# General Considerations During Pilot Plant Scale-up

In every emerging drug manufacturing  industry or an already existing one, there is always a need to  have an intermediate batch scale representing procedures and simulating that used for commercial manufacturing. In order to develop a reliable and practical method of manufacture that affects an orderly transition from laboratory to routine processing in a full-scale production facility, the following should be considered.

## 1. Reporting responsibilities

In order to facilitate smooth transfer of products from a laboratory scale to a commercial scale, there is need for be adequate records and reporting arrangement. How effective a pilot plant is may be determined by the ease with which new products or processes are brought into routine production.

To achieve this, there should be a good relationship and effective communication between the pilot plant group and the other groups (Research and Development, processing, packaging, engineering, quality assurance/control, regulating and marketing) with which they interact during the process.

## 2. Personnel Requirement

Those employed during the scale up process should be individuals with qualifications required for position in a pilot plant organization. It should be a blend of good theoretical knowledge of pharmacy and some practical experience in the pharmaceutical industry. Practical experience in pilot plant operations is also invaluable.

The type and level of education within the group is equally important as they have to understand the intent of the formulator as well as understand the perspective of the production personnel. The number of people in a pilot plant depends in the number of products being supported and on the level of support required.

## 3. Space Requirements

The space requirements of a pilot plant are of four types:

### a. Administrative and information processing

There should be adequate office and desk space for both the scientists and technicians to facilitate proper documentation of their activities and observations. This should be adjacent to the work area but sufficiently isolated to permit people to work without undue distraction.

### b. Physical Testing Area

There should be an adequate working area where the analysis and physical testing of samples can be performed (in-process quality control analysis) which helps in early identification of production error. This area should provide permanent bench top space for routinely used physical testing equipment like balances, pH meters, viscometers etc.

### c. Standard pilot plant equipment floor space

This has to do with where all the relevant equipment used in the pilot plant scale up techniques is kept. The equipment should be available in a variety of sizes known to the representative of all production capability. This arrangement helps make sure of the quality of the scale up data collected, as well as being prudent with expensive materials.

Intermediate size and large or full scale production equipment are essential in evaluating the effects of scale up on research formulations and processes. Equipment should be made portable where possible since the utilization of pilot plant equipment is occasional or sporadic and dependent on project assignments. Utilization of this area is most effective when it is subdivided into areas for different dosage forms (solid, semi-solid, liquid and sterile products).

### d. Storage Area

Separate provision should be made for the storage of active ingredients and excipients. Different areas should be provided for the storage of the in-process materials, finished bulk products from the pilot plant and materials from the experimental scale-up batches made in the production. Storage area for packaging materials should also be made available.

## What is a pharmaceutical plant layout?

Pharmaceutical plant layout/ factory layout refers to the allocation of space and the arrangement of machines, furniture and other important administration and necessary services needed in a production process within a factory building in other to perform the various unit operations involved in the manufacturing process of dosage forms in a cost effective manner and with the least amount of handling in processing the product from the receipt of raw material through the distribution of the finished product.

## Features of a good pharmaceutical plant layout

A good pharmaceutical plant layout should possess the following characteristics

 There should be adequate floor space for machines installation and utilization

 The machines should be properly arranged to facilitate minimum material handling is necessary for low cost processing.

 The layout should facilitate smooth and continuous flow of production process from one point to another without any form of delay

 It must incorporate adequate health, safety and security features such as first aid box, fire extinguisher, emergency exit and access point

 A good layout should allow effective supervision, coordination and control of the production processes

 There should be room for adjustment and modifications whenever the need arises.

## Advantages of a good pharmaceutical plant layout

The advantages of a good pharmaceutical plant layout includes but are not limited to

* Optimum use of available floor space for production operations
* Improved quality of product due to reduced chances of cross contamination
* Efficient arrangement for receipt, transportation, storage, and delivery of raw material and finished goods.
* Low cost of material handling
* Minimized loss due to waste and spoilage
* Conducive working conditions resulting in improved efficiency.
* Increased productivity with reduced risk of human error
* Minimized risk of occupational hazards/ low incidence of occupational hazards
* Minimized cost and efforts in supervision of production processes.
* Provision of control and supervision operations at appropriate points

## 4. Raw Materials

One responsibility of pilot plant operation is to approve and validate the active and excipient raw materials used in the formulation of pharmaceutical products. This should not be taken for granted. This is because pilot scale up, in itself, does not guarantee a smooth transition.

