A CURRENT REVIEW ON PILOT PLANT SCALE UP TECHNIQUES: FOCUS ON SUPAC (SCALE UP AND POST APPROVAL CHANGES)

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ABSTRACT

In modern context, as per market demand there is surely an augmentation or decrease in production, this is called SUPAC. Distinct recommendations are made for those diverse sorts of SUPAC in by various regulating organizations for manufacture of items. Here SUPAC guidelines and post approval adjustments are are provided for production in this review study. determined that SUPAC guideline line offer benefits as: This Review Focus on Reduced processing period for site transfers, saving operational overhead & maintenance expenditures. More quicker deployment of equipment and method improvements, better yield & Reduce failure investigations. More quicker adoption, increase in lot sizes and Manufacture of fewer uncommercial stability batches and Reducing stability testing/costs.

Keywords : SUPAC, Post approval changes, Lot size , Site Transfer, Stability.

INTRODUCTION

The Pilot plant is a Combination Innovation building and Production plant, which integrates followings;

- Development,
- Interventions aimed at fostering growth and maturity in young children,
- Producing Medical Equipment and Supplies,
- Technology Assessment,
- Enhance and expand
- Transport to manufacturing facilities

A pilot plant may also be described as the well before production system which contains innovative production technology and generates modest quantities of new technology-based items. Scale-up is indeed the process of raising a batch size or even a technique of adapting the very same process to various output quantities.

The Pilot scale studies must comprise;

- Current Good Manufacturing Practices (cGMP) environment,
- Highly trained and competent staffs,
- Equipment support,
- Facility of thorough and careful study of the formula.

The criteria that need to be determine for effective product scale up include;

- The prerequisites,
- Training,
- The reporting connections,
- Responsibility of staff.

The pilot plant, supply and processing methods must be examined, verified and completed throughout the scale up. and plant plays a significant part in the technology assessment, scale up but also transfer operations of new goods.

Pilot plant scale up processes includes:

The primary actions takes place during scaling up at the initial stages are;

- Technical factors of process development,
- Technical considerations of scaling up,
- Organisation responsibility
- Determination of responsibilities of technology transfer team,
- Technology transfer documents,
- FDA pre-approval inspection preparation.

Major technical aspects:

- The scaling up an pilot plant contains important technical factors that include;
- In early development,
- Identification of important components,
- Control of essential components,

- Identification of formulation variables,
- Control of formulation variables,
- Modeling a pilot plant equipment to production regions equipment.
- Identification of important process parameters.
- Identification of operating ranges for the pilot plant equipment
- Collection of data on Product and process.

Objectives of Pilot plant scale up:

- Avoidance of the challenges linked with the scale-up.
- Production and processes controls guidelines preparation.
- To identify the important elements of the process
- Preparation and supply of Master Manufacture Formula for manufacturing.
- Evaluation and Validation of process and equipment.
- Examination of a formula for determine the batch stability.

