BP 702 T. INDUSTRIAL PHARMACYII (Theory)

UNIT-I PILOT PLANT SCALE UP TECHNIQUES

INTRODUCTION:

- The Pilot plant is a Hybrid Development facility and Manufacturing unit, which integrates followings;
  - Development,
  - Early development activities,
  - Clinical supply manufacture,
  - Technology evaluation,
  - Scale up and
  - Transfer to production sites,
- A ***pilot plant*** can also be defined as the pre-commercial production system which includes new production technology and produces small volumes of new technology-based products (Fig 1).
- ***Scale-up*** is the process of increasing the batch size or a procedure for applying the same process to different output volumes.
- The Pilot plant studies must include;
  - Current Good Manufacturing Practices (cGMP) environment,
  - Highly trained and skilled staffs,
  - Equipment support,
  - Facility of through and close examination of the formula.
- The factors that must be determine for successful product scale up are;
  - The requirements,
  - Training,
  - The reporting relationships,
  - Responsibility of personnel.
- The pilot plant, production and process control must be evaluated, validated and finalized during the scale up.
- The pilot plantplays an important role in the technology evaluation, scale up and transfer activities of new products.

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,
  - Organisation responsibility
  - Determination of responsibility of technology transfer team,
  - Technology transfer documentation,
  - FDA pre-approval inspection preparation.

Major technical aspects:

- The scale up of pilot plant includes *major technical aspects* that are;
  - In early development,

- Identification of critical components,
- Control of critical components,
- Identification of formulation variables,
- Control of formulation variables,

- Simulating the pilot plant equipment with manufacturing areas equipment.
- Identification of critical process parameters.
- Identification of operating ranges for the pilot plant equipment
- Collection of data of Product and process.

Objectives of Pilot plant scale up:

- Avoidance of the problems associated with the scale-up.
- Production and process controls guidelines preparation.
- To identify the critical features of the process
- Preparation and providing of Master Manufacturing Formula for manufacturing.
- Evaluation and Validation for process and equipment.
- Examination of the formula to assess the batch stability.

***Significance of Pilot Plant*:**

- Standardization of formulae.
- Review of range of relevant processing equipment.
- Optimization and control of production rate.
- Information on infrastructure of equipment during the scale up batches.
- Information of batches physical space required for equipment.
- Identification of critical features to maintain quality of a product.
- Appropriate records and reports to support GMP.

