ANALYSIS OF THE INTRODUCTION OF NEW TECHNOLOGIES TO EVALUATE THE PERFORMANCE OF PHARMACEUTICAL UNIT OPERATIONS

by

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B.S. in Industrial Biochemical Engineering, Autonomous Metropolitan University (1994)

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ABSTRACT

Evaluation of the performance of pharmaceutical unit operations is carried out to ensure that the finished drug's quality meets FDA standards. Blending is a common and important operation on the manufacturing of solid oral dosage forms. The main performance criterion for blending is given by the blend's homogeneity, which is determined by sampling and off-line sample analysis. These operations are costly, time consuming and can be a source of contamination and errors.

We review the current state of the art in blending and propose a Laser Induced Fluorescence (LIF) system as an on-line technology alternative to sampling and analysis for the evaluation of blending performance. We evaluate the impact of the introduction of such a system in the life cycle of a drug in terms of its economic impact, through NPV economic analysis and system dynamics modeling, and we examine the regulatory and policy implications associated with its implementation.

We evaluate the economic impact of implementing an on-line homogeneity detection system and demonstrate that it is a viable alternative to current blend homogeneity detection methods.

Thesis Supervisor: Professor Charles L. Cooney
Title: Professor of Chemical Engineering

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And last, I would like to thank my beautiful Mishy, whose companionship has brought so much joy into my life.

DEDICATION

I would like to dedicate this work to my grandmother, Carmela Calzada, whose memory I always carry in my heart, and to my mother, whose love has truly been the motivation behind all my accomplishments.

CONTENTS

Chapter 1
INTRODUCTION

The effective introduction of a new technology is not just a question of buying the right equipment. Technical change in organizations is a multi-dimensional and continuous process. Maximum return on investment is unlikely to be realized unless technical innovation is accompanied with organizational innovation; ways of working and management structures also have to be redesigned when new technology is introduced.

Technical change can be viewed as a trigger to processes of organizational decision-making in which critical strategic choices emerge. The adoption of process innovations entails particular challenges for a firm, both at the organizational level and at the knowledge-base level. The implementation of a new technology has technical, legal, economic, educational and managerial implications.

In the case of the development and manufacturing of medicinal products, the situation is further complicated by the need to comply with the strict regulations by which the pharmaceutical industry must abide. Every unit operation in a pharmaceutical process needs to undergo a validation procedure, which involves analyzing the performance of critical steps of the process to insure it does what it is supposed to do and does it repeatedly.

One of the most common unit operations in the preparation of solid dosage forms (mainly, tablets) is physical blending of an active drug substance with one or more excipients; the purpose of this operation is to achieve a homogeneous mix of the materials. As a criterion for completion, an off-line measure of blend homogeneity is currently used [4, 6, 12, 20]; this measure is time consuming since it involves sampling and off-line analysis, and it places a major limitation on the reduction of cycle time. Furthermore, sampling itself can introduce errors [11, 25].

Improvement of blending technology has mainly revolved around the physical structure of the blender (size, form, and axis of rotation) as well as on the upstream operations, that may contribute to the ability of a powder mix to blend homogeneously [2, 16].

Technologies which can reduce or eliminate off-line analysis have only recently begun to be examined and developed. Techniques such as near-infrared spectroscopy have been used to develop devices which can quickly assess blending performance [11]. An alternative to this technique consists of a device which uses laser induced fluorescence (LIF) in a probe mounted on the blender, which allows for immediate assessment of the blend's homogeneity by illuminating with a laser and then measuring the fluorescent response, which is proportional to the active ingredient's concentration at a particular point. By eliminating off-line analysis, total cycle time of the operation is reduced, and by avoiding sampling errors, the final tablet's quality is assured; additionally, the new LIF probe permits a better utilization of the equipment and a reduction of labor cost. The expected result is a reduction in variability.

As a process innovation, the use of the LIF probe would change the current practice of product development and process validation, and have an impact on manufacturing process efficiency.

In order to determine the impact of this new technology and to choose among different alternatives, it is important to use a consistent and robust method to evaluate the technology in terms of powder blending performance, as it relates to:

1. Cost / productivity
2. Quality
3. Cycle time
4. Safety

The consequences of a technical innovation are not always predictable in detail and unexpected benefits as well as difficulties are bound to arise. Planning is thus consistent with an experimental, learning approach in which new and unforseen opportunities need to be seized, and challenges overcome.

The consequences of technical change depend on the objectives being pursued, and these in turn are influenced by the decision-making style that directs the investment. Technical change is rarely aimed at a single outcome and usually reflects a pattern of objectives concerning new technology and accompanying changes to organizational processes and structures [3]. There is considerable scope for creative choice in the establishment of that pattern of objectives.

The introduction of the LIF device into process development and/cr manufacturing, may have an impact in different organizational strucutres, mainly:

1. Work of staff running the systems:

   a) Reduction of amount of routine manual work (for instance, sampling and transporting of samples);

   b) Reduction of the number of people involved in the operation or process (elimination of the need to analyze material off-line).

The technical characteristics of an innovation affect how it changes the work of staff, and how well it helps the user's performance. These characteristics include:

- Accuracy: correctness of the output information.
- Reliability: consistency and dependability of the output information.
- Timeliness: availability of the output information at a time suitable for use.
- Relevancy: degree of consensus between what the user wants and what is provided.
- Confidence in the system: certainty about system production.

Labor requirements change with the introduction of a new technology. In the case of the LIF, some manual operations, such as sampling, which are inherently prone to error, would be substituted by the automated system of real time homogeneity measurement. Additionally, the need for sample analysis from the bulk granulation would be eliminated at the various stages of

the development and validation processes, and would only be required at the end point of the manufacturing process.

The ability of innovations, such as the LIF, to provide more accurate, consistent and timely information about performance can be used to give managers a much clearer picture about performance in their department.

2. Access to information: Faster access to information of critical process parameters allows to shorten the cycle time for development of new products and to improve the efficiency of current manufacturing practice.

3. Structure: Division of production control, process planning and order processing may change.

4. System inter-dependencies: Closer inter-dependencies between stages of the process.

5. Decision-making and power: Local decision-makers are provided with the information they need to make better judgements. This will shift the distribution of power from the analytical laboratory to the operation's supervisor who will determine on-site, with the aide of the LIF probe, the end point of the operation which will, in turn, be the key parameter to validate the process.

6. Safety: Safety is increased by eliminating handling of the active ingredient during sampling and analysis.

The context in which a new technology is introduced, and the choices that arise during its implementation stage can be summarized as follows (Figure 1.1) [19]:

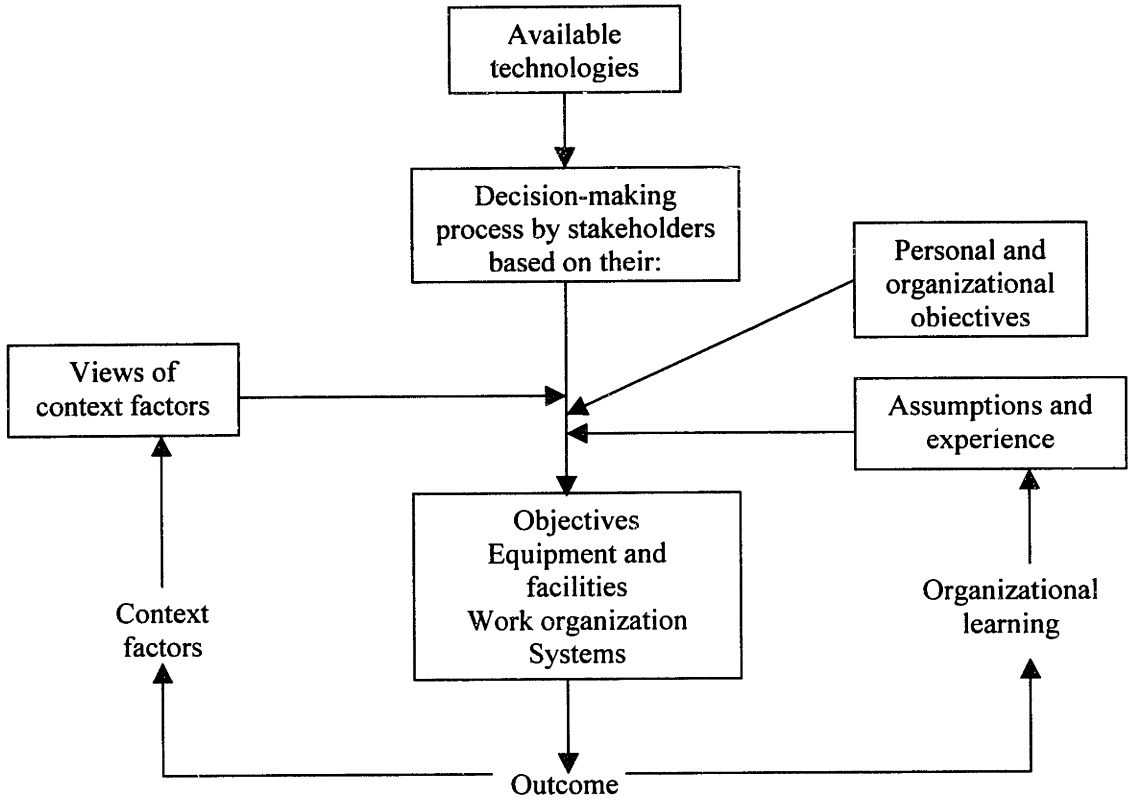


Figure 1.1
Context and Choice of New Technology Implementation

A key organizational concept is flexibility. A dynamic planning approach to evaluate the impact of innovation will provide a tool to determine the real benefits that on-line homogeneity assessment will have on the various stages of the process, compared to sampling and off-line analysis, as well as to understand the influence of the new technology in the process variables that have a direct impact on the performance of the operation of blending.

Chapter 2
BACKGROUND

PHARMACEUTICAL PROCESSES

The research and development of a new drug comprises a series of stages, from the discovery and analysis of a compound with a specific therapeutic effect until the commercialization of the packaged medication. Figure 2.1 summarizes the different specialties needed and the activities performed during the research and development of a new drug application [24]:

Once the dosage form has been defined at the Definition stage, the manufacturing process is developed and validated. It is noteworthy that this process can take up to 7 years (from year 5 to year 12). The development of the manufacturing process involves various stages. In the case of solid oral dosage forms, such as tablets, the formulation must first be prepared in a form suitable for compression on a tablet press (this process and the product obtained thereby is referred to as the granulation). Then, the process is scaled-up and the first clinical batches are produced (Phase I). In Phase III (set up of technology), the process is validated and ready for full commercial production.

A granulation must have good flow properties for precise volumetric feeding of the material to the die cavity, compressibility to form the compact, and lubricant properties for ejection of the tablet. The methods used for preparing tablet granulations are wet (Figure 2.2) and dry (Figure 2.3) granulation and direct compression (Figure 2.4) [18]. The first step in each method is to prepare a mixture of the drug and some or all of the excipients. The wet and dry granulation methods are designed to improve the flow and compressibility of the powder, which would otherwise be unsuitable for making tablets. When the formulation has good flow and compressibility properties, the ingredients are mixed and directly compressed into tablets. The choice of methods depends on the properties and dose of the drug, available equipment and regulatory issues, among others.

