WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Pilot Plant Scale-Up Condiserations for Solid Orals

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DOI: https://doi.org/10.55248/gengpi.4.723.40723

A B S T R A C T

Background: Pharmaceutical industry pilot plant is defined as a part of this industry where a lab scale formula is transformed into a viable commercial product by the development of reproducible practical procedures for manufacturing. A pilot plant is a small industrial system which is operated to generate information about the behaviour of the system for use in design of larger facilities for large scale production.

Objectives: To study and collect the information regarding pilot plant scale-up considerations for solid orals, and to report the same.

Keywords: Pilot plant scale-up, objectives, aspects, considerations.

1. INTRODUCTION

A chemical plant is an industrial process set-up that manufactures or processes various chemicals on a large scale. It is a place where money, material, man, method and machine are brought together for the manufacturing of the products out of chemicals. A pilot plant is a small industrial system which is operated to generate information about the behaviour of the system for use in design of larger facilities for large scale production. Pilot plant is a relative term wherein plants are comparatively smaller than that of full-scale production plants. These are built in a range of sizes. Pilot plants are designed for learning and are typically more flexible at the expense of economy.[1]

Pharmaceutical industry pilot plant is defined as a part of this industry where a lab scale formula is transformed into a viable commercial product by the development of reproducible practical procedures for manufacturing.[2]The pilot scale is also called as immediate batch scale where drug products are manufactured by a procedure which is fully representative of and stimulatory to that of manufacturing scale.[3]Whereas scale-up is next to pilot scale process where the batch size, for example mixing, is increased or a procedure for the same process is applied for different output volumes, for example, tableting.[4]

Scale up is the process of creating a prototype using information from a pilot plant model. As a natural aspect of pharmaceutical development, scaling up of formulation design occurs from first-in-human through all clinical trial stages and into commercialization. The batch size increases at each stage of process development, starting with laboratory-scale batches that may be quite small to support preclinical and early clinical stages, then moving up to pilot batches used in process development, and finally to the production-scale batches required to support commercialization. Unsurprisingly, the production process is significantly impacted by the size, speed, and power of the equipment used, which must match the batch-size requirements for efficient production.[5]

2. OBJECTIVES OF PILOT PLANT SCALE-UP

Regardless of the batch's size and intended usage for stability testing and clinical trials, to provide an orphan medicine to a more limited number of patients, or to The goal of a commercial product is always to serve a bigger population; regardless of the production scale, the end product must be equal to the original formulation design. It is typically impossible to predict the impacts of a scale expansion many times over during the development stage. Large-scale processing plants cannot be successfully designed only based on laboratory data. For example, new formula can be processed for large scale only after its examination to determine its ability to withstand batch-scale and process modification. Thus, the main objective of pilot plant is to perform trial experiments on small scale to find critical parameters, mistakes and investigations on a small scale for making profits on a large scale.

Evaluation and validation of process and equipment's, identification of the critical features of the process, designing guidelines for production and process controls, provide master manufacturing formula with instructions for manufacturing procedure, avoid the scale-up problems etc. are some of the important objectives of pilot plant studies. The other objectives include investigation of a product and process on an intermediate scale before large amounts of money are committed to full-scale production, understand what makes these processes similar, identify and eliminate many scale-up problems before investing large sum of money on a production unit and to maintain the chemical attributes of the product, its quality and efficacy even though the production processes are modified as a result of sample size increase and equipment changes.

3. ASPECTS OF PILOT PLANT SCALE-UP

3.1. Functions of Pilot Plant Scale-Up

Figuring out the layout and physical space needed for associated functions in order to scale up effectively.

Determining whether raw materials are continuously available that meet the requirements needed to make the product.

Controls for the production process are evaluated, verified, and finalised.

Provision of sufficient records, reports, and other materials to support Manufacturing Practices (GMPs).

To give historical development information on the tools and training used in the formulation production process.

To design and evaluate practical product reprocessing methods.

In order to ensure that a scale-up process is in control and that each level of the process keeps the stated properties that were initially planned, it is important to define its crucial features.