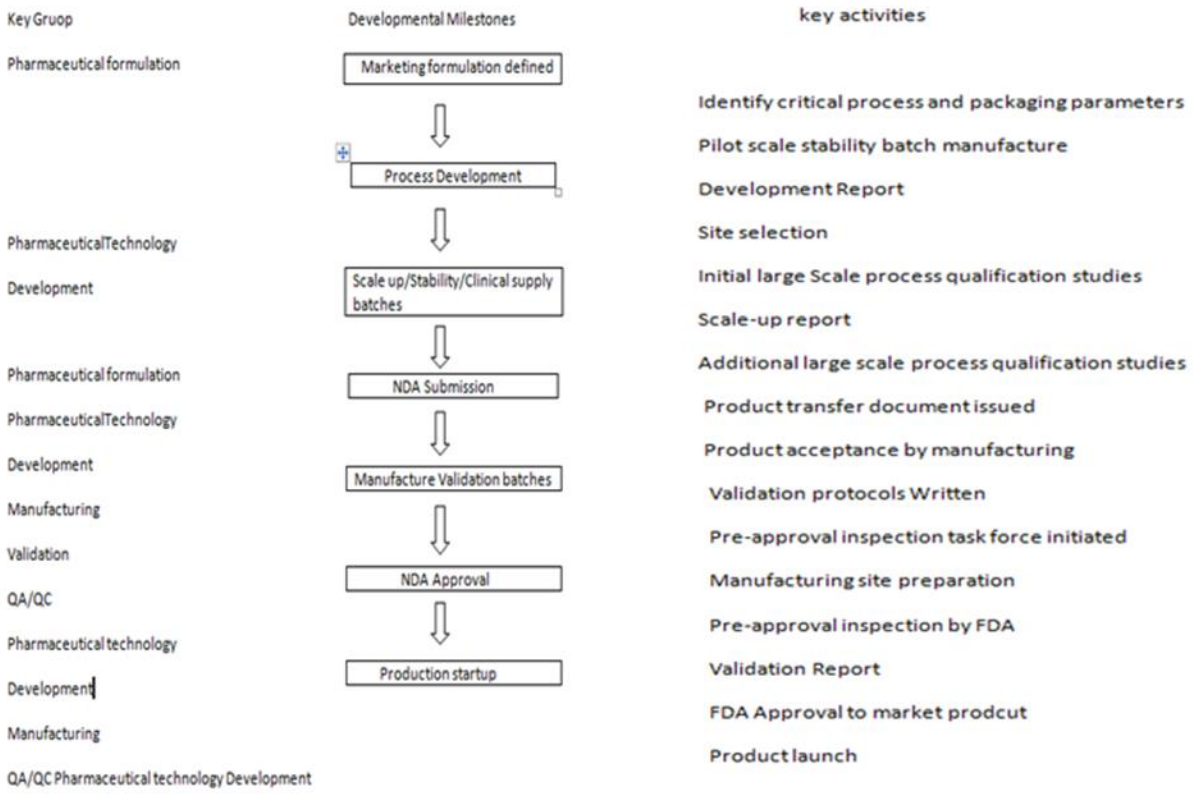

Figure :1 The framework Illustrates the link between different functions throughout transfer of technology from the pilot plant towards the production facility

Significance of Pilot Plant:

- Standardization of formulas.
- Review of range of applicable processing equipment.
- Optimization and management of manufacturing pace.
- Information about infrastructure of equipment in during scale up batches.
- Information about batches physical space necessary for equipment.
- Identification of important elements to sustain a product's quality.
- Relevant records and reports that support GMP.

PILOT PLANT SCALE UP CONSIDERATIONS FOR SOLIDS:

The following issues must be carefully examined before scaling up a solid dosage forms;

- Batch size from moderate to big scale manufacturing.
- Different sorts of equipment.
- Use of advanced instruments with increased volume load.
- Varying sizes of equipment.

Material Handling:

The handling of ingredients is significantly different and important to manage cautiously in large-scale and medium-sized manufacturing first from laboratory scale The features of materials including density, size, form as static charge must have been taken into consideration when implementing the processing stages such;

- Lifting and tilting of drums,
- Vacuum loading system,
- Screw feeding systems,
- Metering pump systems.

Each material handling system should deliver the precise quantity of the component to the destination.The cross contamination should be avoided whenever a system involves exchange of material for more than a product phase. This is done by usage of proven cleaning technique for the equipment.

Chemical Weighing:

The improper substances and amounts can result in cross contamination or products containing products during chemical weighing.

A central weighing department ought to have for all the processing regions due to following benefits;

- Centralization of duty,
- Avoidance of duplicate weighing facility,
- Lower labour cost.

A chemical weighing department should be constructed to offer supervision, checkers, lightening, dust collection, sufficient sanitation, correct weighing equipment, provision for sink and drain board, cabinets, vacuum supply system, printing scale facility with metres for liquids. During weighing of dye but very powerful medications, an separate room should be supplied.