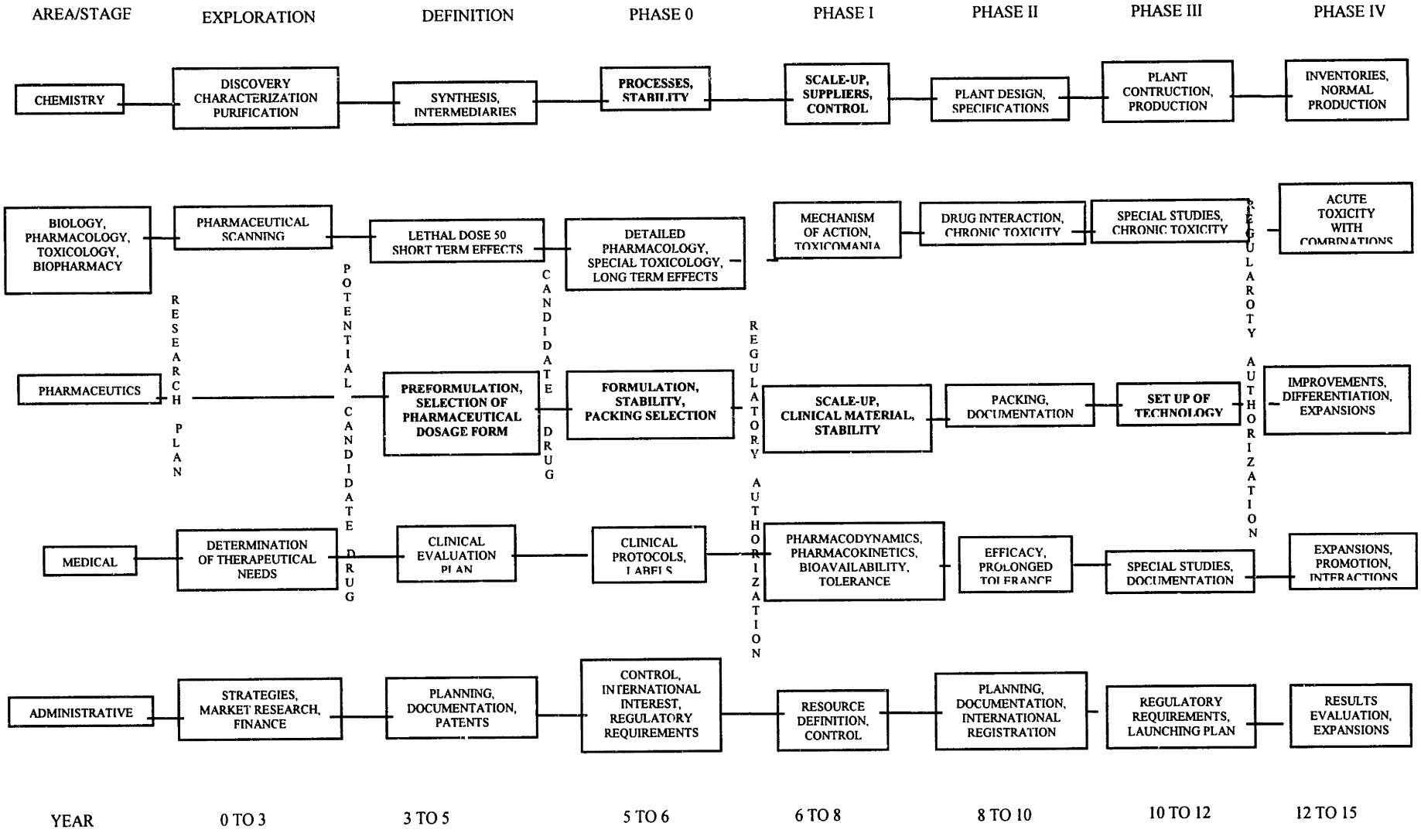


Figure 2.1
Typical activities of the research and development of a new drug

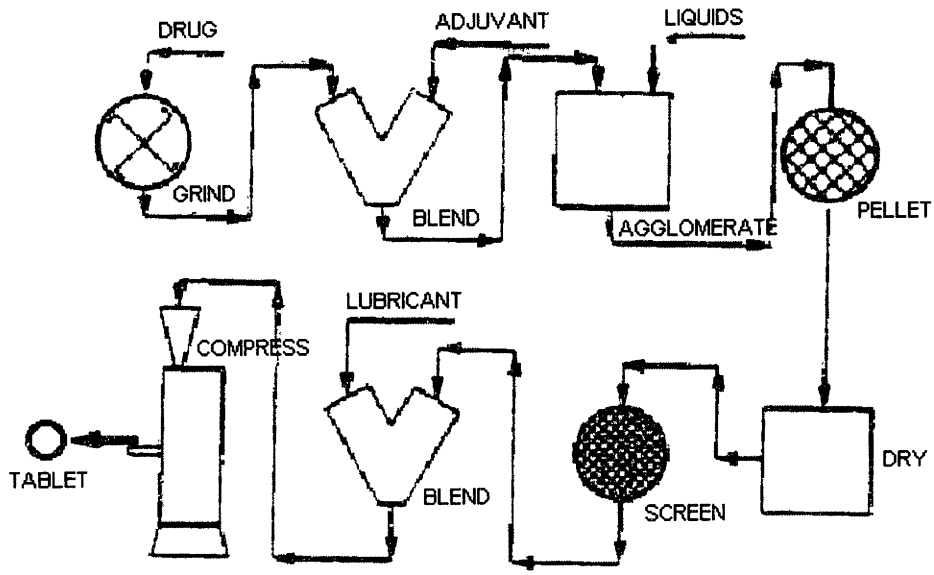


Figure 2.2
Wet Granulation

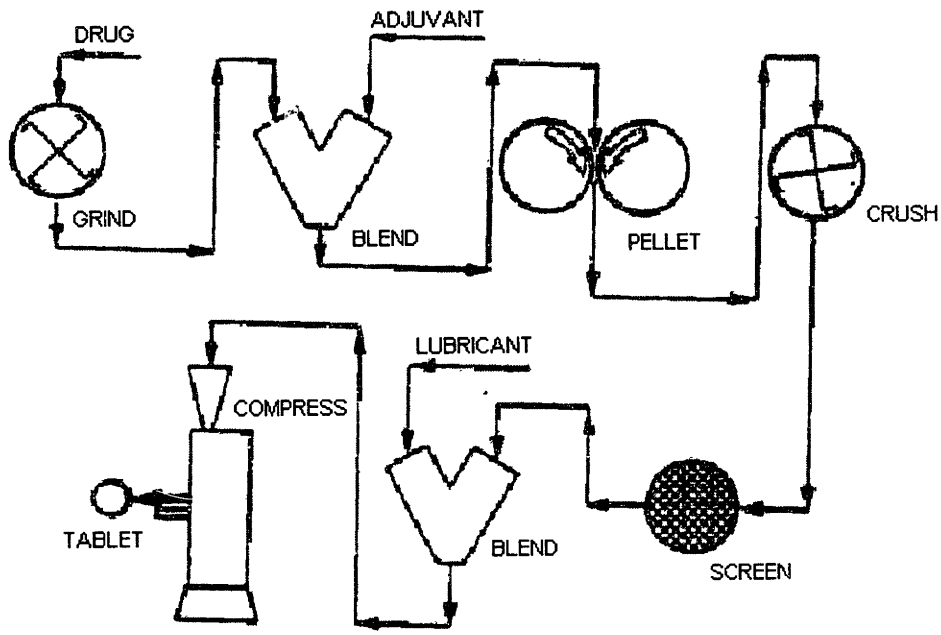


Figure 2.3
Dry Granulation

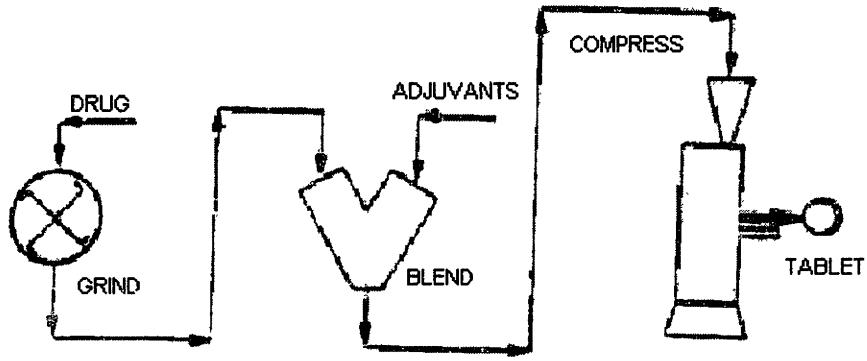


Figure 2.4
Direct Compression

BLENDING

Mixing can be defined as the putting together of ingredients. Blending is a form of mixing, whose objective is to obtain dosage units, each of which will contain the same ratio and amount of ingredients per batch.

The mixing of solid particles is accomplished through three principal mechanisms:

1. Diffusion: particles are redistributed by random movement.
2. Convection: groups of adjacent particles move from one place to another.
3. Shear: slip planes are formed, changing the configuration of the ingredients.

The mixing of a particulate system differs from that of liquid systems in three important respects [24]:

1. There is no particulate motion equivalent to the molecular diffusion of gases and liquids. The rate at which the randomization of the constituent particle occurs is entirely dependent on the flow characteristics or handling pattern externally imposed on the particles. There is no relative movement of the particles without an energy input to the mixture.

2. Although the molecules of a single-phase liquid system may differ, and may diffuse at different rates, they will ultimately achieve a random distribution within the confines of the system. Particulate and granulator components do not usually have the constant properties of molecular species and can differ widely in physical characteristics. Thus, a mixing motion which depends on identical particulate properties is unlikely to achieve its objective. More commonly, such a "mixer" would produce a grading or segregation of particles according to such characteristics as size, density, resilience, etc.

3. The ultimate element of the particulate mixture is several degrees of magnitude larger than the ultimate molecular element of the liquid mixture. This means that samples withdrawn from a randomized particulate mixture will have a coarser texture or poorer mixture quality than would the equivalent samples taken from a gaseous or liquid mixture.

The unit operation of solid-solid mixing can be separated into four principal steps:

1. Expansion of the bed of solid particles.
2. Application of three dimensional shear force to the powder bed.
3. Mixing and randomization of particles.
4. Maintaining randomization (no segregation) after mixing has stopped.

Initially, when dry materials or particles are loaded into a mixer, they form a static bed. Before mixing or interparticulate movement can take place, this static bed must expand, as a result of mixing forces. Particles will change their relative positions only when subjected to movement. It must be noted that before a particle bed can expand for mixing, there must be room for it to expand; that is, there must be enough void space remaining in the mixer after it has been charged with the ingredients to be blended, which is the reason why blenders are usually loaded at only 40 to 60 % of their maximum capacity.

Once particle movement is possible with the expansion of the powder bed, shear forces are necessary to produce movement between particles. Tension and

compression forces merely change the volume. Induction of movement in all three directions requires adequate three dimensional stress, resulting in the essential random and sometimes turbulent particle movement. Once movement begins, the particles may randomize or segregate depending on both the type of movement imposed on the system and on the physical characteristics of the constituents. Should these forces be inadequate, dead spaces in the form of particle agglomerates in the powder bed move together without mixing with adjacent particles, resulting in a poor mix.

Once the desired mixing has been attained, it is essential that the particles in the mix cease movement such that the system may exist in a state of static equilibrium without segregation taking place since the mixing of particles is often a readily reversible process and also a process in which the point of equilibrium can vary along a production line. A well mixed batch of particles can be unmixed almost completely at a subsequent process stage if incorrectly handled. Segregation or "unmixing" can, therefore, occur not only in the mixing unit but also throughout the entire process.

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling.

Segregation is the tendency of particles to separate out according to size and/or density [9]. Segregation occurs within a mixer when differences in particulate properties cause a preferential movement of particles to certain regions of the mixer. Difference in most particulate properties can in certain circumstances cause a non-random movement of particles but the properties which mainly cause segregation are, in order of importance [18]:

1. Particle size
2. Shape
3. Density
4. Resilience

Segregation of solids can also be caused by overmixing: excessive mixing may mean mixing for too long in a batch mixer. Thus, while a good mix may be produced after a relatively short period of mixing, segregation may dominate after this time and reduce mixture quality. It is important to appreciate that more mixing, i.e., mixing more energetically or for more time, may do more harm than good.

A major influence on the mechanisms of mixing and segregation within a powder are the flow characteristics of the powder. A different mixing and handling approach is required for free-flowing and for cohesive powders (a free-flowing powder flows consistently but its particles have high individual mobility, which can promote interparticulate segregation; on the other hand, cohesive powders flow intermittently, if at all, but do not exhibit gross segregation).

Particle size is an important variable in determining the flow characteristics of a mixture [23]:

1. Materials with a size greater than 75 μ segregate readily.
2. The reduction of particle size below 75 μ reduces segregation but it may still be detectable down to about 10 μ.
3. Below 10 μ no appreciable segregation occurs.

Other mixture properties can also influence the flow characteristics of the mixture. The addition of small quantities of moisture can transform a strongly segregating mixture into a cohesive and non-segregating mixture. A mixture containing coarse particles can be free of segregation if the major component has a fibrous shape. If one component in an otherwise coarse mixture is very fine, the fine particles can "coat" the coarser ones. In this situation the very fine particles lose their freedom of movement and a high quality, non segregating mixture can result.

The best way to avoid segregation is to ensure that the components of the mixture have the same particle size. Small differences in particle size can result in considerable segregation within a free-flowing mixture and it is not usually possible to obtain an exact matching of particles.

Having a free flowing powder is an important requirement in pharmaceutical operations, so segregation has to be minimized rather than eliminated. This can be done by careful choice of the properties of the mixture and of the method of mixing and handling.

Segregation has consequences in the collecting of samples from a powder mass for size or chemical analysis, in the feeding of materials to either tabletting machines, packaging machines or reactors and in other powder-handling operations.

Several general approaches are used in industry today for dealing with potentially difficult mixing problems [18, 23].

The first problem encountered is usually one of uniformity: a low dose, high potency active ingredient needs to be dispersed in a diluent to make a tablet that is large enough to compress, and to monitor the tablets weight with ease. Dilution of the active ingredient on a small scale may be done by serial dilution. In dry state, where a direct compression tablet is desired and can be made successfully with the proper combination and ratio of diluents, the active ingredient must be of a small enough particle size to allow relatively large numbers of particles to be distributed to each dosage unit. When this occurs, surface electrical charge problems may arise. Assuming a minimum of surface and other problems, the active ingredient to be blended into the final granulation is usually milled or passed through a small screen with enough diluent to obtain an amount of triturate that is easily handled. The mill may have knives or hammers at medium to high mill speeds, depending on the degree of dispersion required.

After the active ingredient has been passed through the mill, the mill is cleared of active ingredient by passing another portion of diluent through the mill, adding to the triturate. The triturate and "mill cleaning" diluent are added to the mixer with about one half of the remaining diluent and mixed for 10 to 15 min in a mixer without high speed

agitation, such as the tumbling mixers or the sigma blade, ribbon, or conical screw mixers. The remainder of the diluent and additives, such as the disintegrating and lubricating agents, are then added to the mixer for the final mixing.

A second alternative may be used if high speed agitation equipment is available, such as V-shaped or double cone blenders with agitator blades, or high speed granulating equipment, with a chopper blade. This type of equipment permits adding all the ingredients to the mixer at one time. No premixing is required because the mixing action is so intense. Mixing times are relatively short and must be watched carefully so that unwanted size reduction does not take place with the more friable materials, if present.