To manage and regulate the production pace and anticipated market demands.

3.2. Applications of Pilot Plant Scale-Up

Pilot plant scale up technique is used to evaluate results of laboratory trials and to make product and process corrections and improvements. In addition, it can be employed to test, verify and validate new production technology and/or procedures using small volumes of products produced by new technology, mainly for the purpose of learning about the new technology. The knowledge so obtained is then used for design of full-scale production: systems for commercial products. In addition, pilot scale can also be used for identification of further research objectives as well as to support investment decisions. In pharma sector it is used for producing small quantities of product for sensory, chemical and microbiological evaluations, and limited market testing or furnishing samples to potential customers, and also for shelf-life and storage stability studies. It is used to determine possible saleable by products or waste stream that 9 requires treatment before discharge. It gives data that can be used in making a decision on whether or not to proceed to a full-scale production process. In addition, based on outcome of pilot scale studies it can be used to design and contact a full se plant or to make certain modifications in an existing plant.[6]

3.3. Significance of Pilot Plant Scale-Up

Using high-speed production equipment, reproducible manufacture of an experimental formulation is required for pilot plant scale-up approaches. A product must be able to be processed at a greater scale, frequently with equipment that mimics that used in the development laboratory, for a pilot scale up to be effective. Plot plant studies actually play a vital role in formula standardisation, assessing a variety of pertinent processing equipment, and optimising and regulating desired production rates.[7]

In addition, & has significance in obtaining information with regard to infrastructural requirements for equipment's and processes for the scale up batches. Identification of critical parameters in order to maintain quality of a products and generating appropriate records and reports to support GMP are important issues.

3.4. Checklist for Pharmaceutical Pilot Plant Scale-Up

As the professional scale-up personnel, we have to carefully plan each technology transfer and scale up events with concern Contract Manufacturing Organization (CMO) A CMO, sometimes called a Contract Development & Manufacturing Organization (CDMO) a company that serves other companies in the pharmaceutical industry on a contract basis to provide comprehensive services from drug development through drug manufacturing. Following is the checklist of the key considerations for Pharmaceutical Pilot Plant Scale-Up.

- The Right People
- The Right Equipment
- The Right System

- The Right Price
- The Right Location.[8]

4. GENERAL CONSIDERATIONS FOR PILOT PLANT SCALE-UP

A pilot plant is a must to have section that can be found in all new and an already existing drug product manufacturing industry. In pilot plants, products are produced with an intermediate batch size which represents procedures and simulations that can be used during the commercial manufacturing Pilot plant scale-up must include a close inspection of the formula to determine its ability to withstand large scale and process modification. In order to develop a reliable and practical method of manufacturing pharmaceutical products following issues need to be considered.[9]

The considerations of pilot plant, for example tablets, include parameters such as granulation feed rate, compression parameters, temperature, rate of drying etc. which has a critical role in its development. The general considerations include type of product such as solid liquid, semisolid or gaseous dosage forms size of product depending on the goals; evaluation methods of product and process; purpose of producing samples of product such as for evaluation market testing or furnishing to potential customers. The other considerations include location either near R&D facility or at an existing plant. It also includes interpersonal relation such as a close liaison between R&D and pilot plant staff. In addition, labour requirements such as engineering staff, skilled operators and maintenance staff and pilot plant costs that may exceed those of usual plant production costs are also need enough consideration. The pilot plant may be used for training personnel for a full-scale plant. A review of a range of relevant processing equipment's to determine which would be most compatible with the formulation as well as the most economical, simple and reliable in producing the product is equally important.[10-14] Various considerations that affect an orderly transition of methods and procedures from laboratory to routine processing in a full scale production facility are described below.