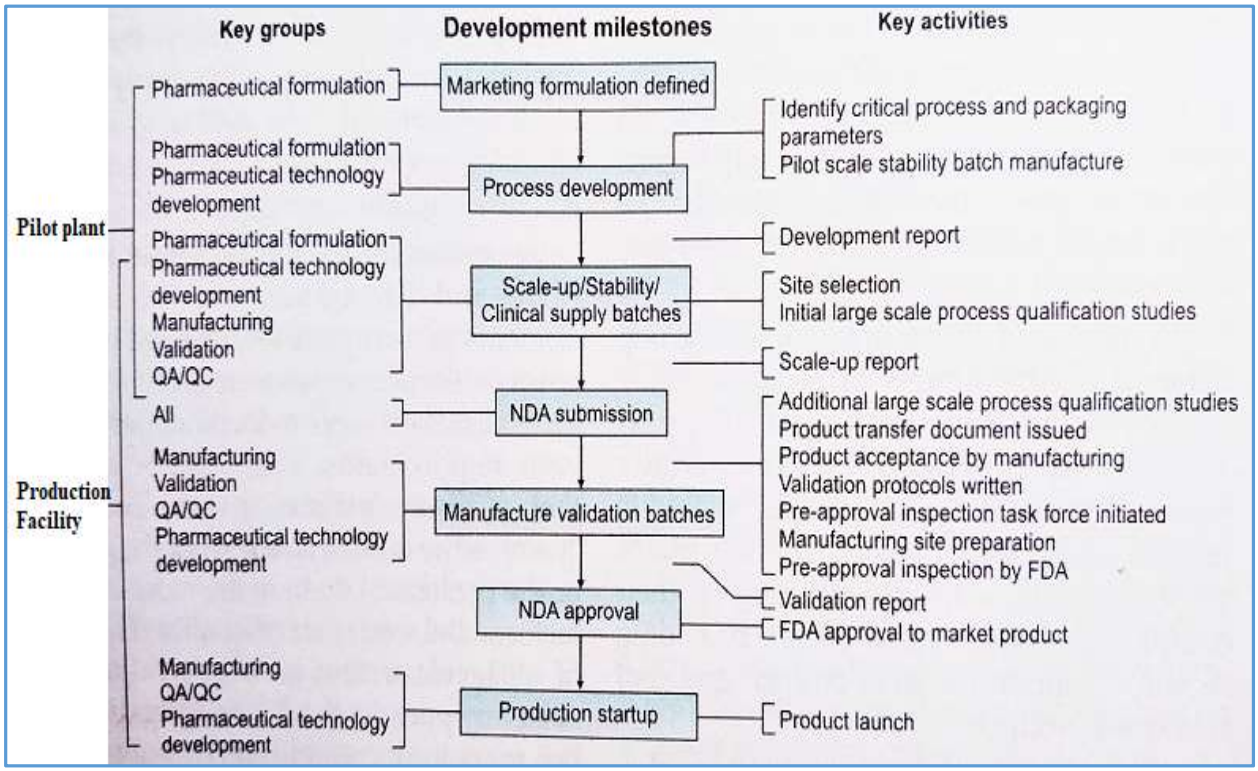

Fig 1. The layout of the relationship between different activities during technology transfers from the pilot plant to the production facility.

GENERAL CONSIDERATIONS:

Reporting Responsibility:

- The objective of the reporting responsibility in Pilot plant is to facilitate the transfer of a product from the laboratory into production.
- The effectiveness of Pilot plant is determined by the ease with which the new product or process is brought into routine production.
- This could be possible if a good relationship exists between the pilot plant group with other groups (Research & Development, Processing, Packaging, Engineering, Quality Assurance, Quality Control, Regulatory and Packaging) of the company.
- The formulator who developed the product can take the product into the production.
- The formulator continues to provide the support to the other departments even after the transition into the production has been completed.

Personnel requirements:

- The Qualification required for a person to work in pilot plant organization are;
  - Good theoretical knowledge on blending
  - Pharmaceutical industry experiences.
  - Ability to develop good relationships with other personnel.
  - Good communication skill (Writing and speaking).
  - Practical Experiences in production areas about formulation, process and equipment.
  - Should be able to understand the intent of the formulator and perspective of production personnel.
  - Must have minimum knowledge on Engineering, Electronic and Computer.
  - Must have knowledge on Physical, Chemical, Biochemical and Medical attributes of dosage form.
  - Must be aware on the principle of GMP Practices.
- The individual responsibilities should be clearly understood by the individuals, which must be recorded.

Space requirements:

The space required in pilot plant is divided into 4 areas that are as follows;

- Administration and information area:
  - Adequate office and desk space should be provided for both scientists and technicians.
  - The space should be adjacent to the working area.
- Physical testing area:
  - This area should provide permanent bench top space for routinely used physical- testing equipment.
- Standard equipment and floor space:
  - The sufficient specified space must be there for free installation, operation and easy maintenance of the equipment.
- Storage area:
  - Storage area for in process materials, finished bulk products, retained samples, experimental production batches, packaging materials (segregated into approved and unapproved areas).

- Controlled environment space allocated for storage of stability samples.
- Separate provisions for API and excipients further segregated into approved and unapproved areas according to GMP.

Training:

- The various departments that are responsible for compliance of GMP are;
  - Engineering
  - Quality control
  - Material handling
  - Warehousing and distribution
  - Purchasing.
- Depending on complexity of the job, each person involved in manufacturing, Processing, packaging and holding of a drug product, must receive the GMP and other specific training.
- The employee those need training are divided into the following categories;
  - New employees.
  - Those employees who are assigned with a new job.
  - Those employee whose performance a task falls below required standard.