If the active ingredient cannot be successfully dispersed in a dry state (this is usually determined in the developmental stages of the product), it is dissolved in the granulating solution solvent and wet granulated in the premixed diluents and internal additives.

Slow drying of the wet granules may cause migration of the solubilized materials, possibly including the active ingredient, in the granulating solution. This could cause uniformity problems in the dry granulation which might show up in the final dosage unit if the granulation is not milled to a small enough particle size. This problem may prevented by rapid drying in a fluid bed drier or by granulating in a fluid bed granulator.

The mixing process must be optimized by reducing materials handling to a minimum. This includes premilling, premixing and mixing times.

In general, poorly flowing cohesive powders can be mixed by using high shear equipment, such as high speed granulators or even the fluid bed granulator. The use of this equipment for mixing poorly flowing ingredients requires some experimentation to determine the amount and type of shear required and the mixing time to yield a uniforms mixture.

In some instances where new mixes are put into production, more mixing may take place than is needed. Very thorough mixing affects lubricity of a granulation. In

many cases where poor lubrication is noted, it is the result of too intimate mixing of the lubricant (i.e., the lubricant is dispersed too well throughout the mixture).

Usually, working directions call for the lubricant to be added initially in a direct compression mixture or added with the remaining external ingredients during the final blend of a dried, milled, wet granulation. If poor lubrication during compression of the granulation is noted, a number of steps may be taken, other than increasing the concentration of the lubricant (the new drug application permitting):

a) The mixing time may be decreased if it does not affect the homogeneity of the overall mixture. This is particularly useful if high shear mixing equipment is used and the mixing time has not been optimized (the blend time may be too long initially). It may even be necessary to change mixers before the lubricant is added, using a lower shear mixer.

b) The lubricant may be added only for the last 5-10 minutes of mixing. The higher the mixing shear, the shorter the mixing time required to obtain satisfactory lubrication dispersion.

EQUIPMENT

Mixers can be divided into two broad categories: batch-type and continuous (Table 1) [18]. The most prevalent type used in the pharmaceutical industry is the batch type, which mixes a sublot or total lot of a formula at one time (i.e., all ingredients are placed in the mixer, the materials are mixed, and the mixture is removed as one unit lot or sublot). The continuous mixer, on the other hand, is usually dedicated to a single high-volume product. Ingredients are continuously added to the mixer and collected from the continuous discharge. The lot size is usually determined by a specified length of mixing time, which may range from 8 to 24 hr or longer, depending on the process.

TABLE 1

MIXER CLASSIFICATION

1. **Batch-Type**
    - Rotation of the entire mixer shell or body with no agitator or mixing blade (Convection Mixing: group of particles moves and breaks apart):
        * Barrel
        * Cube
        * V-shaped
        * Double cone
        * Slant double cone
    - Rotation of the entire mixer shell or body with no a rotating high-shear agitator blade:
        * V-shaped processor
        * Double cone formulator
        * Slant double cone formulator
    - Stationary shell or body with a rotating mixing blade:
        * Ribbon
        * Sigma blade
        * Planetary
        * Conical screw
    - High-speed granulation -- stationary shell or body with a rotating mixing blade and high-speed agitator blade -- (Shear Mixing):
        * Barrel
        * Bowl
    - Air-mixer --stationary shell or body using moving air as agitator -- (Diffusion Mixing):
        * Fluid bed granulator
        * Fluid bed dryer
2. **Continuous type**
    - "Zig Zag"

a) *Batch Type Mixers*

The first general class of mixers are those which create particle movement by rotation of the entire mixer shell or body. A schematic of the four types listed in Table 1 is seen in Figure 2.5 [18]. Neither barrel nor cube mixers are used to any great extent in industry at present. However, V-shaped and double-cone blenders, in sizes from 10 to 150 ft^3 or larger, are used extensively for blending. The term "blending" is used in relation to these pieces of equipment because they mix the dry powders with a minimum of energy imparted to the powder bed. V-blenders consist of two hollow cylindrical shells, usually joined at a 75-90° angle; the mixing vessel is connected to a rotating shaft, causing a tumbling motion of the powders as the vessel is rotated [4]. The relating shell blenders are used only for dry mixes and have no packing glands (seals) around shafts entering the chamber to cause potential problems. Modifications such as the addition of baffles to increase mixing shear have been made to these types of blenders.

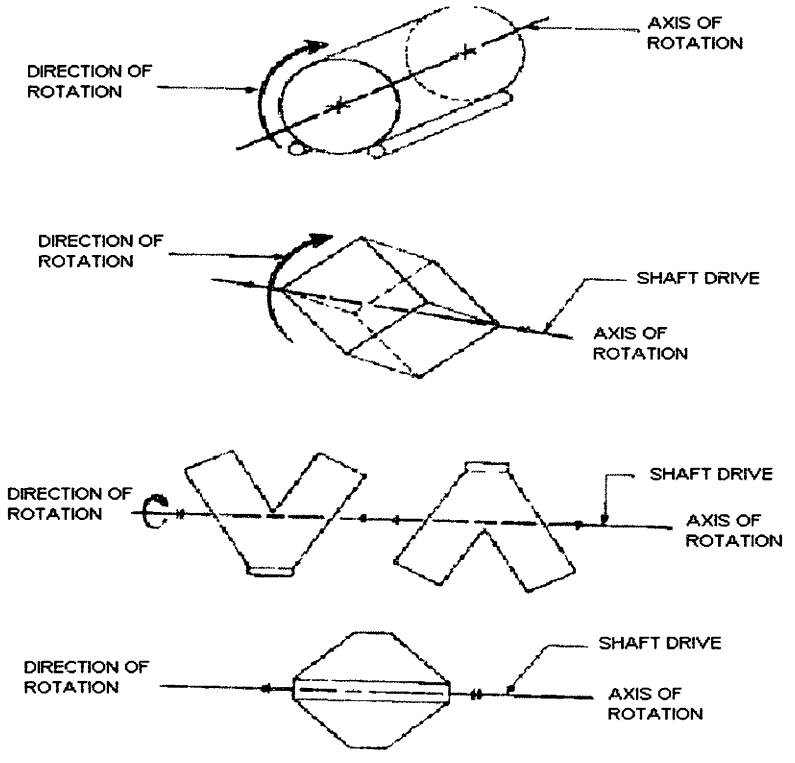


Figure 2.5

Rotating shell blenders: (A) Barrel Blender, (B) Cube or Bin Blender, (C) V-shaped Blender, (D) Double Cone Blender

The advantages of using V-shaped blenders and double-cone blenders include:

1. Minimal attrition when blending fragile granules
2. Large-capacity equipment available
3. Easy to load and unload
4. Easy to clean
5. Minimal maintenance

The primary disadvantages are:

1. High head space needed for installation
2. Segregation problems with mixtures having wide particle size distribution and large differences in particle densities
3. The tumbling-type blenders are not suitable for fine-particulate systems because there is not enough shear to produce particle agglomeration
4. If powders are free-flowing, serial dilution is required for the addition of low-dose active ingredients

These blenders are operated by adding material to be blended to a volume of approximately 50 to 60% of the blender's total volume. Blending efficiency is affected by the load volume factor, as shown on Table 2 [23].

TABLE 2

EFFECT OF POWDER FILL ON BLENDING TIME OF DOUBLE-CONE BLENDERS

Volume % of blender filled with powder charge	Approximate blend time (min) in production-size blenders
50	10
65	14
70	18
75	24
80	40

Blender speed may also be a key to mixing efficiency, because the slower the blender, the lower the shear forces. Although higher blending speeds provide more shear, they may also result in more dusting, causing segregation of fines; that is, as the blend is tumbling, the fines become airborne and settle on top of the powder bed after blending has ceased. There is also a critical speed which, if approached, will diminish blending efficiency of the mixer considerably. As the revolutions per minute (rpm) increase, the centrifugal forces at the extreme points of the mixing chamber will exceed the gravitation forces required for blending, and the powder will gravitate to the outer walls of the blender shell. It should be noted that bench scale blenders turn at much higher rpm than the larger blenders, usually in proportion to the peripheral velocity of blender extremes.

Both V-shaped and double-cone blenders usually have a variable-speed drive to adjust the mixing speed of the shell. However, the speed of industrial blenders is normally a set parameter, and no adjustment of the rpm's takes place. The double-cone blender is usually charged and discharged through the same port, whereas the V-shaped blender may be loaded through either the shell hatches or the apex port. Emptying the V-shaped blender is normally done through the apex port.

The second general class of mixers, shown schematically in Figure 2.6 [18], is a modification of the tumbling blenders with the addition of a high-speed (1200-3000 rpm) agitator mixing blade. This agitator gives added versatility to the tumbling blenders by virtue of the high shear attainable. The advantages with the addition of the agitator bar to the tumbling blender include:

1. Good versatility, in that both wet and dry mixing can be accomplished in the blender.
2. A wide range of shearing forces may be obtained, with the agitator bar design permitting the intimate mixing of very fine as well as coarse powder compositions.
3. Serial dilution not needed when incorporating low-dose active ingredients.

The disadvantages include:

1. Possible attrition of large, more friable particles or granules in a mixture as a result of the high-speed agitator mixer.

2. Scale-up can prove to be a problem, in that direct scale-up based on geometry, size and peripheral velocity often does not work.
3. Cleaning may be a problem, because the agitator assembly must be removed and the packings changed for a product changeover.
4. Potential packing (seal) problems (packings are used to prevent leakage through the shaft entrance into the mixing chamber and to prevent the blender contents from contaminating the bearings).

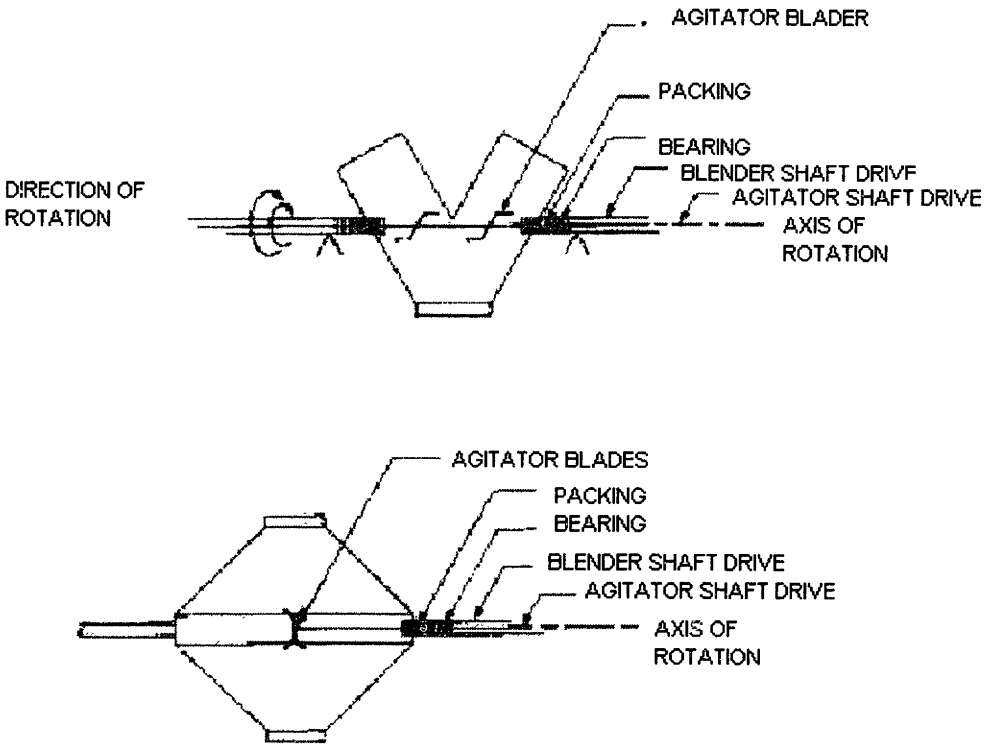


Figure 2.6

Rotating shell blenders with agitator mixers:

(A) V-shaped Blender, (B) Double Cone Mixer

Most mixers with agitator bars are also available with a liquid-dispensing system, separate or incorporated into the agitator bar, so that a solid-liquid blend can be easily prepared without stopping the mixer for the addition of the granulating liquid. These units, known as processors, have a steam jacket around the shell of the blender for heating the wet granulation, and a vacuum system to remove the granulating liquids during drying. In essence, the entire granulating and drying step is accomplished in one piece of equipment. A schematic of the operation is shown in Figure 2.7 [18].