Tablet mixing and Granulation:

Blending and Granulation:

Powders to be utilized as encapsulated or for being granulated must be carefully mixed to guarantee optimal medication distribution. Improper blending at this point might result in discrete areas of the sample either be high or low on potency to prevent drug content fluctuation. Steps are also made to guarantee that all the components are free of. The lumps and agglomerates may be eliminated by conducting screening or milling of the materials should be done to prevent flow difficulties, quasi compression and encapsulation processes, to promote content homogeneity of the product. In blending, segregation and mixing process takes place which relies on particle size, shape, hardness and density.

Dry Blending and Direct Compression:

- Different blenders used in blending include V- blender, double cone blender, Ribbon blender, Slant cone blender, Bin blender,
- Different blenders used in blending include V- blender, double cone blender, Ribbon blender, Slant cone blender, Bin blender,
- The elements influencing the optimization of mixing operation with direct compression materials are;
- The sequence of adding ingredients to the blender.
- The mixing speed - Planetary type mixer, Tumbling Mixer, Cone Type Mixer.
- The mixing time –It impacts compressibility of Finished Material.
- The use of additional dispersion equipment with the mixer - Use chopper cell in Twin Shell Mixer.
- The mixing action - Controlled either by Mechanics of the Mixer.
- The blender loads Maximum operating volume and usual functioning range.

Slugging (Dry Granulation):

- The dry powder can really be compacted directly owing to inadequate flow and compression characteristics.
- The slugging is done by utilising the Tablet Press of 15 tons.
- During compression, slugs were broken down by Hammer Mill having acceptable particle size distribution.
- The granulation by dry compaction may also be performed by moving powders between two roller which exert pressure of 10 Tonnes per linear inch.

Wet Granulation:

- The most prevalent grounds claimed to warrant granulating are;
- To give excellent flow characteristics to the material,
- To improve overall apparent density of the particles,
- To modify a particle size distribution,
- Uniform distribution of active substances.

Traditionally, wet granulation has been carried out utilizing Sigma blade mixer and Heavy-duty planetary mixer. Wet granulation may also be made utilizing tumble blenders equipped with high-speed chopper blades. More recently, the usage of multifunctional "processors" that are capable of executing all activities necessary to create a completed granulation, such as dry blending, wet granulation, drying, sizing or lubrication inside a continuous process in a single equipment.

- The elements that influence the Fluidized Bed Granulator include;
- 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 popular traditional technique of drying a granulation remains the rotating hot air oven, that is heated whether by steam or electricity. The main parameters that consider a part of scale-up of such an oven drying process include airflow, air temperature, or the depth of granulation on the trays. If the agglomeration bed is far too wide and too dense, the dryer would be ineffective, but if soluble dyes also included, migration of the color to a surface of both the granules. Drying periods at specific temperatures and airflow levels must be defined for every product, and for each individual oven load. Fluidized bed dryers are just an appropriate option to a circulating hot air ovens. The main criteria examined as part of scaling up fluidized bed dryer are optimal loads, rate of airflow, input air temperature and humidity. The specifications to be regarded for drying process through using Tray Dryer for scale up are Air flow, Air temperature, Depth of a granulation just on trays, Monitoring of the drying process through the use of temperature and moisture probes but also Drying times at stipulated temperatures and air flow rates for every product. The Parameters to be addressed for the drying process by utilizing a Fluid Bed Dryer for scale up are Optimum load, Air Flow Rate, Inlet Air Temperature and Humidity of the entering air.

Reduction of Particle size:

Compression variables that may be impacted by the particle size distribution include flowability, compressibility, uniformity of tablet weight, content uniformity, tablet hardness, and tablet colour uniformity. First stage in this method is to figure out the size distribution of granulation to use a succession of "stacked" sieves with decreasing mesh apertures. Particle size reduction of the dry granulation of production size batches may be carried out by running the all material through with an oscillating granulator, a hammer mill, a mechanical sieving device, or in some situations, a screening device. As part of the scale-up of a milling or sieving process, the lubricants and glidants, which in the laboratory are normally applied directly to the final blend, are usually added to the dried granulation during the sizing procedure. This is done because some of these additives, notably magnesium stearate, tend to agglomerate when introduced in high amounts to the granulation in a blender.