The employee get trained on following activities as per the GMP and FDA guidelines that are;

- Technical environment
- Dealing with potent or dangerous chemicals
- Working with system of weights and measures
- Checking of manufacturing steps, containers, equipment and drying racks.
- Identification of packaging.
- Proper stock rotation system.
- Raw material inspection.
- Quality validation.

Review of the Formula:

- The objective of each ingredient and its contribution to the final product manufactured on small scale equipment must be thoroughly understood.
- The modification in formulation during the scale up is possible to be done in phase III trial, so that sufficient time could be available for generation of meaningful long term stability data in support of a proposed New Drug Application (NDA).

Raw materials:

- One major responsibility of a Pilot plant is the approval and validation of active and excipient raw materials used in the Pharmaceutical products.
- This is because the raw materials used during the small scale formulation trials may not be representative of the large volume shipment of material due to change in raw materials properties like particle size, shape, morphology, bulk density, static charges, rate of solubility, flow property and colour.
- An alternative supplier must be arranged as stand by basis which must validate the batches for manufactured products.

Relevant Processing Equipment:

- The selection criteria for one equipment to produce effective product within the proposed specifications are equipment must be economic, simple (In installation, handling, cleaning and maintenance), efficient and most capable of consistently producing a product.

- The size of the equipment should be such that experimental trials can be run that are meaningful and relevant to the production sized batches.

Production Rate:

- For determination of production rate, size and type of equipment required, the immediate and future market requirement must be considered.
- The selection of process and equipment to produce batches at a frequency need following considerations that are;
  - The time required to clean the equipment between the batches.
  - The product loss in the equipment during the manufacture.
  - The number of batches that need to be tested before release of product.

Process Evaluation:

- Things that should be critically examined during the Process Evaluation are;
  - Order of addition of the components including adjustment of their amount.
  - Mixing speed ant time.
  - Rate addition of granulating agent, solvents and drug solutions.
  - Heating and cooling rates.
  - Filter size for liquids.
  - Type and nature of filter media used for liquids.
  - Screening size for solids.
  - Drying temperature and time.
  - Fan speed.
- The basis for process optimization and validation is the knowledge on effect of above mentioned parameters on the in process and finished product quality.
- The objective of process validation to ensure the selected process could be able to produce quality products at various critical stages of production.
- This is possible by critically monitoring the within the batch variation of measurable parameters like content uniformity, moisture content and compressibility.
- Some measurable change in the materials may take place during the processes like milling, mixing, heating, cooling, drying, sterilizing, compacting and filling, should be evaluated.
- The process remains validated only if there is no change in the formula, quality of the ingredients and equipment configuration.
- The manufacturing process and quality control information should be reviewed on an annual basis and should be followed by re-validation to ensure that changes have not occurred.

Preparation of Master Manufacturing Procedure:

The Master Manufacturing Procedure includes followings;

- The Process or Manufacturing Direction.
  - Process direction should be precise and explicit.
  - Must be written in a simple manner which should be easily understood by the operator.
- The Chemical Weight Sheet.
  - Identification of chemical required.
  - Quantities of chemical to be added.
  - Order of chemicals to be added.
  - The name and Identification number of the ingredient must be mentioned.
- The Sampling Direction.

- Time of sampling of finished product.
- Manner of sampling of finished products.

➢ The Batch record direction.
- The batch record directions should include specification for addition rates, mixing times, mixing speeds, heating and cooling rates and temperature.

➢ The In-Process Specification.
- Must mention a simple and easy access specification for easy understanding of operators.

➢ The Finished Product Specification.
- The drug in the dose specified.
- The self-life of the product.
- The capability of the process.
- The reliability of the test methods.
- The stability kinetics of the product.

The periodic revalidation, GMP and monitoring of finished product test results via control charts are essential to maintaining consistent product quality.

GMP Consideration:

➢ The check list of the GMP items that should be a part of the scale-up or new product or process introduction including following;
- Equipment qualification.
- Process Validation.
- Regulatory schedule preventive maintenance.
- Regular process review and revalidation.
- Relevant writing standard operating procedures.
- The use of competent, technically qualified personnel.
- Adequate provision for training of personnel.
- A well-defined technology transfer system.
- Validated cleaning procedures.
- Arrangement of material to avoid cross contamination.