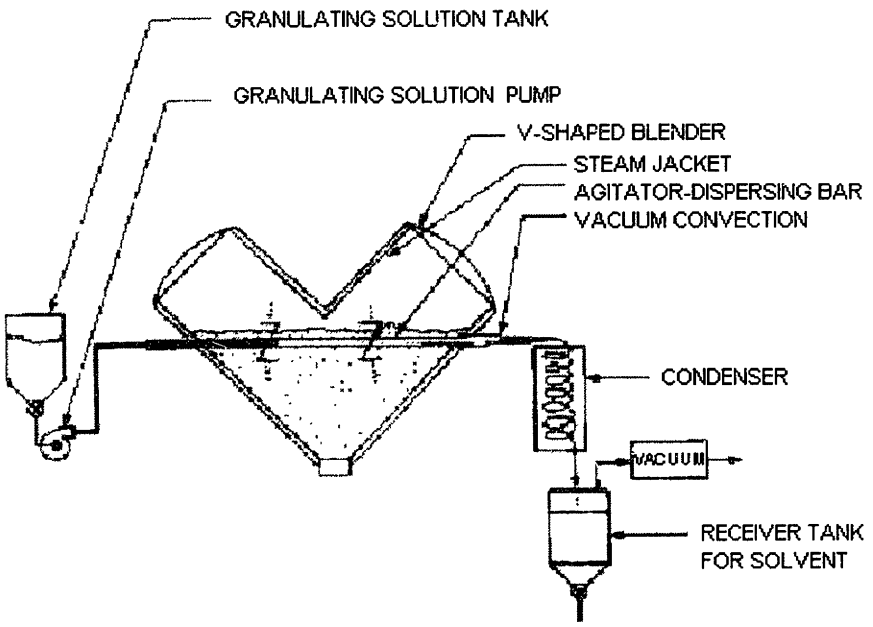


Figure 2.7
V-shaped Blender Processor

A typical sequence of operating steps for the processor would read as follows:

1. Preparation of the granulating solution and adjustment of the feed rate through the pump.
2. Charging the blender with the ingredients to be granulated.
3. Turning on the vacuum to 15 in. Hg and start the condenser unit.
4. Premixing of the dry solids at normal processor-shell rpm and running the agitator mixer during blending.
5. Pumping granulating solution into the processor and turn on full vacuum (30 in. Hg).
6. Mixing until granulation is properly set up (then the processor is stopped, the vacuum relieved, and the granulation examined).
7. Shutting off the agitator mixer and reduction of the blender-shell speed to a minimum.
8. Drying until the solvent collector contains the specified quantity of solvent to be removed from the granulation.
9. Check of the loss on drying (LOD) after drying is completed. Emptying the granulation into a hopper or drums for further processing.

The problems encountered with the operation include packing gland (seal) leakage under vacuum, and the granulation sticking to the sides of the blender shell. These problems can often be overcome by careful packing of the agitator mixer packing gland(s), optimizing the shell temperature and granulation composition, optimizing the rate of addition of granulating solution, and developing the proper sequence of steps during granulating. The processors are loaded and unloaded the same way as are V-shaped and double-cone blenders.

The third general category of mixer is mechanically different from the tumbling-shell type of blender; that is, the mixing forces are transferred to the powder bed by blades moving in a fixed (non movable) shell which contains the ingredients. The blades naturally have different configurations for each design, and move the solid-solid or liquid-solid mixtures by the force exerted through a motor-driven drive shaft. Schematics for the most commonly used designs are shown in Figure 2.8 [18].

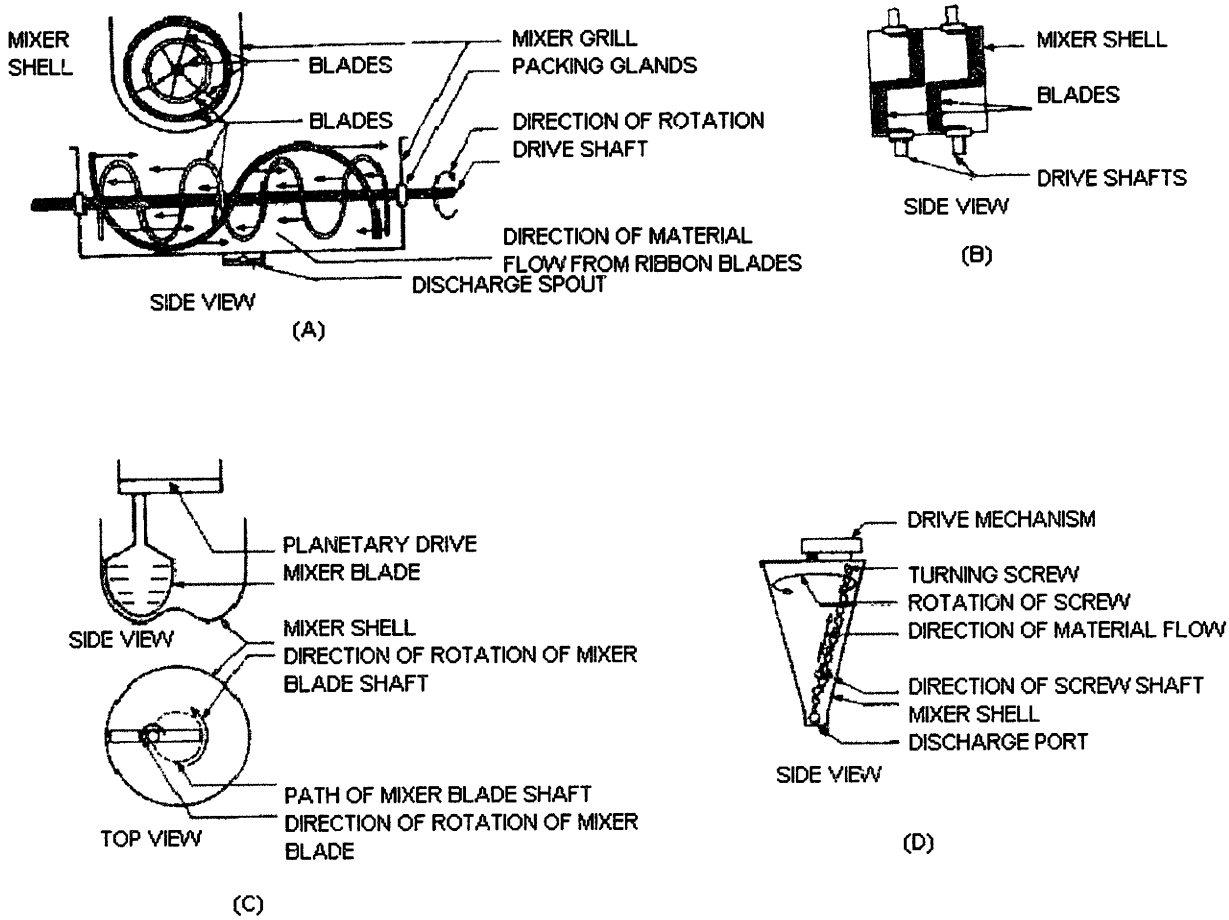


Figure 2.8

Fixed shell, moving blade mixers: (A) Ribbon Mixer, (B) Sigma Blade Mixer, (C) Planetary Mixer, (D) Conical Screw Mixer

The fourth category of mixers include the high-speed granulators. These are stationary-shell mixers with a large mixer-scraper blade which mixes the ingredients, eliminates dead spots in the mixer container, and presents the mixer contents to a high-speed chopper blade that intimately mixes the ingredients. The higher mixing intensity results in denser granules when compared to low speed mixers. The higher density of

the granules produced in vertical high shear mixers are assumed to be due to the fact that in the vertical mixer the granules are assumed to be thrown extensively against the wall by the centrifugal forces.

Also, the differences in size distributions of granules produced in horizontal and vertical mixers are due to differences in the construction and rotations speeds of the mixing tools.

The major advantage of the changeable bowl mixer seems to be a reduced risk of contamination since the seals are kept away from the product.

The energy consumed in high shear mixers is converted completely into heat in the moist mass. The temperature increase depends on the rotation speed as well as the size and shape of mixing tools. The increase in temperature during the process can be more than 40 °C and can be up to 110 °C without application of heat; for this reason, some mixers are equipped with a cooling jacket.

In the high shear mixers (horizontal, vertical and the changeable bowl mixer), the mixing, densification and agglomeration of wetted materials are achieved as a result of shearing and compaction forces exerted by the main impeller. Most of these equipment are equipped with a chopper rotating at a very high speed (1000-3000 rpm) in order to break lumps into the bowl in a few minutes.

Wet granulation is accomplished in mixers equipped with mechanical agitators of different sizes and shapes rotating at different speeds. After liquid addition, the material is normally wet massed for a few minutes in order to obtain further densification and granule growth.

Schematics of the barrel type and bowl type are shown in Figure 2.9 [18].

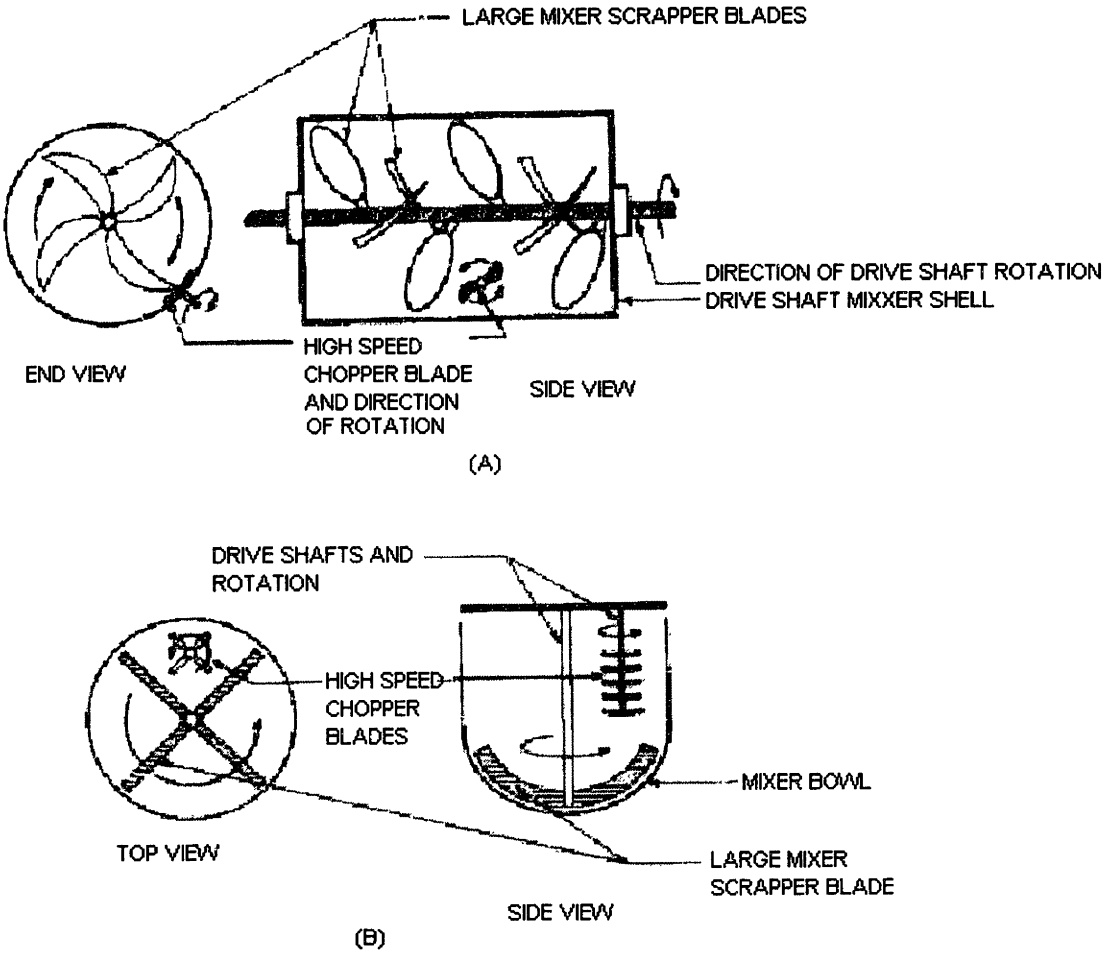


Figure 2.9

High Speed Granulators: (A) Barrel Type, (B) Bowl Type

The advantage of this equipment is its extremely rapid, intimate solid-solid or liquid-solid mixing. Granulating time may be only 6-10 min long, which includes dry blending and wet granulating. The product usually has a fairly uniform wet granule size of 14-18 mesh (1400-2400 μ) which needs no further wet milling or screening. The granules are usually emptied directly into a fluid-bed drier.

Disadvantages may include product contamination from the packing gland where the shaft passes through the mixer shell. This has been remedied somewhat by the use of mechanical seals or air-flushed packing glands; air at low positive pressure is continually flushed through the glands into the mixer to prevent contamination of the bearings with the product and contamination of the product from the bearing grease and other substances. A second disadvantage may be the limited batch size, because there is some expense limit in purchasing larger models of the equipment. As with bowl mixers, this may necessitate the use of a second larger tumbling blender when sublots made in the high speed granulator are to be blended.

Because mixing is so rapid, it is standard procedure to time the mixing accurately or put an ammeter or wattmeter on the high copper motor to determine the end point of wet mixing. Care must be taken during dry mixing because too long a mixing time may cause unwanted particle size reduction, which could change the characteristics of the final granulation.

The last general category of mixer is the air mixers, which have a stationary shell or body using moving air as the agitator. Figure 2.10 [18] shows a general schematic of the fluid-bed granulator, which mixes very intimately and efficiently. By fluidizing the power bed, enough shear is developed to mix beds of some of the smallest particles with very gentle action. The action is so gentle that even soft granules mix with little or no attrition.