- Processing Equipment's
- Production Volume
- Process Optimization and Validation
- Master Manufacturing Procedure
- Good Manufacturing Practice (GMP)
- Transfer of Analytical Methods
- Personnel Requirements
- Space Requirements

-Administrative and Information Processing

-Physical Testing Area

-Equipment Floor Space

-Storage Area

5. PILOT PLANT SCALE-UP CONSIDERATIONS FOR SOLID ORALS

5.1. Laboratory Scale-Up

Once a formulation scientist develops a laboratory scale product and/or process, the first step toward commercialization is to scale it up at a pilot plant level. The purpose of this scale-up is to assure that the data, information, and findings observed for small scale (bench-top scale) batches are reproducible during comparatively larger pilot scale manufacturing. This is because not all formulations and/or processes behave in the same. manner at all manufacturing scales. The main objective of pilot plant manufacturing is to define any changes in the formulation or process that must be made when the product is produced on a larger commercial scale. Laboratory bench scale batches are usually of 1 to 5 kg in batch size, whereas pilot scale batches range from 10 100 kg depending on the working capacity of the pilot plant facilities. A solid dosage form, for example tablets, is the most common dosage form among the pharmaceutical products. For most large pharmaceutical companies tablet production is the most preferred dosage form produced.[15,16]

Pharmaceutical processes involved in solid dosage form manufacturing of tablets fall into granular products and directly compressible products

(a) Granular Production

Granular products are routinely manufactured as dry granulation or wet granulation using a series of equipment's known as the equipment train. For granular products, following typical equipment train is used for tablet processing,

i. Granulator (for example, high shear, low shear, top spray)

ii. Dryer (for example, fluid bed or tray drying)

iii. Mills (for example, oscillating, impact, or conical)

iv. Blender (for example twin shell blending or tote/bin blending)

v. Compression (for example, rotary tablet press)

vi. Tablet coater (for example, film or sugar)

Granular products are more consistent in their production and it is easier to incorporate various materials such as drugs or excipients. These materials are typically compressed using normal tablet press which operates at pressure of 4 tons or less. The major limitation of these products is the increased cost in capital equipment because they usually are much complex to produce as a result of a lengthy equipment train. This complex train may lead to lengthy processing times it takes to complete the manufacturing because these products involve increased process complexity. It is important to consider material movement between various equipment's in the train as well as to know how it can be handled, for example, manually or by mechanical transfer. In order determine how these products will be handled on a larger manufacturing scale it is must to investigate the effects of mechanical material transfer Dry granulation is done using tablet press designed for slugging which operates at pressures of about 15 tons Slugs range in diameter from 1 inch to 4 inch depending upon slugging properties of materials. Some materials are more difficult to compress and require more pressure per unit area to yield satisfactory compacts. If an excessive amount of fine powder is generated during the milling operation the material must be screened and fines are recycled through the slugging operation.[16]

(b) Directly Compressed Tablets

Granulation by dry compaction usually achieved by allowing powders to pass through between two rollers that compact the material at pressure of up to 10 tons per linear inch. A very low-density material requires roller compaction to achieve sufficient bulk density to permit compression, for example, densification of aluminium hydroxide. Pilot plant personnel should determine whether the final drug blend could be more efficiently processed by direct compression than by conventional processing to produce a granulation with the required tableting properties. For directly compressed tablet products a typical equipment train used for processing involves:

i. Blender (for example, twin shell blending, or sigma/ribbon blade mixing)

ii. Compression (for example, rotary tablet press)

iii. Tablet coater (for example, film or sugar)

The direct compression products are relatively easier to produce because of simple manufacturing process or equipment train that overall requires less processing time. The limitation of this process is that the product quality and reproducibility are much more dependent on the quality of raw materials. Thus, it is essential that the raw material vendors provide raw materials with consistent quality that meet the predefined specifications. If there are no appropriate raw material specifications, then this may lead to processing problems such as segregation or finished product testing issues like weight variation and content non uniformity.[17]

Amongst various existing types of manufacturing equipment, there are no issues with obtaining equipment required for pharmaceutical solid dosage form processing. There may be differences with respect to equipment design and specifications for each individual type of process. This can be further elaborated with following examples,

i) High-shear granulators: Change configuration such as top driven or bottom driven, granulator size, number and arrangement of chopper blades, configuration of mixing or impeller blade, tip speed of blade etc.

ii) Tray dryers: Dryer size, volume of air, number, size and area of trays, drying temperatures etc.