Facilities:

- To minimise cross contamination in scale up and to assist the cleaning of equipment properly, following facilities must be supplied that are;
- Presence of separate room with availability of extra 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 of stainless steel or non-dust material system,
- Air condition system is encouraged but if lacking, window must be screened,
- Use of a multipurpose processing system.

Granulation Handling and Feed System:

The handling of the final granulation in the compressed area is either by Hand scooping for tiny level or through sophisticated automated handling system using vacuum or mechanical system for big size. The features the material like size, size distribution that flow property impacts the tablet attributes like medication standard consistency, tablet weight, thickness and hardness. For effective cleaning, advanced material handling systems such long lengths transfer tubes, valves, vacuum but also pneumatic pumps should be employed.

Tablet Compression:

- The tablet press binding precedent duties as during 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 crushed tablet.
- The lengthy trial runs at press speeds is often chosen to find out the probable compression difficulties such as clinging towards the punch surface, tablet hardness, capping, and weight fluctuation discovered.
- High-speed tablet compression relies on the capacity of the press to communicate with granulation.

During choice of high speed press parameters that should be examined are;

- Granulation feed rate.
- Delivery mechanism should not modify the overall particle size distribution.
- System should not create separation of fine and coarse particles.
- It should produce static charges.
- The die feed system is able to feed the die cavities sufficiently in the brief length of time while the die is traveling beneath the feed frame.
- The smaller the tablet, the more difficult it is to obtain a consistent high press rate.
- For high-speed machines, triggered die feed systems with such a range of feed paddles with variable speed capacities, are essential.
- Compression of the granulation normally happens as a single event when the heads of the punches travel over the lower and beneath the top pressure rollers.
- This allows the punches to penetrate the die to a predetermined depth, compacting the granulation to the thickness of the gap specified between the punches.
- The rapidity and dwell time between when the press event happens is regulated by the speed of the press is turning and by size of compression rollers.

- Larger the compressions roller, the much more progressively compression force applied and released.
- Slowing down the press speed or utilizing bigger compression rollers will typically minimize capping in a formulation.
- The last process is the ejection of compressed tablets from die cavity.
- During compression, the granulation is compressed to form tablet, linkages within compressible material must be created which results in sticking.
- High amounts of lubricant or over mixing may result in a soft tablet, reduction in wettability of the powder and an extension of the dissolving period.
- Binding to die walls may also be addressed by making the die to be 0.001 to 0.005 inch broader at the top section than at the middle in order to release pressure during ejection.

Tablet Coating:

Many improvements in Sugar coating (Carried in conventional coating pans), owing to new advancements in bringing greater (Conventional sugar coating pan converted to perforated pans and fluidized-bed coating columns), changes in safety and requirements. The development of new polymers have led in a move between aqueous coating material to aqueous film coating.The tablets must be adequately hard to survive the tumble to which they are exposed whether in the coating pan or the coating column.Some tablet core materials are inherently hydrophobic, and in these circumstances, film coating with an aqueous system may need particular formulation of the tablet core and/or the coating solution. A film coating solution may have been discovered to perform well with a specific tablet in a small lab coating pan but may be absolutely inappropriate on a production scale. To promote the efficient coating the tablet should not be constructed as flat surface or sharp edges.

Encapsulation of Hard Gelatin Capsules:

The High Speed machine is used to create the capsule by employing the processed powder blend with following particle properties such particle size distribution, bulk density, compressibility to enhance excellent flow property. This promotes the creation of compacts of the proper size and of sufficient cohesion to be filled into capsule shells.

Filling of capsule is done by two filling systems;

- Zanasi or Martelli create slugs in a dosator.
- Hofliger-Karg Machine

Weight fluctuation in capsules may happen owing to inadequate flow characteristics, incorrect lubrication and plug adhering to the dosator plunger surface. Overlay lubrication may produce issues in weight fluctuation, disintegration, dissolution and Bioavailability.The properties of granulation and the completed products are highly impacted by the kind and size of equipment used for mixing, granulating, drying, sizing and lubricating.