Transfer of Analytical Methods to Quality Assurance:

➢ Analytical methods developed in research must be transferred to the QA department.
- Transfer process includes the following aspects;
- Review the process to make sure that the proper analytical instrument is available.
- Personnel should be trained to perform the test.
- Reliability of the test should be checked.
- At last assay procedure should be reviewed before transfer.

PILOT PLANT SCALE UP CONSIDERATIONS FOR SOLIDS:

➢ The following points to be carefully consider during scaling up the solid dosage forms;
- Batch size from intermediate to large scale production.
- Each stage of operation.
- Different types of equipment.
- Use of sophisticated instruments with larger volume load.
- Various sizes of equipment.

Material Handling:

The handling of materials is quite different and necessary to handle carefully in medium and large scale production from the laboratory scale (Mostly poured by hand or scooped).

- The characteristics of materials like density, size, shape and static charge must be taken into consideration while adopting the processing steps like;
  - Lifting and tilting of drums,
  - Vacuum loading system,
  - Screw feeding systems,
  - Metering pump systems.
- Any material handling system must deliver the accurate amount of the ingredient to the destination.
- The cross contamination must be prevented if a system uses transfer of materials for more than one product step.
- This is accomplished by use of validated cleaning procedure for the equipment.

Chemical Weighing:

- The incorrect ingredients and quantities may lead to cross contamination and misbranded brand during chemical weighing.
- A central weighing department should have for all the processing areas due to following advantages;
  - Centralization of responsibility,
  - Avoidance of duplicating weighing facility,
  - Lower labour cost.
- A chemical weighing department should be designed to provide supervision, checkers, lightening, dust collection, adequate sanitation, proper weighing equipment, supply of sink and drain board, cabinets, vacuum supply system, printing scale facility and meters for liquids.
- For weighing of dye and high potent drugs, a separate room must be equipped.

Tablet blending and Granulation:

Blending and Granulation:

- Powders to be used for encapsulation or to be granulated must be well blended to ensure good drug distribution.
- Inadequate blending at this stage could result in discrete portions of the batch being either high or low in potency to avoid drug content variation.
- Steps should also be taken to ensure that all the ingredients are free of.
- The lumps and agglomerates can be removed by doing screening or milling of the ingredients should be done to avoid flow problems, non-reproducible compression and encapsulation process, to facilitate content uniformity of the product.
- In blending, segregation and mixing operation takes place which depends on particle size, shape, hardness and density.

Dry Blending and Direct Compression:

- Different blenders used in blending are V- blender, double cone blender, Ribbon blender, Slant coneblender, Bin blender, Orbiting screw blenders, vertical and horizontal high intensity mixers.

- The factors affect the optimization of blending operation of directly compressible materials are;
- The order of addition of components to the blender.
- The mixing speed – Planetary type mixer, Tumbling Mixer, Cone Type Mixer.
- The mixing time –It affects compressibility of Finished Material.
- The use of auxiliary dispersion equipment with the mixer – Use chopper cell in Twin Shell Mixer.
- The mixing action – Determined by the Mechanics of the Mixer.
- The blender loads Optimum working volume and normal working range.

Slugging (Dry Granulation):

- The dry powder cannot be compressed directly due to poor flow and compression properties.
- The slugging is done by using the Tablet Press of 15 tonnes.
- After compression, slugs are broken down by Hammer Mill with suitable particle size distribution.
- The granulation by dry compaction can also be achieved by passing powders between two roller which put pressure of 10 Tonnes per linear inch.

Wet Granulation:

- The most common reasons given to justify granulating are;
  - To impart good flow properties to the material,
  - To increase the apparent density of the powders,
  - To change the particle size distribution,
  - Uniform dispersion of active ingredients.
- Traditionally, wet granulation has been carried out using Sigma blade mixer and Heavy-duty planetary mixer.
- Wet granulation can also be prepared using tumble blenders equipped with high-speed chopper blades.
- More recently, the use of multifunctional "processors" that are capable of performing all functions required to prepare a finished granulation, such as dry blending, wet granulation, drying, sizing and lubrication in a continuous process in a single equipment.
- The factors that affecting the Fluidized Bed Granulator are;
  - Process Inlet Air Temperature,
  - Atomization Air Pressure,
  - Air Volume,
  - Liquid Spray Rate,
  - Nozzle Position and Number of Spray Heads,
  - Product and Exhaust Air Temperature,
  - Filter Porosity.