iii) Fluid bed dryers: Granule bed height, volume of air, drying temperatures etc.

iv) Size reduction/separation mills: Type of mill and mechanism involved (for example, oscillating, conical, air, jet) etc.

v) Blending: Blender capacity, shape, configuration, use of extended blender leg etc.

vi) Tablet compression: Feed mechanism (for example, gravity or force fed), type of feeder, turret speed, dwell time, feed frame speed, pre-compression and final compression capabilities, insertion depth, type of dies, tools etc.

vii) Tablet coating: Type of spray nozzle, atomizer spray settings, spray pattern, spray rate, air volume etc.

viii) Additional facilities: Air conditioning, humidity control, type of material transfer (for example, manual or mechanical) etc.

5.1.1. Manufacturing Equipment Attributes

In the scale up processing in pilot plants, it is always preferred to use equipment of similar design at both laboratory and pilot scale to obtain the reproducible results. However, in case of novel solid dosage forms, or new processes done at laboratory scale, similar pieces of equipment's in pilot scale may not be available. In some cases, the process may be so unique that pilot plant as well as at larger scale similar equipment may not yet exist or are not

readily available without significant customization, for example, vacuum foam dryer for processing thermolabile drugs. In such situations, it is necessary to work with existing process equipment manufactured to design and configure suitable equipment that meets the requirements set by the formulation development scientists and/or process engineers, example, conventional freeze dryer. It is always advisable to work with existing pharmaceutical equipment manufacturers and is helpful as they are familiar with current Good Manufacturing Practices (CGMPs). At the same time look for the opportunities available with the other manufacturers for equipment that may have similar manufacturing attributes.
It is well known fact that pilot batches are of approximately 1/10 of the scale used for commercial manufacturing While scale-up to pilot or commercial scale there may be significant differences with respect to the type and design as well as manufacturer of the processing equipment. There may also be differences within a particular manufacturer's line) for equipment as the capacity of the equipment increases in size. An important consideration that should be made at the start of pilot scale is the processing time. This is because the main intention is to manufacture at a commercial scale and the processing time has a significant impact on the operational efficiency f manufacturing plants. The goal is to make a very robust formulation using a particular process, and if it comes at the expense of a lengthy processing time, the manufacturing plant may reject the process as it may lead to increased labour costs. Comp process and lengthy processing time reduces the operational efficiency of plants It may reduce ability of plant to manufacture other products as most of the processing equipment in the plant is shared with other product or process. Thus, when developing a process, reasonable attempts need to be made to keep processing times and equipment utilization to a minimum. There are many examples wherein a process developed at laboratory scale by the formulation scientist underwent a significant change to the formulation or process at pilot scale. This issue is well handled by inclusion of process engineer either from R&D or from the manufacturing plant into the scale-up team. The process engineer can bring some helpful insights that the formulation scientist may not be aware of, such as availability of pilot and manufacturing plant equipment, design and process capabilities of pilot or manufacturing plant equipment and the familiarity with different or similar types of processes.[18, 19]

5.1.2. Availability of Raw Material

The well-established materials usually do not pose any problem in terms of its availability in large quantities. The new chemical entities (NCEs) are generally available in very limited quantities as they are made in small chemical synthesis batches and being new, they are expensive to produce. Depending on the NCE, there may only be few hundreds of grams or a few kilograms of material available for use. In such situations, experimental trial may be limited and thus must have a well-planned experimental design to conserve such material. As mentioned earlier, the development of many pharmaceutical products using well established raw material is relatively cheaper when compared to NCES. The cost will not generally be figured out at large to the experimental plan and thus a thorough evaluation is more easily possible.

