockets seals and cuts out the filled capsules.

Accogel Process

This is another rotary process involving a measuring roll, a die roll, and a sealing roll. As the measuring roll and die roll rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll. The continued rotation of the filled die roll converges with the rotating sealing roll, where a second gelatin sheet is applied to form the other half of the capsule. Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

Bubble Method

The Globex Mark II capsulator produces seamless, one-piece soft gelatin capsules using a "bubble method."

A concentric tube dispenser simultaneously discharges molten gelatin from the outer annulus and the liquid content from the inner tube. Using a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets, forming a liquid medicament core within a molten gelatin envelope. The droplets assume a spherical shape under surface tension forces, and the gelatin congeals as it cools. The finished capsules must be degreased and dried.

Scale-Up and Post-Approval Changes (SUPAC) Guidelines

Introduction

Scale-Up and Post-Approval Changes (SUPAC) refer to the processes involved in scaling up production and implementing changes made after a drug product has received regulatory approval. These changes may include modifications to the composition, manufacturing process, equipment, or manufacturing site. Such alterations often impact the chemistry or manufacturing process of the drug product.

Depending on anticipated or unforeseen requirements, variations in raw materials, processes, equipment, manufacturing sites, or batch sizes may occur, potentially affecting the quality of the drug or finished product. Therefore, it is essential to predict

and evaluate the impact of any changes on the product's quality. The extent of any adverse effects resulting from such changes depends significantly on the specific dosage form involved [37].

SUPAC Guidelines - History

In 1991 and 1992, the American Association of Pharmaceutical Scientists (AAPS), the United States Food and Drug Administration (FDA), and the United States Pharmacopoeia (USP) organized two workshops. These workshops focused on discussing the key aspects of modifying drug product procedures or compositions after regulatory approval had been granted.

The discussions during these workshops covered various types of changes, including modifications to the formulation or composition of the product, alterations in manufacturing processes, scaling up the production processes, and adjustments to the manufacturing site or campus where operations were conducted.

Ultimately, the FDA published the outcomes of these workshops in the form of a guideline document titled "Scale-Up and Post-Approval Changes" (SUPAC).SUPAC, which stands for "Scale-Up and Post-Approval Changes," encompasses the process of scaling up as well as post-approval modifications related to the product's composition, production processes, manufacturing equipment, and site location.

Advantages and Disadvantages of SUPAC

The implementation of SUPAC offers several benefits. It simplifies the monitoring of scale-up processes by personnel from the production and quality assurance departments. In addition, within the larger spaces of the production division, it facilitates the procurement of excipients and medicinal supplies that have already been approved by the quality control team. The installation, maintenance, and repair of equipment also become more efficient with the involvement of experts from the engineering department.

However, SUPAC does come with certain drawbacks. One major disadvantage is the reduced face-to-face interaction between formulators and production personnel during the manufacturing process. Furthermore, challenges may arise in situations involving changes in packaging activities, analytical testing laboratories, or the manufacturing site's location.

Purpose of Guidance

The SUPAC (Scale-Up and Post-Approval Changes) guidelines provide clear instructions for sponsors of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and

Abbreviated Antibiotic Drug Applications (AADAs) regarding post-approval changes.(38) These changes may involve the following aspects of an immediate-release solid oral dosage formulation

1. Components or Composition
2. Manufacturing Site
3. Scale-Up or Scale-Down of Manufacturing
4. Manufacturing Process and Equipment:

The guidance outlines the following key elements to ensure consistent product quality and performance;

1. Levels of Change – Categorization of changes into minor, moderate, or major.
2. Recommended Tests – Chemistry, manufacturing, and control (CMC) tests for each change level.
3. Dissolution/Bioequivalence Tests – In vitro dissolution and/or in vivo bioequivalence tests corresponding to the level of change.
4. Documentation – Specific supporting documents required for each change level to meet regulatory expectations.

This guidance ensures that the Center for Drug Evaluation and Research (CDER) receives all necessary information to maintain product consistency and compliance during post-approval modifications [39].