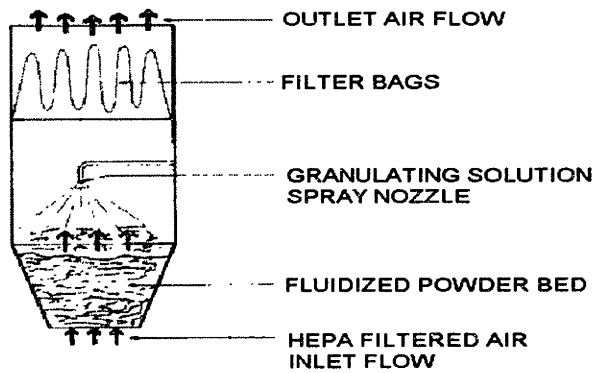


Figure 2.10

Fluid Bed Granulator Mixer

b) Continuous Mixers

Continuous mixing in the pharmaceutical industry is reserved for large volume products that require 8-24 hr per day mixing year around to meet marketing demands. In all cases of continuous mixing, the ingredients to be mixed are carefully and accurately metered into the mixer at one end and are discharged at the other end as a homogeneous mix ready for further processing. The batch size is determined by a specific period of mixing time, so that lot numbers of raw materials and weighing records can be traced to reflect the composition of the final product from day to day.

The primary problems with continuous mixing are associated with materials handling technology and raw material properties. Materials handling technology problems are merely planning and selecting the auxiliary equipment to be used with a particular continuous mixing process. Such equipment as storage hoppers, automatic weighing units, conveying methods and metering equipment must be selected to handle the formula ingredients and scheduled volumes. There must also be enough flexibility to enable the producer to increase or reduce the process throughput to meet the market demands. The materials handling system must be continuously monitored for accuracy of blend composition, and accurate operating record must be maintained.

There are several continuous mixers that can be used in the pharmaceutical industry. Two of the most commonly used are the barrel type and the rotating shell type. Depending on the size of the continuous blenders, very large quantities (500 tons/hr) of materials may be blended if required. Points to take into consideration when selecting a mixer include: design and build features (main shaft size and type - hollow or solid -, agitator construction - ribbon or paddle -, seal designs, and material thickness), drives (size, quality, motor efficiencies, service factor), ease of cleaning, surface finish, unloading characteristics (material must be able to be discharged without segregating). Different results may be desired and this also needs to be considered: product homogeneity, agglomeration reduction, mixing time.

The following chart (Figure 2.11) summarizes the mixer selection process [18, 23], in terms of the characteristics of the mixer and the properties of the materials to be mixed.

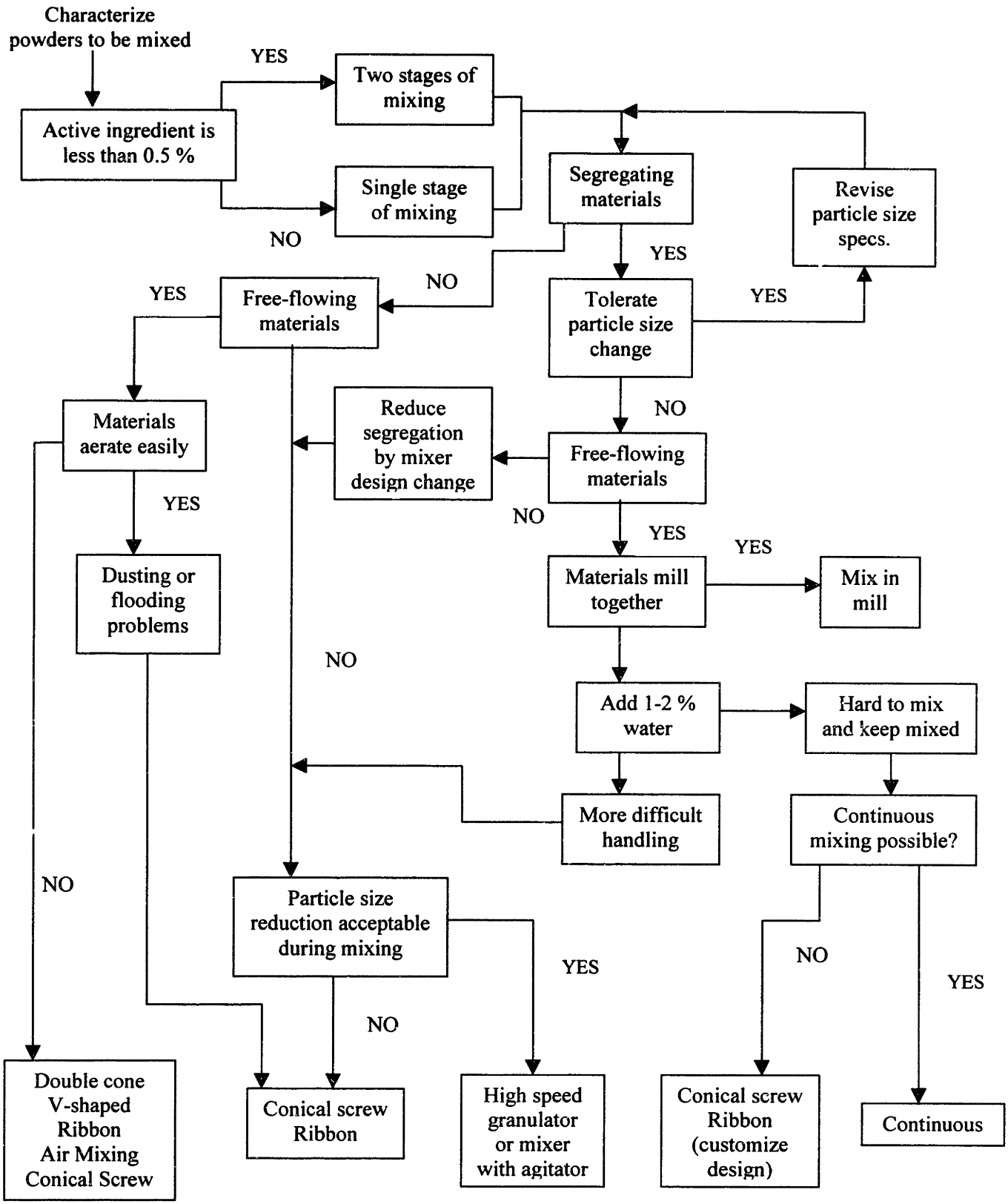


Figure 2.11
Mixer Selection Flowchart

Mixing and segregating mechanisms cannot usually be separated within a powder-handling system. The final mixture quality will be determined by the relative importance of the two mechanisms but ideally segregation should be eliminated or at least suppressed in favor of the mixing operation.

From a practical point of view, it is necessary to learn how to use production equipment to achieve the same results obtained with a formula on both the development and pilot scale levels. The scale-up to large mixers can be a very discouraging and frustrating step in putting a tablet formula into commercial production. This is primarily so because there are no hard and fast rules or equations that direct one to the use of a particular size and type of mixer during scale-up. Results are usually empirical, and the starting points depends heavily on the experience of those responsible for the project.

The frustration and problems in scale-up are further amplified by the fact that the tablet and/or granulation production department already has on hand specific sizes and types of mixers, and the mixing unit operation for a new formula must be adapted to this equipment. Unless the product has a large potential market and/or is a large volume product necessitating expansion of facilities, one does not normally have the luxury of selecting and purchasing a new blender suited for a specific new product. In addition to these aspects of the commercial mixing unit operation, production scheduling often requires that a product have the potential of being mixed using several types of mixers.

APPROACHES TO EVALUATE BLENDING PERFORMANCE

To monitor blending performance in terms of mix homogeneity, acceptable performance guidelines must be determined. These guidelines can be established by assays of the material or completed mixes in either trial or production mixers. In order to achieve the desired homogeneity, it is important to consider the effect of the various process variables in the unit operation of blending. Table 3 shows the variables that affect each critical performance measure.

TABLE 3
VARIABLES THAT AFFECT THE BLENDING OPERATION

Cycle time	Quality	Cost	Safety
• Duration of the run	• Particle size	• Cycle time	• Contamination during sampling
• Turn around time	• Mass flow	• Quality	• Certainty of analysis results
• Active ingredient concentration	• Sequence of ingredient addition	• Labor	
• Percent loading of mixing jar	• Liquid addition rates	• Process rates of upstream and downstream equipment	
	• Speed of rotation		
	• Percent loading of mixing jar		

Some variables have an effect on more than one performance measure, since these parameters are interrelated. For instance, total cycle time has a direct effect on the cost of the process (the longer the cycle time, the higher the cost) and so does the quality of the process (a lower quality process may yield unacceptable product that will need to be reprocessed, incurring in higher costs).

Controlling these parameters is very important because the results of the blending operation have an effect on subsequent steps of the process:

- Weight variation of the final tablet can occur because of poor powder flow, flooding or inadequate particle size range.
- Punch binding, sticking or filming may be due to inadequate lubrication, fine or coarse particles or to adhesive components being badly mixed.
- Punch and die abrasion will occur if abrasive components are not blended separately with the lubricant.
- Capping, laminating and picking will be produced by weak granules or inadequately bond powder.
- High friability and disintegration problems occur when the lubricant is not well blended.

- Mottling occurs when the dye is unevenly distributed.
- Doughy mass may be due to overmixing.
- Color and/or drug migration may be due to a failure to frequently mix the granulation during drying.

It is essential to isolate the mixer's performance from other variables and to make sure that the process is started with a good mixing specification which is followed consistently. This means using the same order of ingredient addition, consistent mixing times after each addition, and the same procedure for taking quality control samples from the mixer regardless of who's taking the samples. Also, raw material quality must be checked to detect if the ingredients properties are the same each time or if particle size distribution or other properties vary from batch to batch.

Mixing Models

As previously stated, mixing is a process that produces a random distribution of particles, and it is dependent on the probability that an event happens in a given time. The law of mixing appears to follow a first order decay [4, 23]:

$M = A(1 - e^{-kt})$

where:
M = degree on mixing
t = time
A and k = constants that depend on mixer geometry, its use, and the physical characteristics and proportions of the materials being mixed

Therefore, mixing results are a function of time, and although the initial rate of mixing may be very rapid, the end point or perfect mix is not attainable because of the asymptotic characteristic of the aforementioned equation (Figure 2.12). However, in practice, specifications are set as to the "degree of mixedness" acceptable to achieve an even distribution of the active ingredient throughout the blend.

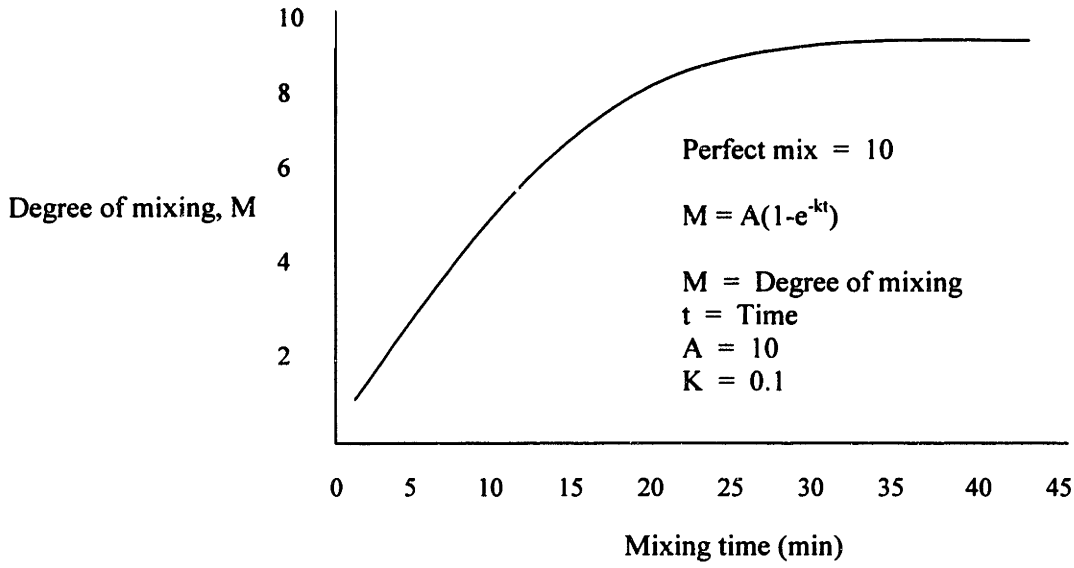


Figure 2.12

Plot of first order decay for mixing

To measure and compare homogeneity or "degree of mixedness", mixing indices are used. These are used to follow a mixing process with time, to compare mixers, to compare the mixing operation as it is scaled up and to investigate the mechanism of mixing in a given piece of equipment. The majority of mixing indices involve some comparison of the measured standard deviation S of the samples of the mixture under study with the estimated standard deviation of a completely random mixture σ_r. The standard deviation of a completely unmixed system σ_0 is sometimes also used (Table 4) [18].

TABLE 4

MIXING INDICES

Mixing Index	Comment
$M = \sigma_r / \sigma$	Ratio less than 1
$M = (\sigma_0 - \sigma) / (\sigma_0 - \sigma_r)$	Ratio less than 1
$M = (\sigma_0^2 - \sigma^2) / (\sigma_0^2 - \sigma_r^2)$	Ratio less than 1
$M = \sigma / \sigma_r$	Ratio greater than 1
$M^2 = (\log \sigma_0^2 - \log \sigma^2) / (\log \sigma_r^2 - \log \sigma_o^2)$	

These indices reflect the properties of the mixture and the extent to which the sample composition deviates from the mean. Auto-correlation and cross-correlation techniques have been used to assess the degree of mixedness of multicomponent solids mixtures. Other mixing models have been based on the random nature of the process, using a stochastic approach to analyze and understand the process. Finally, other models have been developed under the assumption of a structural analogy to the mathematical description of the diffusional mass transport.