5.1.3. Granulation

The findings of experiments which are documented as reports during pilot plant phase needs to be taken into consideration while scaling-up for larger production. A formulator and process engineer should make necessary alterations to the process at large scale manufacturing based on pilot scale findings. The steps or areas where adjustments are to be made should be identified and are typically required to be made so as to reproduce the results found at pilot scale. At pilot scale the area where changes can be typically made include the amount of granulating fluid required to achieve the desired granulation endpoint. For example, increase in batch size by 10-fold such as 2 kg lab scale to 20 kg pilot scale or 50 kg pilot scale to 5000 kg commercial scale generally requires a significance reduction in the amount of granulation fluid. This reduction may be usually 10-20% or more of fluid used at lowers level. This dramatic change is due to increased efficiency of the manufacturing equipment at the larger scale. This type of situation may not hold true for materials or formulations. Some formulations may actually require more of granulating fluid used at lower scale to achieve a desired granulation. The granulation endpoint is based on type of measurement such as power drawn in W. At laboratory scale equipment may not have suitable measuring devices and hence a scientist has to manually measure the impact of changes made on the formulation or process. In fact, the determination of the granulation endpoint is usually based on visual and tactile clues. At this stage of the process the limits are identified and robustness of the process is determined. This experimental determination is a much simpler, easier, faster, and less costly to do at pilot scale than at large manufacturing scale.[16, 20]

5.1.4. Drying

Drying is a critical operation in the tablet manufacturing wherein significant changes may observed. The most important is the drying time, which primarily depends upon dryer capacity to handle amount of air flow. The drying time, being related to the volume of air flow, has the most impact on the process. In addition, during drying under seasonal variations handling processing air humidity for unconditioned air need to be taken into account. There may be increase in fines produced during processing if the formulation is not robust. This increased fine generation may be attributed to increased product attrition within the fluid bed dryer generally, if granules produced during granulation are not robust enough, particles of granules are worn off to generate smaller particle size. This usually is not observed if tray dryer is used. At pilot scale tray dryers are used but when the product is transferred to larger scale manufacturing, it is not advisable to use tray dryers because it has comparatively lengthy drying cycle time. It is advisable at pilot scale to mimic the equipment used at larger scale to evaluate any possible changes. The air handling of the equipment must be investigated to know if the specific equipment has capability to treat incoming air. The pre-treated (dehumidified) air has more drying efficiency than untreated (normal) air and thus may affect the processing time.[21,22]

5.1.5. Milling

Milling or size reduction may significantly affect the scale-up process. As wide variety of mills being employed, they may have significantly different attrition rates and may result in significantly different particle size distributions. In addition, screen sizes used at pilot scale may differ slightly from those used at smaller lab scale as well as at larger commercial scale. Mill speed is another important aspect on which milling efficiency depends and thus need to be taken into account, for example, some mills impart more attrition at higher mill speeds. It is important to match and validate the mill type, screen size and mill speed that is intended to be used at production scale. [21,22]

5.1.6. Blending

The most commonly preferred equipment for blending is V-blender. Blending operation is more predictive as significant studies can be done to identify appropriate changes required to scale up the blending process. Using this blender, it is easier to calculate an approximate blending time. This is because material to be blended moves through nearly constant distance during the rotation of the blender and the distance through which particles travel is easily predicted based on the size of the blender, blending efficiency can be confirmed by blend optimization in various batches processed at lower and higher blending times. Confirmation is usually done by taking blend samples 1-3 times the finished dosage unit. If retesting of the blend sample is required, replicates can be taken. The prominent type of blend sampling is done through thief sampling (static sample) from within a powder bed Blend sampling results may be affected by static charge of particles: and their ability to flow into the sampling cavity. In order to minimize sampling variations caused by sampling error it should be done by one operator only. Blend sampling should be designed to simulate situations such as sampling areas near dead spots or near the axis of rotation.[21,22]