For better encapsulation, required of controlled environmental conditions that include Controlled humidity (RH 45 to 55 %) system in processing and encapsulation (RH 35 to 65 %) room and adequate temperature condition of 15 to 25 °C.

PILOT PLANT SCALE UP CONSIDERATIONS FOR LIQUID ORALS:

The physical structure of a pharmacological product that may be included displays Newtonian or Pseudo plastic flow behavior.

- It conforms to its container at room temperature.
- Liquid dosage forms may be distributed systems or solutions.
- In scattered systems there are two or more phases, where one phase is disseminated in another.
- A solution refers to two or more substances combined homogeneously.

Steps of liquid manufacturing process:

- Planning of material needs.
- Liquid preparation.
- Filling and Packing.
- Quality assurance.
- Critical features of liquid manufacturing
- Physical Plant.
- Heating, ventilation and air regulating system.

The impact of extended processing durations at suboptimal temperatures should be evaluated in terms of repercussions on the physical or chemical stability of components as well as product.

Solution:

The parameters to be considered are for scaling up of solutions are;

- Impeller diameter.
- Tank size (diameter) (diameter).
- Number of impellers.
- Impeller type.
- Mixing capabilities of impeller.
- Rotational speed of the impeller.
- Height of the filled capacity of the tank.
- Number of baffles.

- Transfer system.
- Clearance between Impeller Blades and wall of the mixing tank.

Filtration device (should remove desirable elements but should not eliminate active or adjuvant substances) (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 eliminate. the surface alkalinity of the Stainless Steel) (Pre-reacting the SS with acetic acid or nitric acid solution to remove. the surface alkalinity of the Stainless Steel).

Suspension:

The criteria to be considered are for scaling up of suspension are;

- Versator (To prevent air entrapment) (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 necessary for hydration of the suspending agent.
- Mixing speeds (High speed should not be utilised since it leads to air entrapment) (High speed should not be used as it leads to air entrapment).
- Mesh size (Must be able to remove the foreign particles and sieve determined depending on manufacturing batch size testing) (Must be able to remove the foreign particulates and sieve selected based on production batch size trials).

Emulsion:

The parameters to be examined 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 have to be addressed during the scale up of semisolid goods;

- Mixing speed.
- Mixing apparatus (Could be able to transport semisolid substance from outer walls to the middle and from bottom to top of the kettle) (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 proper handling system at its most viscous stage) (Drive mixing system with appropriate handling system at its most viscous stage).
- Heating and cooling procedure.
- 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 transport viscous material without producing excessive shear and free of entrapped air) (Easily must move viscous material without applying excessive shear and free of entrapped air).
- Following criteria must be consider for selecting the size and kind of pump,

- Pumping rate.
- Pumping pressure necessary should be considered.
- Product compatibility with the pump surface.
- Product viscosity.

SUPAC (SCALE UP AND POSTAPPROVAL CHANGES) GUIDELINES:

SUPAC reflects the adjustments proposed by the US FDA at the time of scale up or approval of NDA / ANDA.

In the process of producing a new medicinal product, the batch sizes employed in the early human trials are modest and the size of the batches is progressively raised (Scale-up) (Scale-up). The scale-up procedure and the adjustments made after approval in the composition, manufacturing method, manufacturing equipment, and change of location have become known as Scale-Up and Post approval Changes, or SUPAC.

The SUPAC Guidelines specify;

The degree of alterations - Minor, Moderate and Major Changes.

Test - Application test, in vitro dissolution and in vivo

Filing - Annual report, changes being implemented supplement and Prior Approval Supplement.

The amount of adjustments may affect on formulation and quality performance in following levels;

- Level 1: unlikely to have discernible Impact.
- Level 2: might have substantial influence.
- Level 3: likely to have substantial effect.

These guidelines include suggestions for post approval adjustments in;

- The components or makeup alter,
- The place of production change,
- The scale-up of production change
- The manufacturing (process and equipment) modification.
- 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 dose forms.