The progress of mixing can also be assessed by a "scale of segregation" which effectively measures the size of the unmixed regions, that is, the regions of segregation within the mixture. Thus, as laminar shear or distributive mixing proceed, the scale of segregation is progressively reduced, which means that the smaller the scale of segregation the better the mixture. The diffusional component of any mixing process becomes more important as completion is approached; the "intensity of segregation" measures concentration variations in the mixtures and, thus, as diffusional mixing proceeds, the intensity of segregation is reduced.

The scale of segregation is an area on the inspected surface which does not have the mean composition of the bulk of the mixture. The divergence from the mean composition could vary from all of the particles in the area of segregation being of one type to a very small composition divergence. The intensity of segregation is a measure of this divergence. The intensity of segregation can be regarded as the amount of dilution that has occurred within the segregated areas.

The "scale of scrutiny" for a mixture is the maximum size of the regions of segregation in the mixture which would cause it to be regarded as imperfectly mixed. It provides a vital link between product specification and the state of mixedness of the mixture. For a particular product, it fixes the scale or sample size at which the mixture should be examined.

Inspection is usually carried out by sampling a representative portion of the mix and analyzing it. This type of off-line monitoring can include visual inspection, colorimetric analysis, bulk density measurements, percent moisture measurement, and

chemical analysis. Although not as widely used as off-process quality assessment, on-line monitoring may be a good alternative to evaluate blending performance. Currently, there are devices such as a shaft-mounted torque meter that senses changes in rheology and general mixer performance while the batch is being processed, as well as devices based on near infrarred technology. Laser Induced Fluorescence techniques are also emerging as an option for homogeneity determination of mixed powders.

In order to determine the need for a new technology to evaluate blending performance, and to be able to choose among technological alternatives, a framework is required to make an assessment of the technologies in terms of the homogeneity of the powder blend. As can be seen in Figure 2.13, dry powder blending performance can be determined in terms of:

1. Cost / Productivity
2. Quality
3. Time
4. Safety

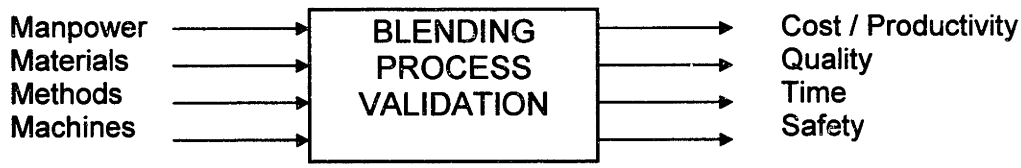


Figure 2.13

Technology Benchmarking to Validate Blending Homogeneity

The following schematic representation (Figure 2.14) summarizes the findings of this chapter in relation to the various variables that affect blending performance and their corresponding metrics.

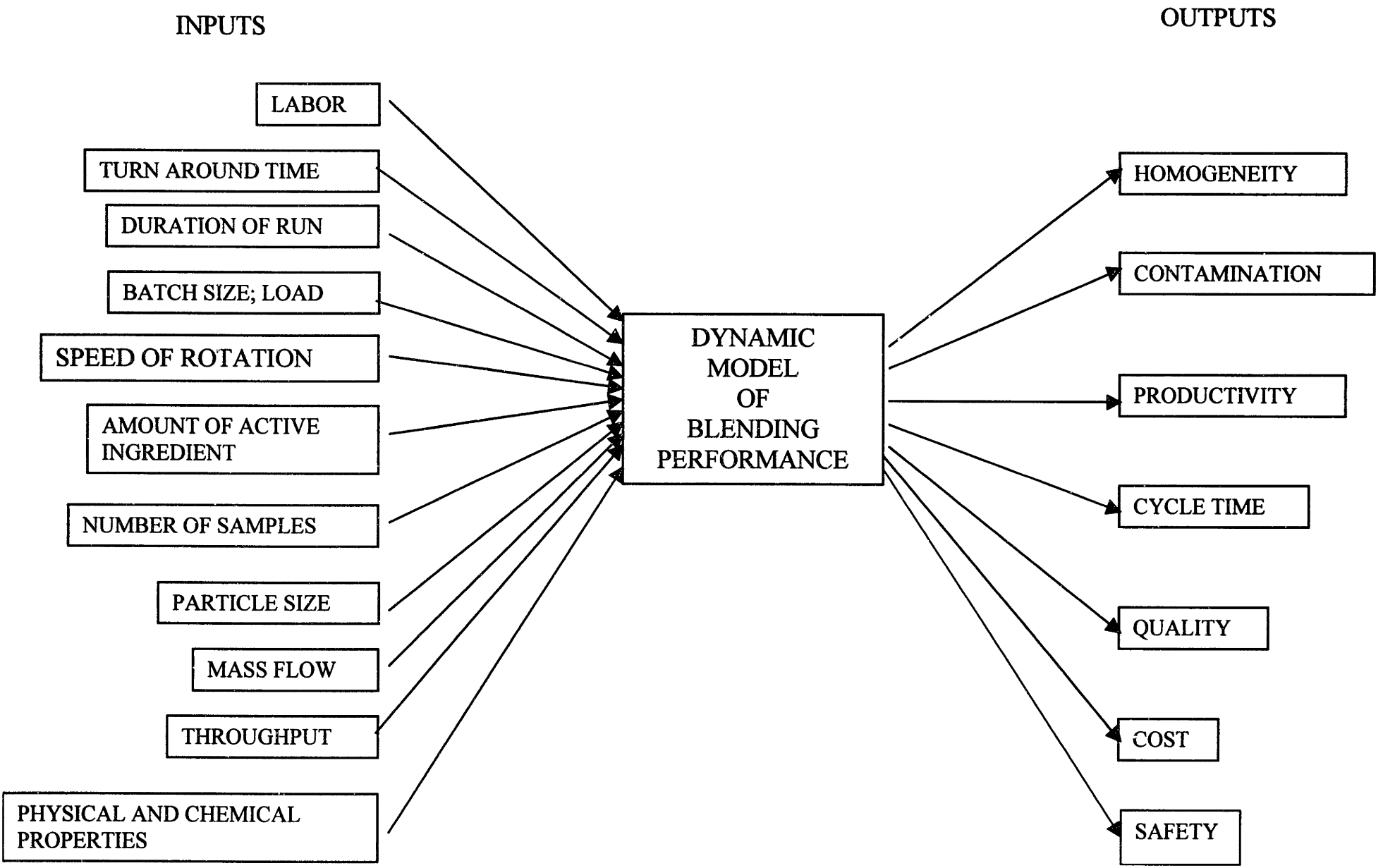


Figure 2.14
Variables and Metrics of the Blending Performance Model

Chapter 3
ASSESSMENT OF HOMOGENEITY

SAMPLING AND ANALYSIS

Sample analysis provides with evidence of a product's compliance or noncompliance with the requirements of the Food, Drug and Cosmetic (FD&C) Act and other acts enforced by the FDA. Briefly, the core of these requirements is the fact that a drug should have the:

- Safety
- Identity
- Strength
- Quality
- Purity

which it purports or is represented to possess, as recognized in the official compendiums (i.e., the United States Pharmacopoeia and the Homeopathic Pharmacopoeia) [28]. The determinations of strength, quality and purity must be made in accordance with the tests or methods of assay set forth in the aforementioned compendiums.

Additionally, the methods, facilities and controls used in the manufacturing, processing, packaging and holding of the a drug must conform to current good manufacturing practice.

The traditional analytical approach to in-process control blend analysis consists of obtaining samples from the blending vessel after a specified period of time; the samples are manually withdrawn from twelve representative locations of the blender (top, middle and bottom portions of the powder bed) and then submitted to the analytical laboratory (which is often remote from the point of manufacture), with the appropriate sample submission forms, for analysis.

Analysis is performed using chromatographic or spectroscopic techniques and a report is issued detailing the analytical results [6]. At this stage a decision is made as to whether to proceed to the next manufacturing process. If the test results do not meet homogeneity criteria for the blend, the previously described process is often repeated.

Sample turnaround can take a significant amount of time and this delay extends manufacturing times and results in expensive materials and/or equipment lying idle awaiting the analytical results before proceeding to the next manufacturing step. Often manufacturing campaigns are designed to allow for the expected delay between sampling and reporting of the analytical data. This built-in delay results in extended and inefficient production schedules.

The analysis is not only time consuming, but may be subject to errors induced by the sampling methods.

Typical sampling of pharmaceutical powder beds invoives the insertion of a multiport thief probe into de powder to collect samples at various depths of the bed. This technique has been shown to introduce errors in assay results [9]. Errors may result from the distortion of the powder bed when a sample thief probe is inserted into the mixture, or the powder can adhere preferentially to the probe and be displaced as it passes through the bed. The flow properties of the powder will determine how easily the probe sample ports are filled and whether the free-flowing components may be preferentially collected.

These factors can all contribute to collection of a sample that is not representative of the mixture. Sampling error can account for approximately 75 % of the variance observed following analysis of drug content in the powder blends [9]. For this reason alone, an on-line noninvasive method is more desirable than traditional methods.

A statistically representative sample should be a random sample in which every member of the population has an equal chance of being chosen. This sample should be representative of the entire blend so that the date are reproducible and valid. Thief sampling has several drawbacks [20], and it also violates the two golden rules of obtaining a respresentative sample:

- A powder should be sampled when it is in motion
- The whole stream of powder should be taken for short increments of time, in preference to part of the strem being taken for the whole time.

Once the sample is submitted to the analytical laboratory, the analyst is responsible for an accurate and complete analysis of the sample and a written report of the analysis. Some of the different types of analysis that may be performed include:

- Original Analysis: Initial examination conducted on a representative portion of the sample.
- Additional Analysis: Additional tests conducted on a sample to perform determinations not covered by the original analysis or to resolve discrepancies.
- Check Analysis: Performed by a second competent and qualified analyst to confirm a finding. Check analysis is necessary on violative regulatory samples.
- Split Sample Analysis: Requires an analysis in addition to that performed by the usual examining laboratory.

From a uniformity perspective, an advantage of blend analysis is that specific areas of the blender which have the greatest potential to be non-uniform may be sampled (Figure 3.1).

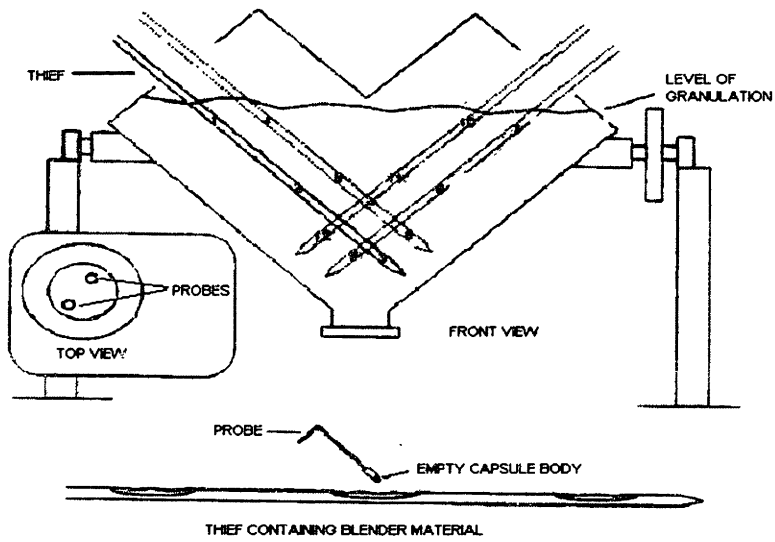


Figure 3.1

Probe Samples from a V-Blender

In some cases, such as for large or tumbler type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle and bottom of each drum should be collected (Figure 3.2).