5.1.7. Compression

The compression is the ultimate test of a granulation and tablet formulation process in determining suitability of compression on high-speed tablet press. While doing this, number of trial runs at press speeds equal to that used in normal production are tried, and only then potential problems of sticking to the punch surface, tablet hardness, capping, and weight variation are detected. The ability of the press to interact with granulation is necessary for high-speed tablet compression. The granulation feed rate should be appropriately monitored. The material should not change the particle size distribution and there should not be any segregation of coarse and fine particles. The die feed mechanism must be capable of quickly and adequately filling the die cavities. The smaller the tablet, the more difficult it is to get a uniform fill at high press speeds and thus, for such machines, induced die feed systems must be used to eliminate this problem. Such systems are available with a variety of feed provisions and with variable speed capabilities so that optimum feed for respective granulation can be obtained Granulation compression usually occurs as a single event. In this case, the heads of the punches pass over the lower and under the upper pressure rollers allowing punches to penetrate in the dies to a preset depth. The thickness of compact is equal to the gap set between these punches. The granulation is compressed to form a tablet during compression. There must be formation of bonds within compressible material which results in sticking. The use of high percentage of lubricant or over blending may result in softer tablets with decreased wettability of the powder and an extended dissolution time. The machines used for compression includes high speed rotary machine, multi-punch rotary machine, double rotary machine, upper punch and lower punch machine, and single punch machine.[2]

5.2. Pilot Plant Scale-Up

Once the team scientist which includes formulation scientist and/or process engineer develops a pilot plant scale product or process, the next step is manufacturing at large scale also called commercial scale. This may also be known as full-scale manufacturing. The objective of scale-up batches is to confirm that the data, information, and observations at pilot plant scale are reproducible at full-scale manufacturing. In addition, it also defines any changes needed to be made at large scale. Scale-up batches are initially processed as experimental or feasibility trial batches. These trials are usually performed as a single batch to confirm that the process scale-up is in accordance with the predefined specifications and there are no unexpected results at this scale. Usually enough raw materials and plant time allocation is planned to produce some extra batches to countercheck if there is any need to alter processing parameters. Even the scientist may wish to make additional batches to check if the process is reproducible. Experimental batches may or may not be produced at commercial scale.[23]

5.2.1. Batch Size

The factors that determine size and number of batches to be made at commercial scale are cost of the drug and raw materials and the manufacturing schedule of the plant If equipment needed for the trial batches is within the part of a plant but it is heavily in demand for other products or processes, in such cases it may be difficult to gain access to that area. This is because the plant may need to displace its current marketed products to accommodate the plant trial. These types of feasibility trials are often used for experimental purposes only because there are usually changes required within the process that need to be further explored. Raw materials used for these types of largescale experiments do not require full testing. These factors usually restrict trial batches being used for purely experimental work than for the registration or clinical trials or for human consumption.[6]

5.2.2. New Drug

If new drug is used in manufacturing facility to formulate a product, then it requires performing a cleaning validation for such drug. This is must to prove that once the manufacturing of products using this new drug is completed, the carryover of this drug is lower than the permitted levels. Operational limits include biological activity levels of 1/1000 of the usual therapeutic dose, analytical detection levels of 10 ppm, and organoleptic levels of no detectable residue or odour when utilising flavours in the process.

5.2.3. Feasibility Trial

A feasibility trial is an analysis that takes all of a product's/process's relevant factors into account including economic, technical, legal and scheduling considerations to ascertain the likelihood of completing the product/process successfully. Once the feasibility trial is successfully completed and any corresponding changes are made to the formulation and/or process, a qualification trial begins Qualification trial serves to reproduce the findings, data, and observations reported during feasibility batches Material produced at this stage generally has more relined material specifications and testing requirements are significantly more than those for feasibility batches. Products made during these trials may be used for human use or clinical trials if the batches are produced under strict GMP conditions. The factors that affect the success of a feasibility trial include similarity in design of the equipment used during the laboratory and pilot plant phases of development, changes required in the process, fluid volume required for granulation, drying time, screen size, blending time, tablet, press tooling etc.

5.2.4. Material Transfer

There may be certain technological transfer issues which arise during feasibility or qualification trials that may require some changes to be made, for example, material transfer. Usually, at bench and pilot scales, material transfer is done manually. However, at commercial scale the volume of material is usually too big to move manually and thus technology is employed to facilitate the manufacturing process. These include material conveying equipment's such as drum lifters, drum inverters, screw feeders, vibratory hoppers or vacuum transfer units. The vacuum transfer equipment's can impose certain problems if material has a tendency to segregate This is possible with materials, for example, those have wide particle size distributions or have a two or more peaks in their particle size distribution The vibratory system may cause a percolation effect that smaller particles are driven down in between larger particles causing powder bed to segregate. This could be visually seen at the top of the powder bed, where larger particles are rising to the top of the powder bed.[11]

5.2.5. Overages of Materials

In scaling-up to commercial level usually overages of materials may be needed. This is because the type of material transfer at large scale is quite different from that used at smaller scales. Thus, some of the equipment's used for material transfer may cause selective loss of material. In order to compensate for this loss an overage may be added with sufficient justification to determine the appropriate overage needed for specific equipment. It should always be remembered that cGMP require that formulations are made to their 100% of label claim.