Drying:

- The most common conventional method of drying a granulation continues to be the circulating hot air oven, which is heated by either steam or electricity.
- The important factors to consider as part of scale-up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays.
- If the granulation bed is too deep or too dense, the drying process will be inefficient, and if soluble dyes are involved, migration of the dye to the surface of the granules.

- Drying times at specified temperatures and airflow rates must be established for each product, and for each particular oven load.
- Fluidized bed dryers are an attractive alternative to the circulating hot air ovens.
- The important factors considered as part of scale up fluidized bed dryer are optimum loads, rate of airflow, inlet air temperature and humidity.
- The parameters to be considered for drying process by using Tray Dryer for scale up areAir flow, Air temperature, Depth of the granulation on the trays, Monitoring of the drying process by the use of moisture and temperature probes and Drying times at specified temperatures and air flow rates for each product.
- The Parameters to be considered for the drying process by using a Fluid Bed Dryer for scale up are Optimumload, Air Flow Rate, Inlet Air Temperature and Humidity of the incoming air.

Reduction of Particle size:

- Compression factors that may be affected by the particle size distribution are flowability, compressibility, uniformity of tablet weight, content uniformity, tablet hardness, and tablet color uniformity.
- First step in this process is to determine the particle size distribution of granulation using a series of "stacked" sieves of decreasing mesh openings.
- Particle size reduction of the dried granulation of production size batches can be carried out by passing all the material through an oscillating granulator, a hammer mill, a mechanical sieving device, or in some cases, a screening device.
- As part of the scale-up of a milling or sieving operation, the lubricants and glidants, which in the laboratory are usually added directly to the final blend, are usually added to the dried granulation during the sizing operation.
- This is done because some of these additives, especially magnesium stearate, tend to agglomerate when added in large quantities to the granulation in a blender.

Facilities:

- To avoid cross contamination in scale up and to facilitate the cleaning of equipment effectively, following facilities must be available that are;
  - Presence of separate room with availability of more space,
  - Must have granulation as unit operation,
  - Must have washing and drainage facilities,
  - Must have cold, hot water and steam supply system,
  - Platform should be with stainless steel or non-dust material system,
  - Air condition system is encouraging but if absent, window must be screened,
  - Use of a multifunctional processing system.

Granulation Handling and Feed System:

- The handling of the finished granulation in the compression area is either by Hand scooping for small scale or by sophisticated automated handling system with vacuum or mechanical system for large scale.
- The properties of material like size, size distribution and flow property affects the tablet properties like drug content uniformity, tablet weight, thickness and hardness.
- For efficient cleaning, sophisticated material handling systems like long lengths transfer tubes, valves, vacuum and pneumatic pumps should be used.

Tablet Compression:

- The tablet press performs following functions during the compression are;
  - Filling of an empty die cavity with granulation.
  - Pre-compression of granulation.
  - Compression of granules.
  - Ejection of the tablet from the die cavity and take-off of the compressed tablet.
- The prolonged trial runs at press speeds is generally adopted to find out the potential compression problems like sticking to the punch surface, tablet hardness, capping, and weight variation detected.
- High-speed tablet compression depends on the ability of the press to interact with granulation.
- During selection of high speed press criteria that should be considered are;
  - Granulation feed rate.
  - Delivery system should not change the particle size distribution.
  - System should not cause segregation of coarse and fine particles.
  - It should induce static charges.
- The die feed system must be able to fill the die cavities adequately in the short period of time that the die is passing under the feed frame.
- The smaller the tablet, the more difficult it is to get a uniform to fill high press speeds.
- For high-speed machines, induced die feed systems with a variety of feed paddles and variable speed capabilities, are necessary.
- Compression of the granulation usually occurs as a single event as the heads of the punches pass over the lower and under the upper pressure rollers.
- This causes the punches to penetrate the die to a pre-set depth, compacting the granulation to the thickness of the gap set between the punches.
- The rapidity and dwell time in between this press event occurs is determined by the speed at which the press is rotating and by the size of compression rollers.
- Larger the compressions roller, the more gradually compression force is applied and released.
- Slowing down the press speed or using larger compression rollers can often reduce capping in a formulation.
- The final event is the ejection of compressed tablets from the die cavity.
- During compression, the granulation is compacted to form tablet, bonds within compressible material must be formed which results in sticking.
- High levels of lubricant or over blending can result in a soft tablet, decrease in wettability of the powder and an extension of the dissolution time.
- Binding to die walls can also be overcome by designing the die to be 0.001 to 0.005 inch wider at the upper portion than at the centre in order to relieve pressure during ejection.