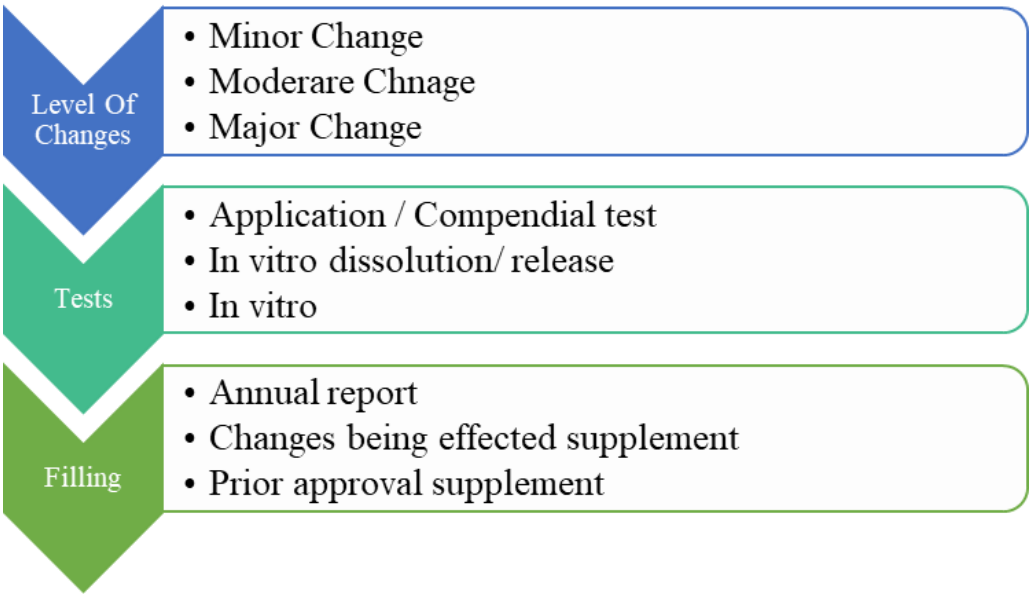


Figure 5: SUPAC Guidelines

Levels of Change [40-41]

1. Minor Changes (Level 1)

These involve changes with minimal risk to product quality, such as adjustments where equipment, SOPs, environmental conditions (e.g., temperature, humidity), and controls remain identical across facilities. Personnel must have equivalent experience and operate within a single campus or facility using unchanged batch records, apart from updates to administrative details or facility location.

2. Moderate Changes (Level 2)

Moderate changes involve adjustments that may impact the product but do not require extensive revalidation. These could include adjacent or similar process modifications where the same equipment type is used under slightly modified conditions, ensuring no impact on the product's critical attributes.

3. Major Changes (Level 3)

Major changes involve significant modifications, such as relocating manufacturing to a new facility where conditions, personnel, or equipment differ substantially, or processes are scaled up or down significantly. These require prior regulatory approval due to their potential impact on the product’s quality or performance.

Site Changes

Site changes refer to relocating the manufacturing site, whether it is company-owned or a contracted facility. Such changes exclude alterations to the scale-up process, manufacturing equipment, or product composition. Any new site must adhere to Current Good Manufacturing Practices (CGMP) inspection (42).

Test documentation and levels of site changes [43].

Levels 1 Changes

Level 1 changes involve relocating manufacturing operations within the same facility or campus where identical equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity), and controls remain unchanged. Personnel at the new location must have equivalent expertise, and the manufacturing batch records should remain unaltered, except for administrative updates or the facility's location details.

Level 2 Changes

Level 2 changes involve transferring operations between facilities situated on an adjoining campus or in adjacent city blocks. These changes require that identical equipment, SOPs, environmental conditions, and personnel common to both locations be utilized. There should be no modifications to

manufacturing batch records except for administrative updates, including facility location changes.

Chemistry Documentation: Updated location details and batch records; no further requirements beyond application/compendial release standards.Stability Testing: Long-term stability data for one batch must be included in the Annual Report.Dissolution Documentation: No additional requirements beyond application/compendial release standards.

Level 3 Changes

Level 3 changes involve relocating manufacturing operations to a facility in a non-adjacent campus or an entirely different geographical location. To qualify as a Level 3 change, identical equipment, SOPs, and environmental conditions must still be maintained, and manufacturing batch records should not be altered, apart from administrative updates such as location and language translations.

Chemistry Documentation: Updated location information and batch records, along with adherence to application/compendial release requirements.

Stability Testing: If substantial data is already available: Stability testing for one batch with three months of accelerated stability data is required in the supplement, while long-term stability data for one batch is included in the Annual Report.

If substantial data is unavailable: Stability testing for up to three batches with three months of accelerated stability data must be reported in the supplement, with long-term data for up to three batches included in the Annual Report.

Filing Documentation: Submission through a "Prior Approval Supplement" with relevant stability data incorporated.