The location changes of manufacture:

Changes in location of the site of manufacturing, packaging activities and/or analytical testing laboratory. Do not include any scale-up adjustments, changes in production (including process and/or equipment), or changes in components or composition.

Current Good Manufacturing Practice (CGMP) inspection.

Level I Changes -

Classification-Single facility with the same equipment, standard operating procedures (SOP's), ambient conditions (e.g., Temperature and humidity) and controls, and people 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 staff, No additional modifications. 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 medium at pH 4.5-7.5 forextended release). Three differentMedia (e.g., Water, 0.1N HCl, andUSP buffer medium at pH 4.5 and 6.8for delayed release)until 80% ofDrug Released.

Filing Documentation- Annual report.

Level III Changes -

Classification– Different campus, Different staff. Test Documentation –

Application/compendial criteria.

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 medium at pH 4.5-7.5 for prolonged release). Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at pH 4.5 and 6.8 for delayed release) till 80 % of Drug Released.

Filing Documentation- Annual report previous permission of supplement.

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

Post-approval modifications in the size of a batch from the pivotal/pilot scale bio batch material to bigger or smaller production batches require for submission of additional information in the application.

Scale-down below 100,000 dose units is not addressed by this advice.

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) (long term stability data).

Level II Changes -

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

Test Documentation –

Chemistry Documentation Application/ compendial release criteria. Notification of modification and submission of revised 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 implemented supplement; annual report (long-term stability data) (long-term stability data).

Manufacturing Changes:

Production modifications may alter both equipment employed in the manufacturing process and the process itself.

i)Equipment –

Level I Changes:

Classification- Alternate equipment of the same design and concepts as automated equipment. Test Documentation – Updated batch records, Application/compendial requirements and stability. Filing Documentation- Prior approval supplement with rationale for modification; yearly report (long-term stability data) (long-term stability data).

Level II Changes:

Classification- Change to equipment of different design and concept.

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

SUPAC – IR - Multi-point dissolution profiles in various mediums.

SUPAC – MR - Multi-point dissolution profiles in various mediums. Filing Documentation- Annual report and modifications being Effected Supplement. ii)Process -

sLevel I Changes:

Classification- Alternate equipment of the same design and concepts as automated equipment. Test Documentation – Updated batch records, Application/compendial requirements and stability. Filing Documentation- Annual report.

Level II Changes:

Classification- This category contains process alterations including adjustments such as mixing times and operating speeds outside the application/ validation limits.

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

SUPAC - IR - Multi-point dissolution profile.

SUPAC- MR - Multi-point dissolution profiles in various mediums.

SUPAC – SS - In vitro release test Documentation.

Filing Documentation- Changes being implemented supplement; yearly report (long term stability data) (long term stability data).

Level III Changes:

Classification- Changes in the kind of process utilised (e.g. wet granulation to direct compression) (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 various mediums.

Filing Documentation- Prior approval supplement with reason; yearly report (long-term stability data) (long-term stability data)

INTRODUCTION TO PLATFORM TECHNOLOGY:

Platform technologies:

Platform technologies are systems that disperse the system out into several levels of abstraction. This is done in order to distinguish between basic – platform – functions, and the application layer that sits on top of, and relies upon, these underlying common services.

Pharmaceutical Platform technologies:

Pharmaceutical Platform technologies are regarded a helpful tool to increase efficiency and quality in medicinal product development. The underlying notion is that a platform, in conjunction with a risk-based strategy, is the most systematic manner to exploit existing knowledge for a given new molecule.Platform technology is becoming a common industrial approach for bioprocessing.

Importance platform technology:

Platform firms move quicker than their conventional competitors. When your core goods and services constantly change, it drives your staff and your business to accept change swiftly.

Types of platform technology:

Operating systems provide the basic services required to use hardware.

1. Computing Platforms. 2) Database Platforms.

   3)Storage Platforms. 4) Application Platforms.

   5) Mobile Platforms. 6) Web Platforms.

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