Tablet Coating:

- Many changes in Sugar coating (Carried in conventional coating pans), due to new developments in coating technology (Conventional sugar coating pan changed to perforated pans or fluidized-bed coating columns), changes in safety and environmental regulations.
- The development of new polymeric materials has resulted in a change from aqueous sugar coating to aqueous film coating.
- The tablets must be sufficiently hard to withstand the tumbling to which they are subjected in either the coating pan or the coating column.

- Some tablet core materials are naturally hydrophobic, and in these cases, film coating with an aqueous system may require special formulation of the tablet core and/or the coating solution.
- A film coating solution may have been found to work well with a particular tablet in a small lab coating pan but may be totally unacceptable on a production scale.
- To facilitate the efficient coating the tablet should not be designed as flat surface or sharpe edges.

Encapsulation of Hard Gelatin Capsules:

- The High Speed equipment is used to prepare the capsule by using the processed powder blend with following particle characteristics like particle size distribution, bulk density, compressibility to promote good flow property.
- This facilitates the formation of compacts of the right size and of sufficient cohesiveness to be filled into capsule shells.
- Filling of capsule is done by two filling systems;
  - Zanasi or Martelli form slugs in a dosator.
  - Hofliger-Karg Machine
- Weight variation in capsules may come due to poor flow characteristics, improper lubrication and plug sticking to the dosator plunger surface.
- Overlay lubrication may create problems in weight variation, disintegration, dissolution and Bioavailability.
- The characteristics of granulation and the finished products are greatly influenced by the type and size of equipment used for blending, granulating, drying, sizing and lubrication.
- For better encapsulation, need of controlled environmental conditions that are Controlled humidity (RH 45 to 55 %) system in processing and encapsulation (RH 35 to 65 %) room and appropriate temperature condition of 15 to 25 °C.

PILOT PLANT SCALE UP CONSIDERATIONS FOR LIQUID ORALS:

- The physical form of a drug product that can be incorporated demonstrates Newtonian or Pseudoplasticflow behaviour.
- It conforms to its container at room temperature.
- Liquid dosage forms may be dispersed systems or solutions.
- In dispersed systems there are two or more phases, where one phase is distributed in another.
- A solution refers to two or more substances mixed homogeneously.

Steps of liquid manufacturing process:

- Planning of material requirements.
- Liquid preparation.
- Filling and Packing.
- Quality assurance.

Critical aspects of liquid manufacturing

- Physical Plant.
- Heating, ventilation and air controlling system.
- The effect of long processing times at suboptimal temperatures should be considered in terms of consequences on the physical or chemical stability of ingredients as well as product.

Solution:

- The parameters to be considered are for scale up of solutions are;

- Impeller diameter.
- Tank size (diameter).
- Number of impellers.
- Impeller type.
- Mixing capability of impeller.
- Rotational speed of the impeller.
- Height of the filled volume in the tank.
- Number of baffles.
- Transfer system.
- Clearance between Impeller Blades and wall of the mixing tank.
- Filtration equipment (should remove desired materials but should not remove active or adjuvant ingredients).
- Passivation of Stainless Steel (Pre-reacting the SS with acetic acid or nitric acid solution to remove. the surface alkalinity of the Stainless Steel).