The raw materials used during small scale formulation trials may not meet the requirements of large volume shipments of materials used in full manufacturing scale. Also active ingredients used in a laboratory scale need to meet up with the rising needs of the product when subjected to scale up.

There may be variations in particle size, shape, or morphology resulting in different handling properties or differences in density, static charges, rate of solubility, flow properties etc., of active/inert ingredients as the batch size increases.

here is need for alternate suppliers of raw materials because a single supplier may sometimes leave the company defenseless with respect to price and supply quality. This means that several batches of products need to be manufactured with these alternate materials and their performance in the formulation and stability of the finished product, evaluated relative to the standard product.

## 5. Relevant Processing Equipment

During scale-up, alternative manufacturing equipment should be considered since most development work has been performed on small and simple laboratory equipment. The equipment that promises to be the most economical, the simplest, the most efficient and the most capable of consistently producing products within the proposed specifications should be evaluated based on the known processing characteristics of the product.

The size of the equipment should be optimized and the ease of cleaning should be considered especially if multiple products are to be manufactured in the equipment.

## 6. Production Rates

The immediate and future market demands of a product should be considered when determining production rates and the type/sizes of production equipment to be used in the production process. The size of the equipment and its utilization should be proportional to each other.

The choice of equipment and process to be used is dependent on product loss in equipment during manufacturing process, time required to clean up equipment between batches and the number of batches needed for testing.

## 7. Process Evaluation

This step critically evaluates the process and optimizes its performance based on that evaluation. Processes that should be examined include the following:

1. Order of addition of components, including adjustments of their amounts.
2. Mixing speed and mixing time.
3. Rate of addition of granulating agents, solvents, solutions of drugs, slurries etc.
4. Heating and cooling rates.
5. Filter sizes for liquids preparations
6. screen sizes for solid preparations
7. Drying temperatures and drying times.

Knowledge of the effect of these important process parameters on in-process and finished product quality is the basis for process optimization and validation. This is accomplished by monitoring the within batch variation of measurable parameters (content uniformity, moisture content and compressibility). This provides data that helps in accessing and identifying where the process is performing as intended and where problem areas may be found.

## 8. Preparation of Master Manufacturing Procedure

This is concerned with the manner of presentation of the manufacturing procedures to facilitate easy compliance and understanding by the processing technicians. The procedures include; manufacturing directives, chemicals weigh sheet, sampling directions, in-process and finished product specifications.

The weight sheet, for instance, should clearly identify the chemicals required in the batch, their quantities and order in which they will be used. To also prevent confusion and possible errors, both names and identifying numbers for the ingredient should be used on batch records and these should correspond with those on the bulk material containers. The process directions should be precise and explicit.

The batch records’ directions should include specifications for addition rates, mixing times, mixing speeds, heating and cooling rates and temperatures. The actual times, temperature and speeds used should be documented. The time and manner in which in-process and finished samples are to be taken from a batch and the way in which they are handled and stored should be clearly specified with the batch record.

## 9. Good Manufacturing Practice (GMP) Considerations

A list of GMP items that should be part of scale up of a new product or process introduction may include the following;

1. Equipment qualification
2. Process validation
3. Regularly scheduled preventative maintenance
4. Regular process review and revalidation
5. Relevant written standard operating procedures
6. The use of competent, technically qualified personnel
7. Adequate provision for training of personnel
8. A well-defined technology transfer system
9. Validated cleaning procedures
10. An orderly arrangement of equipment for easy material flow and prevention of cross contamination.

## 10. Transfer of Analytical Methods to Quality Assurance

All analytical test methods developed in research during scale up of a new product, must be transferred to the quality assurance department. The quality assurance staff should review the process to make sure that the proper analytical instrumentation is available and that personnel are trained to perform the tasks.

Research personal should review the assay procedure and the data obtained during the validation studies to verify that the analytical methods have not been altered in a way that might affect the reliability, precision or accuracy of the tests.