Changes in Batch Size (Scale-Up or Scale-Down) [44-45]

Changes in batch size refer to modifications in the production scale of a pharmaceutical product. These changes may involve scaling up or scaling down from the pivotal or pilot scale bio-batch material to a larger or smaller production batch. Batch size reductions below 100,000 dosage units are not covered under these guidelines. All scale-up changes must be validated thoroughly and, if necessary, inspected by authorized regulatory personnel.

1. Level 1 Changes

Level 1 changeinvolves modifications in batch size up to and including a scale factor of 10 times the size of the pilot bio-batch, under the following conditions:

1. The equipment used for production must be of the same design and operate on identical working principles.
2. Manufacturing must comply with current Good Manufacturing Practices (CGMP).
3. The formulation, manufacturing methods, SOPs, and controls must remain consistent between the test batch and full-scale production batch.

Test Documentation Requirements:

1. Chemistry Documentation: Fulfillment of application and compendial release specifications.

Notification of the change and submission of updated batch records in the annual report.

2. Stability Testing: One batch with long-term stability data reported in the annual report.
3. Dissolution Documentation: No additional requirements beyond application and compendial release specifications.
4. In Vivo Bioequivalence: Not required for Level 1 changes.
5. Filing Documentation: Annual report submission, including long-term stability data.

2. Level 2 Changes

Level 2 changes involve modifications in batch size exceeding a scale factor of 10 times the size of the pilot bio-batch, under the following conditions:

1. The equipment used for production must have a similar design and identical working principles.
2. The manufacturing process must adhere to CGMP guidelines.
3. The same formulation, SOPs, controls, and manufacturing methods must apply to both the test batch and full-scale production batch.

Test Documentation Requirements:

1. Chemistry Documentation: Compliance with application and compendial release specifications. Notification of the change with updated batch records submitted in the filing process.
2. Stability Testing: One batch with three months of accelerated stability data.One batch with long-term stability testing, with results submitted in the annual report.
3. Dissolution Documentation: Case B dissolution testing is required.
4. In Vivo Bioequivalence: Not required.
5. Filing Documentation: Changes must be filed via supplementary submission with justification Long-term stability data must be reported in the annual report.

Manufacturing: Equipment and Process Changes [46-47]

Changes in manufacturing equipment and processes can impact the quality, stability,

and consistency of a product. Such changes are categorized into levels based on the nature and extent of the modifications. Appropriate documentation, testing, and filing are required to ensure compliance with regulatory standards.

1. Equipment Changes [48]

Level 1 Equipment Changes

This category involves minor modifications to equipment, such as:

1. Transitioning from non-automated or non-mechanical equipment to automated or mechanical equipment for material handling.
2. Using alternative equipment with similar design and operating principles, even if the capacity is different.

Test Documentation Requirements:

1. Chemistry Documentation: Compliance with application and compendial release specifications. Notification of the change and submission of updated batch records.
2. Stability Testing: One batch must be subjected to long-term stability testing.
3. Dissolution Testing: No additional requirements beyond application and compendial release specifications.
4. In Vivo Bioequivalence Testing: Not required.
5. Filing Documentation: Changes must be reported in the annual report with supporting data.

Level 2 Equipment Changes

This category involves changes to equipment with a different design or operating principles, potentially affecting the manufacturing process.

Test Documentation Requirements:

1. Chemistry Documentation: Compliance with application and compendial release specifications. Notification of the change and submission of updated batch records.
2. Stability Testing: If significant data is available: One batch with three months of accelerated stability data submitted in a supplement. One batch with long-term stability data included in the annual report.If significant data is not available, Up to three batches with three months of accelerated stability data submitted in a supplement. Up to three batches with long-term stability data included in the annual report.
3. Dissolution Testing: Case C dissolution profile testing is required.
4. In Vivo Bioequivalence Testing: Not required.
5. Filing Documentation: Submission of a prior approval supplement, including justification for the change, with stability data included in the annual report.

2. Process Changes [49]

Level 1 Process Changes

This category includes minor process adjustments, such as changes in mixing time within the validated ranges.

Test Documentation Requirements:

1. Chemistry Documentation: None beyond application and compendial release specifications.
2. Dissolution Testing: None beyond application and compendial release specifications.
3. In Vivo Bioequivalence Testing: Not required.
5. Filing Documentation: Changes must be reported in the annual report.

Level 2 Process Changes

This category includes moderate process changes, such as changes in mixing time or speed of operation, beyond the validated ranges.

Test Documentation Requirements:

1. Chemistry Documentation: Notification of the change and submission of updated batch records.
2. Dissolution Testing: Case B dissolution profile testing is required.
3. In Vivo Bioequivalence Testing: Not required.
4. Filing Documentation: Submission of a supplement, with long-term stability data included in the annual report.