5.2.6. Process Validation

Process validation is a required part of cGMP for pharmaceuticals. These requirements can be found in 21CFR Part 210 and 211 Specific requirements of process validation may vary depending on factors such as nature of the specific product, for example, dosage form; and the nature. of the specific process, for example, granulation direct compression, liquid manufacturing etc. Process validation parameters given below are applicable to any drug product administered to humans or animals Thus, it is important to understand some of the basic terminology used within the process validation.

Following is some of the most commonly used terms relating to process validation.

i) Installation qualification : is the process of testing the processing equipment to ensure that it can reliably operate within the stated limits and tolerances. To effectively demonstrate that new equipment is acceptable for its intended use or purpose, this stage is normally carried out when it is installed. The location where the equipment is being installed typically handles this.

ii) Process performance qualification: A processing trial that establishes confidence that the process is effective and is reproducible. iii) Performance qualification: A process trial that establishes confidence that the finished product produced by a specific process meets the testing requirements for its intended use.

iv) Prospective validation: A procedure validation test carried out ahead of the release of a new product for its intended application to confirm that the predetermined outcomes can be obtained consistently. This is usually done on three successive batches.

v) Validation: It is a process of establishing documented evidence that a specific process will consistently produce a product meeting its predetermined specifications and quality.

vi) Validation protocol: A definitive written plan that describes how the validation will be performed, including the test criteria, sampling intervals and requirements product characteristics, production equipment, and acceptable limits for test results.

vii) Stressed conditions: A set of conditions encompassing the high and low extremes of the processing limits that poses the greatest chance of process of product failure Such conditions may or may not induce product or process failure.

6. DOCUMENTATION

Any industrial process must have adequate recordkeeping and reporting arrangements. The seamless transition of items from a bench size to a pilot or large commercial scale depends on these documents. The ease with which new goods, processes, methods, and procedures are integrated into ordinary production determines a pilot plant's effectiveness. Only when the R&D, processing, packaging, engineering, quality, assurance and quality control, regulatory and marketing department workers with whom they contact during the transfer have solid relationships and effective communication is this possible.

6.1. Forms of Documents

There are various types of documents with varying purposes, natures and lifecycles generated, prepared and maintained during scale-up operations. In the past, it took the form of printed reports. Today with advancement in technologies most of this information and documentation is in the form of soft formats. There should be a sound and efficient document management system. It should provide well organized way of sharing knowledge, information and thinking among the scale-up team members.

6.2. Types of Documents

In the pilot plant scale-up, there are two different kinds of documents: permanent and temporary. Permanent documentation consists of how-to guides, instruction books, training materials, forms, etc. and is used by project team. This documentation is used to support the maintenance and enhancement of the system. For example, design specifications, database definitions, source code, process diagrams etc. Temporary documentation is used only for internal communication such as ideas, issues, control, working papers etc. Once the project is over, the documentation, such as discussion papers, draught documents, interim progress reports, etc., is useless.

6.3. Structure and Circulation of Document

In order to achieve scale-up success easily, the documentation should be constructed in most appropriate and structured form with adequate indexing and controls so that it can be used as knowledge repository. An additional advantage of categorization of the information and documentation is that, items can be released for review, finalization, approval or action without waiting for other non-dependent elements to be completed. This helps the team members only to deal with the content that is relevant to them. They receive it in manageable size s part. The complexity can be minimized by restricting circulation of any given information only to those people with a relevant interest in the specific content.