Suspension:

- The parameters to be considered are for scale up of suspension are;
  - Versator (To avoid air entrapment).
  - Wetting of suspending agent.
  - Addition and dispersion of suspending agents.
  - Selection of the equipment according to batch size.
  - Time and temperature required for hydration of the suspending agent.
  - Mixing speeds (High speed should not be used as it leads to air entrapment).
  - Mesh size (Must be able to remove the foreign particulates and sieve selected based on production batch size trials).

Emulsion:

- The parameters to be considered are for scale up of emulsion are;
  - Homogenizing equipment.
  - Temperature.
  - Mixing equipment.
  - Phase densities.
  - In-process or final product filters.
  - Phase volumes.
  - Screens, pumps and filling equipment.
  - Phase viscosities.

PILOT PLANT SCALE UP CONSIDERATIONS FOR SEMI SOLIDS:

- The following parameters are to be considered during the scale up of semisolid products;
  - Mixing speed.
  - Mixing equipment (Could be able to move semisolid mass from outside walls to the centre and from bottom to top of the kettle).
  - Motors (Drive mixing system with appropriate handling system at its most viscous stage).
  - Heating and cooling process.
  - Component homogenization.

- Product transfer.
- Addition of active ingredients.
- Working temperature range.
- Shear during handling and transfer from manufacturing to holding tank to filling lines.
- Transfer pumps (Easily must move viscous material without applying excessive shear and free of entrapped air).

➢ Following parameters must be consider during choosing the size and type of pump,
  - Pumping rate.
  - Pumping pressure required should be considered.
  - Product compatibility with the pump surface.
  - Product viscosity.

SUPAC (SCALE UP AND POSTAPPROVAL CHANGES)GUIDELINES:

➢ SUPAC represents the changes recommended by the US FDA at the time of scale up or approval of NDA / ANDA.

➢ In the process of developing a new drug product, the batch sizes used in the earliest human studies are small and the size of the batches is gradually increased (Scale-up).

➢ The scale-up process and the changes made after approval in the composition, manufacturing process, manufacturing equipment, and change of site have become known as Scale-Up and Post approval Changes, or SUPAC.

***The SUPAC Guidelines define*;**

➢ The level of changes – Minor, Moderate and Major Changes.

➢ Test – Application test, *in vitro* dissolution and *in vivo*

➢ Filing – Annual report, changes being effected supplement and Prior Approval Supplement.

➢ The level of changes may impact on formulation and quality performance in following levels;
  - Level 1: unlikely to have detectable Impact.
  - Level 2: could have significant impact.
  - Level 3: likely to have significant impact.

➢ These guidelines provide recommendations for post approval changes in;
  - The components or composition change,
  - The site of manufacture change,
  - The scale-up of manufacture change
  - The manufacturing (process and equipment) change.

A) The components or composition changes:

➢ This section focuses on changes in excipients in the drug product.

➢ SUPAC-MR - Excipient critical or non-critical to the Modified drug release.
  - Changes in non-release and release controlling excipients.

➢ SUPAC-SS - Changes in preservative in semisolid formulations.

➢ SUPAC-IR Changes for immediate-release solid oral dosage forms.

B) The site changes of manufacture:

➢ Changes in location of the site of manufacture, packaging operations and/or analytical testing laboratory.

➢ Do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition.

- Current Good Manufacturing Practice (CGMP) inspection.

Level I Changes -

Classification-Single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., Temperature and humidity) and controls, and personnel common.

Test Documentation - Application/ compendia requirements in chemistry, dissolution and *in vivo*Bioequivalence - None.

Filing Documentation- Annual report.

Level II Changes -

Classification–Same continuous campus, Common personnel, No other changes.

Test Documentation–

- Application/ compendial requirements
- Notification of Location of newsite
- Updated batch records
- SUPAC – MR - Multi-point dissolution profiles(15,30,45,60 and 120 min)USP buffer media at pH 4.5-7.5 forextended release). Three differentMedia (e.g., Water, 0.1N HCl, andUSP buffer media at pH 4.5 and 6.8for delayed release)until 80% ofDrug Released.