Level 3 Process Changes

This category involves significant process changes, such as switching from wet granulation to direct compression of dry powder.

Test Documentation Requirements:

1. Chemistry Documentation: Compliance with application and compendial release specifications.Notification of the change and submission of updated batch records.
2. Stability Testing: If significant data is available, One batch with three months of accelerated stability data reported in a supplement.One batch with long-term stability data included in the annual report.If significant data is not available, Up to three batches with three months of accelerated stability data reported in a supplement.Up to three batches with long-term stability data included in the annual report.
3. Dissolution Testing: Case B dissolution profile testing is required.
4. In Vivo Bioequivalence Testing: A bioequivalence study may be waived if a validated in vitro/in vivo correlation (IVIVC) is established.
5. Filing Documentation: Submission of a prior approval supplement with justification for the change.Stability data must also be included in the annual reports.

In-vitro Dissolution

See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12 individual dosage units. Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1 + 1/n \Sigma (R_t - T_t)^2] \times 100\}^{-0.5}$$

Where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

This format is now ready for pasting in MS Word without any changes to the text. (50)

In- Vivo Bioequivalence Study [51-53]

In-vivo bioeqvalence study is a guide and the design of actual study may change based on the drug and dosage form. The overall summary of a study is given below

Objective

The primary objective of the in-vivo bioequivalence study is to evaluate and compare the pharmacokinetic properties (rate and extent of drug absorption) between a modified drug product (post-manufacturing alteration) and the original formulation (pre-alteration), in accordance with regulatory requirements.

Study Design

The recommended study design is a single-dose, two-treatment, two-period crossover model with adequate washout periods between the dosing phases. Participants are randomly assigned to different dosing sequences to ensure balanced representation across all groups.

Selection of Subjects

The number of subjects should be statistically determined to account for intra-subject variability and to achieve the current bioequivalence intervals.

Subjects must meet predefined inclusion and exclusion criteria based on health status and drug metabolism characteristics.

Analytical Method

The selected analytical method must ensure:

I. Specificity: Accurate quantification of the analyte, free from interference by impurities and degradation products.
II. Precision: Consistency in results under both inter-day and intra-day conditions.
III. Linearity: A linear relationship between analyte concentration and instrument response over a defined range.
IV. Accuracy: Closeness of measured values to the true values

V. Sensitivity: Ability to detect the smallest measurable concentrations.
VI. Recovery: High recovery efficiency from the biological matrix.
VII. Stability: Ensuring the stability of samples under defined storage and handling conditions.

Pharmacokinetic Analysis

Pharmacokinetic parameters are derived from plasma drug concentration-time data, including:

- AUC (Area Under the Curve): AUC_{0t} and $AUC_{0\infty}$.
- Cmax: Peak plasma concentration.
- Tmax: Time to reach Cmax.
- Kel: Elimination rate constant.
- T½: Terminal half-life.

Statistical Analysis

Linear Model Analysis: Using software such as SAS or equivalent, a linear model should evaluate period, sequence, and treatment effects on pharmacokinetic parameters.

Two One-Sided t-Test Procedure: 90% confidence intervals for differences between test and reference least squares means should be calculated for pharmacokinetic parameters such as AUC_{0t}, $AUC_{0\infty}$, Cmax, and Tmax.

Study Procedure

Each subject undergoes two treatments (Treatment 1: drug with proposed changes; Treatment 2: drug without proposed changes), following a fasting period of at least 10 hours.

After drug administration (with 240 mL water), subjects must refrain from food intake for at least 4 hours. Post this period, standardized meals are provided as per the study schedule. Water may be provided as necessary, except during the 1-hour periods before and after drug administration. Prohibitions include alcohol, xanthine-containing foods, and caffeine from two days before the study until the last blood sample is collected.

Conclusion

The pilot plant scale-up technique serves as a cornerstone in the pharmaceutical industry, bridging the critical gap between laboratory-scale formulations and full-scale commercial production. By integrating systematic methodologies, it ensures the successful transition of products while maintaining quality, compliance, and efficiency. Through detailed process evaluations, optimization of production parameters, and adherence to Good Manufacturing Practices (GMP), these techniques minimize risks, reduce costs, and expedite market readiness. The emphasis on technological adaptability, personnel training, and regulatory compliance further highlights its

significance in modern pharmaceutical development. Ultimately, pilot plant studies represent a harmonious blend of innovation and practicality, underscoring their vital role in advancing pharmaceutical manufacturing practices.

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