6.4. Documents at Start of Scale-Up

In a short and simple scale-up project, document should be as simple as a spreadsheet in which main documents can be tracked. In bigger scale-up projects a document management toolset should be used. There are many such document management systems available which includes catalogue of all controlled documents and deliverables. The key elements of the documents used in registration of specific information per document includes for example, description, purpose or objective, form and format, responsibilities for production, responsibilities and rights for review, responsibilities for approval, further circulation for information only, retention and usage (temporary or permanent, internal or project deliverable), requirements for update, required protocols for review and quality assurance etc. Temporary paperwork may be kept as a historical record even though something has since changed, but permanent records typically need to be revised if something changes after it has been finalised.

6.5. Documents Tracking Progress and Status

To keep track of the project's state and progress, there are specific documents. It includes planned date of completion, current status and effective date, persons currently updating or reviewing the document, current projected date of completion. The project team members when using the document management system must incorporate further documents as required throughout the project, store and issue a template version of each document as a starting point where appropriate and access model examples and other illustrative examples to provide team members with a guide to the content Secure storage of documents, checking out a copy of a document for update to an authorized team member, checking in an updated version of a document, controlling and capturing document status changes, providing management views and reports of the status of each document, providing team members search access and viewing access to information are some of the important issues related to successful progress of the project. The team member must have ability to consult previous historic versions wherever relevant, and identify changes and determine the reason for those changes. The document flow should be maintained, analysed and updated with the progress of the project.[24]

7. SUPAC GUIDELINES

A successful drug product goes through a scaling-up process many times during its life cycle. The scale-up is nothing but technology transfer of a pharmaceutical product from research to the production scale with simultaneous increase in production capacities. The research or laboratory-scale batches used in clinical trials expand to pilot-scale and finally to commercial-scale production. Some products may also be expanded for their production to other sites within the country or even to other countries. The process of increasing batch size is termed as scale-up, whereas decrease in batch size is termed as scale-down. Usually, these changes are net results of increased or decreased demand from the market. In 1991-92, two workshops were held by the American Association of Pharmaceutical Scientists (AAPS), the US Food and Drug Administration (USFDA) and the United States Pharmacopeia (USP) to explore principles for making process and/or compositional changes in drug products post approval. In addition, these changes ultimately included process changes, process scale changes, and process site or campus changes. The proceedings of these workshops were published as guidance by the USFDA with a title 'Scale-Up and Post Approval Changes or SUPAC. The SUPAC refers to the FDA-recommended testing and filing actions to be taken by a pharmaceutical firm when it changes the manufacturing processes of a drug product that has been approved through NDA and ANDA. The FDA has provided its recommendations to industry in the form of Guidance's. SUPAC is not a regulation but is only a guidance document. It relates only to drug manufacturing and is only available for certain dosage forms. These includes immediate release solid oral dosage forms including tablets, capsules and soft gelatin capsules, modified release solid oral dosage forms including delayed release and extended release; and topical semi-solid dosage forms including suspensions, creams, ointments, emulsions and gels. The purpose of guidance is to provide application information that should be submitted to the Center for Drug Evaluation and Research (CDER) to assure continuing product quality and performance characteristics dosage forms for specified post approval changes. In addition, it defines filing as annual report, change being effected supplement and prior approval supplement. CMC changes are unavoidable due current needs, new findings and continuous improvement. Therefore, all these changes, may be in an investigational or a commercial product, need to be evaluated carefully and follow proper regulations for their implementation. Failure to comply with regulatory requirements for post approval, CMC changes may lead to misbranded or adulterated status for a given product. These recommendations are taken very seriously by manufacturers for marketed products because of the potential safety/efficacy impact on huge number of patients as well as on legal, regulatory and business impact for the sponsors. This approach provides a way for SUPAC in change in components, composition, batch size, manufacturing site, manufacturing equipment, process etc. as per USFDA norms. [15]

8. CONCLUSION

Pilot scale up techniques is one of the important tools for the optimization of large-scale production. The parameters such as granulation feed rate, compression and presence of lubricant and blending will play an important role in the development of pilot plant scale-up techniques to large scale production solid dosage form.

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