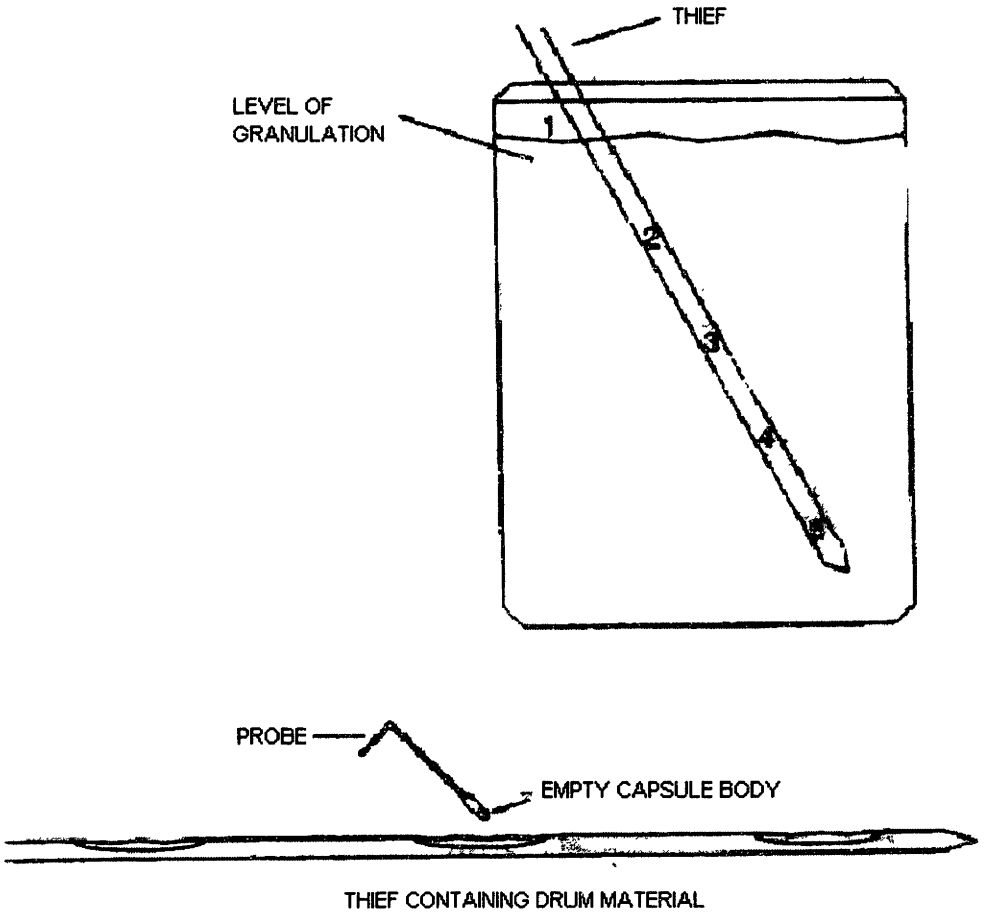
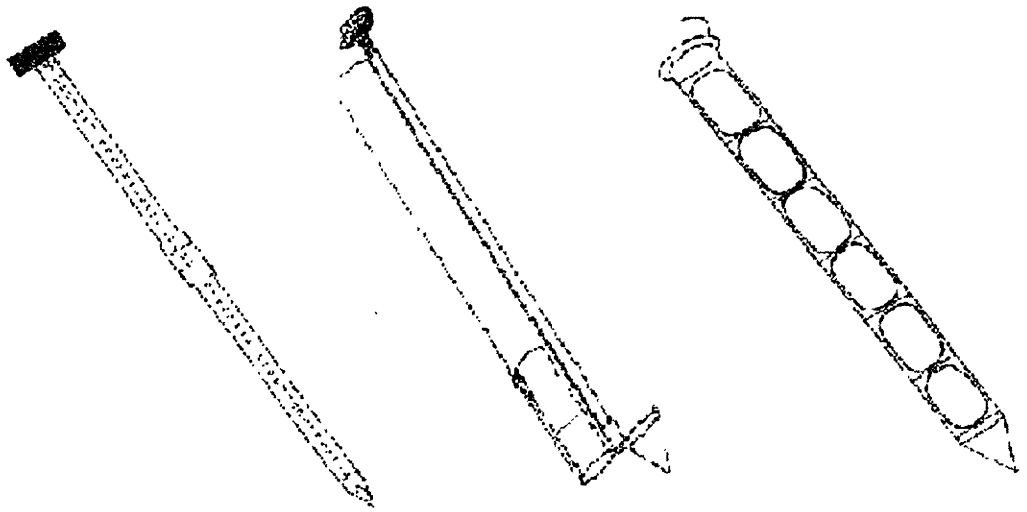


Figure 3.2

Probe Samples from the Drums

In most cases sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. Three of the sample thieves which are frequently used for content uniformity sampling include (Figure 3.3):

1. Single compartment tip sample thief: has fixed chamber volumes equivalent to roughly 120, 250 and 500 mg.
2. Adjustable single compartment sample thief: has adjustable capacity from 0 to 10 g; this thief is usually used for sample sizes of 1 g or more.
3. Multi-compartment segmented grain thief.



(A) (B) (C)

Figure 3.3

Sample Thief Types: A) Single compartment, B) Adjustable compartment, C) Multi-compartment

If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis. Handling must be kept at a minimum to: **a)** assure sample continuity and integrity; and **b)** to decrease the chances for error.

Samples should be the approximate equivalent weight of the final dosage unit. Large granulation sample sizes, such as one ounce provide little information with respect to uniformity. Generally, further mixing occurs after sampling and prior to analysis, which can yield misleading results.

In addition to analysis of blends for dose uniformity and potency, blends are tested for physical characteristics. A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for the comparison of pilot scale batches with production batches and also, when processes are modified or changed. The particle size profile provides useful information for demonstrating comparability. Particle size profiles are particularly important for tablets made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution rate.

Other tests are also typically performed on the granulation, particularly when the wet granulation process is used, for instance, loss-on-drying (LOD) and/or moisture content. If organic solvents are employed, then residual solvent residues are tested. In the validation of a drying process, LOD levels are determined prior to, during and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase with the validation phase used to confirm the adequacy of the process. As with other specifications and processes, the investigator should review the data used to support the drying process and determine the significance (if any) of variable drying times and levels.

In terms of blend homogeneity, the most important test performed on the finished product (i.e., the tablet) is uniformity of content. According to the United States Pharmacopoeia, this test is performed as follows [28]:

1. A sample of 30 dosage units is selected.
2. 10 dosage units are assayed individually, according to the product's monograph, as stated in the USP.
3. In the case of tablets, the requirements are met if the content of each of not less than 9 of the tablets is within the limits of 85 % and 115 % of the average of the tolerances specified in the potency definition of the product's monograph, and if the content of none of the tablets falls outside the limits of 75 and 125 % of that average.
4. If the content of not more than 2 tablets falls outside the limits of 85 % and 115 %, each of the remaining 20 dosage units must be assayed.
5. The requirements are met if the content of each of the additional 20 tablets falls within the limits of 85 % and 115 % of the average.

Sampling and analysis are not only performed on the finished product. During the development and validation of the manufacturing process, the bulk granulation is continuously sampled and analyzed at various critical points. For instance, during a validation run at least 12 samples need to be taken and it is mandated that three runs in a row must yield the expected homogeneity results.

Sampling and analysis of the bulk and active ingredient are important to assess the progress of the blending operation in terms of homogeneity and to assure that the final dosage form will have the desired uniformity of content, however, the amount of time and resources invested in these operations is considerable, and methods to determine blending performance on-line might be helpful to achieve a cost reduction while maintaining the high quality standards required by the FDA.

THE LIF PROBE

Photoluminiscence is a process in which the incidence of radiation upon a sample causes emission of radiation by the sample; one of this luminiscent processes is fluorescence, which can be induced either by visible ultraviolet light or by X-rays or electrons [15]. When the emission of fluorescence is induced by X-rays, the process is called laser induced fluorescence.

This principle has been applied to a device which can irradiate samples with a blue laser and evaluate the wavelenght absorption and reflection.

The basic configuration of the device consists of a probe unit containing a light source which can generate a series of light pulses. An indexing system mounted on the blender, or else, an infrared data transceiver, determine the timing of the pulses which, for instance, may be programmed to acquire data each time the blender completes a revolution (Figure 3.4).

The device is capable of a sample rat of 10 milllion per hour in measurement of concentrations of surface ingredients. Its linear resolution is less than 50 μ which allows for the assessment of particle size distribution on blending results.

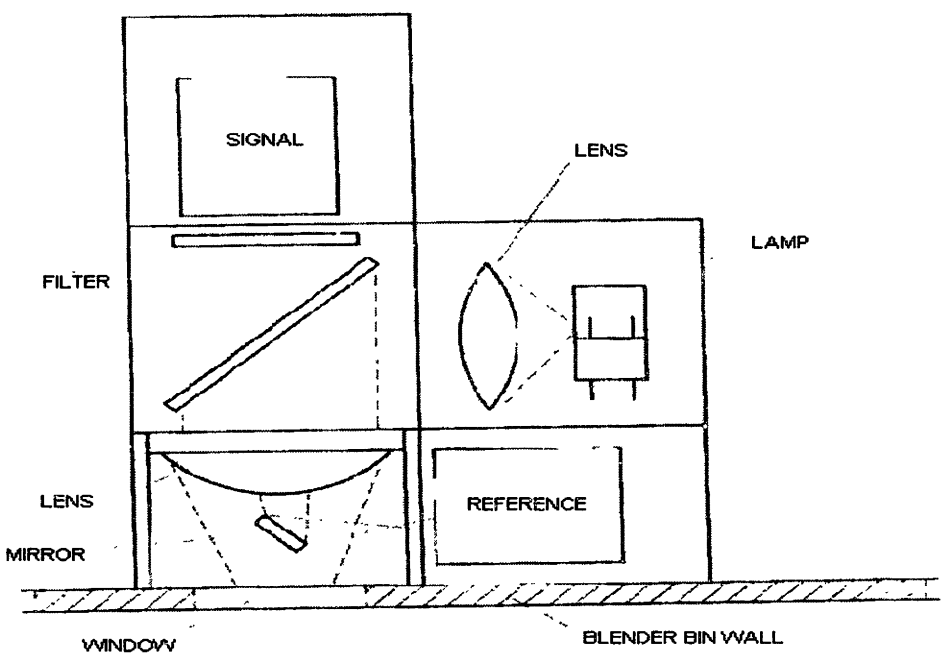


Figure 3.4

Schematic representation of LIF Probe

The probe unit is designed to be mounted directly on blenders rotating at speeds of up to 60 rpm (Figure 3.5); both the unit's power supply and the communications between the probe and the process controller are wireless, and the unit interfaces with an optically compatible glass portal on the blender. Real-time data transfer from the probe is comptabile with an industry standard data transfer system.

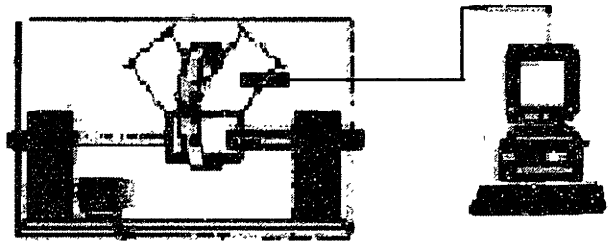


Figure 3.5
LIF Homogeneity Detection System

The sampling speed and linear resolution of LIF should allow real time and in-process measurement of dry powder blending. The LIF device would be implemented via fiber optic probes at multiple points of a blender. This permits the real time monitoring of blending kinetics without interfering with the process. At the proximity of the probe (defined by the probe's location and resolution range of the technique), the laser irradiation elicits different but specific fluorescent reflectance from the individual blending components within the resolution domain. Through the probe, the relevant laser induced flucrescent signals are acquired at a rapid sampling rate and then quantified according to the characteristic wavelengths of the individual components. As a result, in-process and real time blending kinetics at multiple location within the equipment can be attained.

A product innovation such as this, developed by a small, technology-based unit, can be the process equipment adopted by a large unit to improve its high-volume production of a standard product. From the point of view of a pharmaceutical company,

the LIF device would be categorized as a process technology, that is, as a technology which is instrumental to some other end. In this case, the end is to improve the drug development process.

Compared to product technologies, the adoption and implementation of process technologies tend to be more disruptive and often more toward the radical end of the incremental-radical spectrum (Figure 3.6) [19]: process technologies such as the LIF device require complex implementation-focused analytical models that include individuals (operators) and stakeholder groups (analytical laboratory, quality control and quality assurance departments, operators, marketing, etc.) and thus, require a more complicated system change that must account for externalities such as the stringent regulatory context in which pharmaceutical companies operate: FDA approval of the production processes is required, and other norms to follow include GMP (Good Manufacturing Practice) and SOP (Standard Operating Procedures).

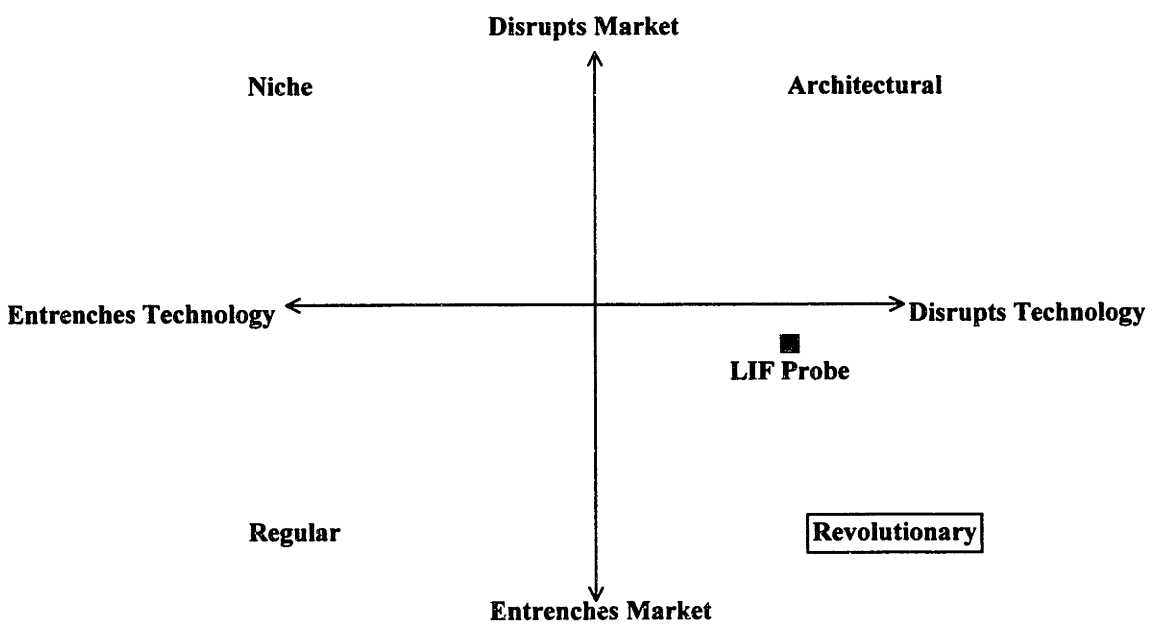


Figure 3.6

Categorization of the LIF Probe in a Continuum of Change

The LIF probe's capacity to influence a firm's existing resources, skills and knowledge places the LIF probe as a revolutionary innovation: the device has the potential of reducing the operation's cycle time and cost and to assure the quality of the formulation throughout the various stages of manufacturing, from the initial blending of the bulk granulation to the final tablet; by doing this, it opens an opportunity to change the established technical and development system and obtain a higher degree of confidence in the unit operation's performance.