Filing Documentation- Annual report.

Level III Changes -

Classification– Different campus, Different personnel.

Test Documentation –

- Application/compendial requirements.
- Notification of Location of new site.
- Updated batch record.
- SUPAC - IR: Multi-point dissolution profile in the application/compendial medium.
- SUPAC - MR: Multi-point dissolution profiles (15, 30, 45, 60 and 120 min) USP buffer media at pH 4.5-7.5 for extended release). Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at pH 4.5 and 6.8 for delayed release) until 80 % of Drug Released.

Filing Documentation- Annual report prior approval of supplement.

C) Changes in Batch Size (Scale-Up/Scale-Down):

- Post-approval changes in the size of a batch from the pivotal/pilot scale bio batch material to larger or smaller production batches call for submission of additional information in the application.
- Scale-down below 100,000 dosage units is not covered by this guidance.

Level I Changes -

Classification- Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch.

Test Documentation – Updated batch records application/compendial requirements stability.

Filing Documentation- Annual report (long term stability data).

Level II Changes -

Classification- Changes in batch size beyond a factor of ten times the size of the pilot or biobatch, No other changes.

Test Documentation –

- Chemistry Documentation Application/ compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

- Dissolution Documentation-Case B testing.
- *In Vivo* Bioequivalence - None.

Filing Documentation- Changes being effected supplement; annual report (long-term stability data).

D) Manufacturing Changes:

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

i)Equipment -

Level I Changes:

Classification- Alternate equipment of the same design and principles as automated equipment.

Test Documentation – Updated batch records, Application/compendial requirements and stability.

Filing Documentation- Prior approval supplement with justification for change; annual report (long-term stability data).

Level II Changes:

Classification- Change to equipment of different design and principle.

Test Documentation – Updated batch records, Application/compendial requirements and stability.

- SUPAC – IR - Multi-point dissolution profiles in multiple media.
- SUPAC – MR - Multi-point dissolution profiles in multiple media.

Filing Documentation- Annual report and changes being Effected Supplement.

ii)Process -

Level I Changes:

Classification- Alternate equipment of the same design and principles as automated equipment.

Test Documentation – Updated batch records, Application/compendial requirements and stability.

Filing Documentation- Annual report.

Level II Changes:

Classification- This category includes process changes including changes such as mixing times and operating speeds outside of application/ validation ranges.

Test Documentation – Updated batch records, Application/compendial requirements and stability.

- SUPAC - IR - Multi-point dissolution profile.
- SUPAC- MR - Multi-point dissolution profiles in multiple media.
- SUPAC – SS - *In vitro* release test Documentation.

Filing Documentation- Changes being effected supplement; annual report (long term stability data).

Level III Changes:

Classification- Changes in the type of process used (e.g. wet granulation to direct compression).

Test Documentation – Updated batch records, Application/compendial requirements, stability, bio-study and IVIVC.

- SUPAC - IR - Multi-point dissolution profile.
- SUPAC- MR - Multi-point dissolution profiles in multiple media.

Filing Documentation- Prior approval supplement with justification; annual report (long-term stability data).

INTRODUCTION TO PLATFORM TECHNOLOGY:

Platform technologies:

- Platform technologies are systems that distribute the system out into different levels of abstraction. This is done in order to differentiate between core – platform – functions, and the application layer that sits on top of, and draws upon, these underlying common services.

Pharmaceutical Platform technologies:

- Pharmaceutical Platform technologies are considered a valuable tool to improve efficiency and quality in drug product development. The basic idea is that a platform, in combination with a risk-based approach, is the most systematic method to leverage prior knowledge for a given new molecule.Platform technology is becoming a popular industry approach for bioprocessing.

Importance platform technology:

- Platform companies move faster than their traditional counterparts. When your core products and services frequently change, it forces your employees and your organization to embrace change quickly.

Types of platform technology:

- Operating systems provide the basic services required to use hardware.
  - Computing Platforms.
  - Database Platforms.
  - Storage Platforms.
  - Application Platforms.
  - Mobile Platforms.
  - Web Platforms.

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