However, technologies such as this may have limitations. For instance, the active ingredient needs to fluoresce in order to be detected with the LIF device. Appendix I provides information about the fluorescence of the active ingredients of the top 30 drugs in the US market (as of 1997), and about the dosage forms in which they are administered.

Appendix I provides useful information in terms of the amount of drugs administered as either tablets or capsules, and also in terms of the percentage of these drugs likely to fluoresce when illuminated by a laser:

1. 85 % of the listed drugs are administered in solid oral dosage form.
2. 70 % of these drugs' active ingredients would fluoresce under normal operation conditions when analyzed with the LIF probe.

This information sets a base-case scenario, where it is possible to assume that at least 60 % of all the new drug applications would be subject to being analyzed with the LIF probe.

Building trust in the new detection process is a very important issue, not only in terms of the end-users (pharmaceutical companies which manufacture solid oral dosage forms) but also in relation to the validation of the new technology by the FDA and the validation of the new on-line homogeneity detection process, which eliminates the need for sampling and off-line analysis since the device determines the blend's homogeneity (according to USP criteria) while the mixing process is taking place inside the blender.

The confidence in the probe may therefore not be as high as that for the current methods, although in terms of time and money savings, the LIF device is potentially a better choice than the alternatives. Figure 3.7 represents this phenomenon, where confidence in current off-line technology is compared to that in the innovation.

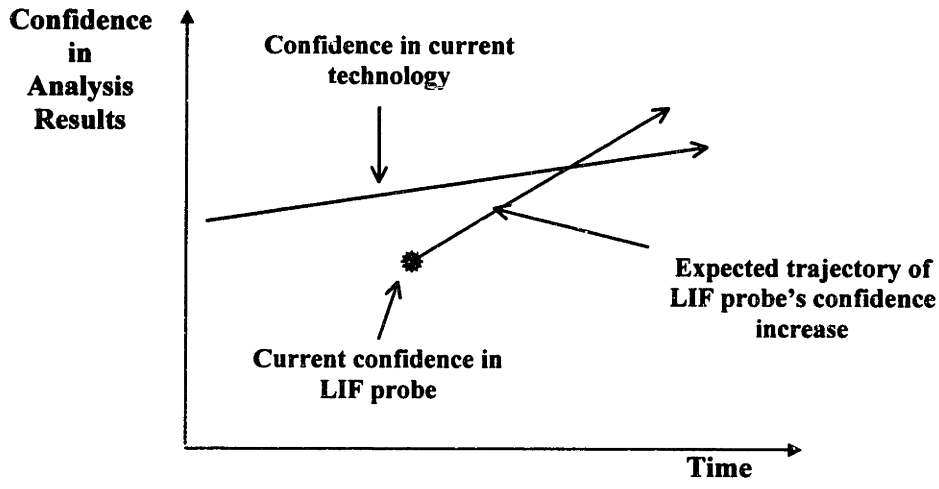


Figure 3.7

Assessment of Confidence in the New Technology

The introduction of any process innovation requires time to allow the users to familiarize themselves with its use. In the case of the LIF probe, there is also a need to build confidence with the regulatory authorities in order to substitute current blending performance evaluation techniques with the new technology.

The potential to implement LIF in a noninvasive fashion, which would eliminate the need to interrupt the process for manual sampling, and the high accuracy of the technique (reported to be better than 99.999%) may bring about the desired increase in confidence in the technology, by both the end users and the regulatory authorities.

Chapter 4
ECONOMIC EVALUATION

Innovation in the pharmaceutical industry is a complex and expensive process. Investment in Research and Development (R&D) has increased more than 10 times since 1965 whereas sales have only increased approximately 5 times (Figure 4.1) [10]. Pharmaceutical companies invest from 10 to 20 % of their annual sales in R&D; the average cost of the development of a new drug can reach 300 million dollars and last for 8 to 15 years, of which approximately 2-3 years are spent in getting approval from the health authorities (mainly, the FDA).

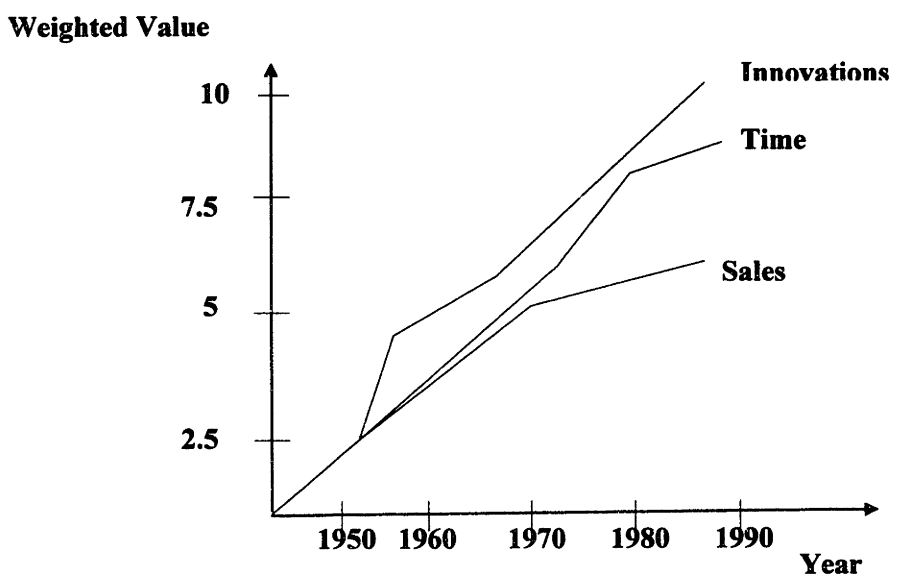


Figure 4.1
Drugs Sales vs. Cost and Time spent in R&D

Process innovations can be as important as the development of a drug *per* se. Through the process, it is possible to achieve important time and cost savings, as well as to assure the quality of the final product. In particular, the LIF system would have a direct impact in two important stages of the development process (Figure 4.2):

1. Development of the manufacturing process with reduction in the time to market of a new drug.
2. Validation of the manufacturing process with cycle time reduction.

To insure continuous production of new medicines, a company with an average development time of 8 years must support over 100 projects. Once a project is approved, the entry in a new product category is likely to have regulatory and commercial constraints. Both the pace of regulatory approval and the price after regulatory approval represent a great hurdle to the developing firm. However, hourly sales of $114,000 of a billion dollar product are a powerful incentive to accelerate development by a day ($2.8 million), a week ($20 million) or a quarter ($250 million).

An additional factor that impels accelerated development is the diminishing period of marketing exclusivity. With development taking an average 12 years, as little as five years of exclusivity will remain before patent expiry and potential generic competition (this is due to the fact that patents are filed before the active compound enters the development stage).

Given the challenge that pharmaceutical companies face to improve the productivity of their R&D departments and of their overall operations, the need of an innovation strategy becomes evident. Some of the strategic choices available to the industry to increase R&D productivity include:

- Collaboration with smaller companies for outsourcing of specific activities.
- Establishment of a collaborative portfolio with universities, leading to an increased flow of "pre-incubated" projects into the industry.
- Formation of more independent research units that are responsible for one or several areas of research.
- Successful assimilation of new technologies.

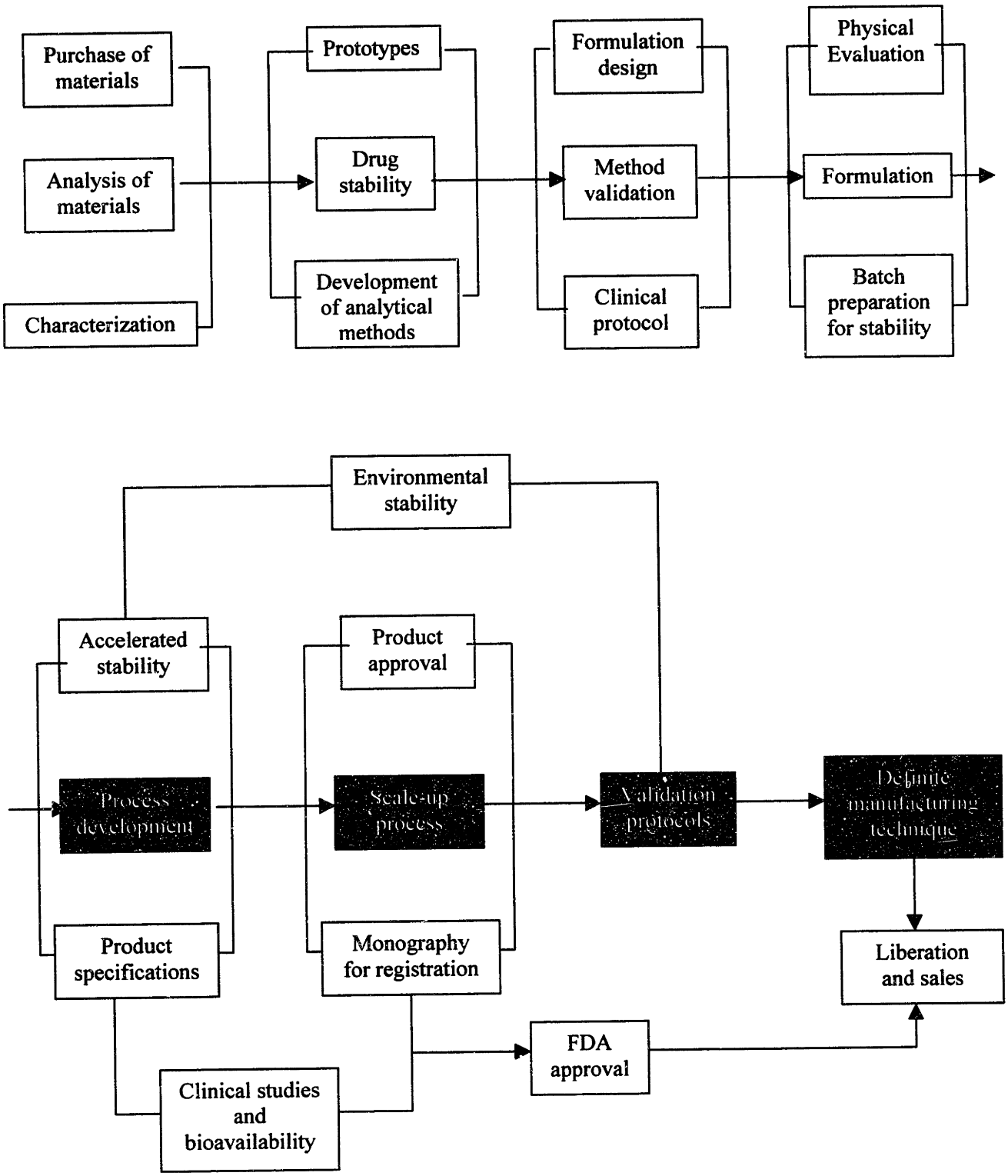


Figure 4.2
Drug's Development Process

PROCESS DEVELOPMENT

One of the results of using the LIF probe may be the reduction of the time needed to perform the tasks associated with the development of specifications for blending parameters for new drugs and, thus, a reduction in the time to market of the new drug. This would not only offer the firm an important competitive advantage through increased profits, but also an opportunity for cost savings, in an industry where each additional day a drug is delayed to enter the market can cost the company more than 1 million dollars. Also, the return on the investment of the development of a new drug is dependent on the lifespan of the drug's patent since, once the patent expires, generics enter the market and the revenues of the original drug may drop significantly. Perhaps the most important impact of this new technology will be felt in the drug development process as a whole, by reducing the manufacturing process development time as well as its validation time and, thus, allowing to achieve a reduction in the time to market of a new drug. The importance of this cycle time reduction lies in the high opportunity costs associated with delaying a drug's entry to market.

The development of a drug's manufacturing process includes the scale-up of the methods used in the laboratory for the development of the drug's formulation. Scale-up activities would be facilitated through a rapid detection of the blending end-point (since there would be no need to perform time tests to determine the optimal time for blending a particular mix). The process is characterized and challenged in order to determine the specifications, that is, the ideal and marginally acceptable values for each metric in the process or unit operation. In the case of blending, one of the most critical parameters to consider is time (duration of the run).

Multiple experiments are carried out to determine the optimal blending time of a new drug, and sampling and analysis have to be done for each one. These experiments are labor and time consuming, and they could be eliminated by the use of the LIF probe, since the device has the capacity of determining, in only one run, the operation's end point (that is, the point where the blend meets the required homogeneity criteria) in real-time. Therefore, the determination of the optimal time for blending is reduced to running one single batch and letting the probe analyze the mix as it begins to blend together.

In order to determine the optimal blending time of a formulation, the usual procedure is to run a batch in a blender and measure its "degree of mixedness" at various intervals of time (Figure 4.3).

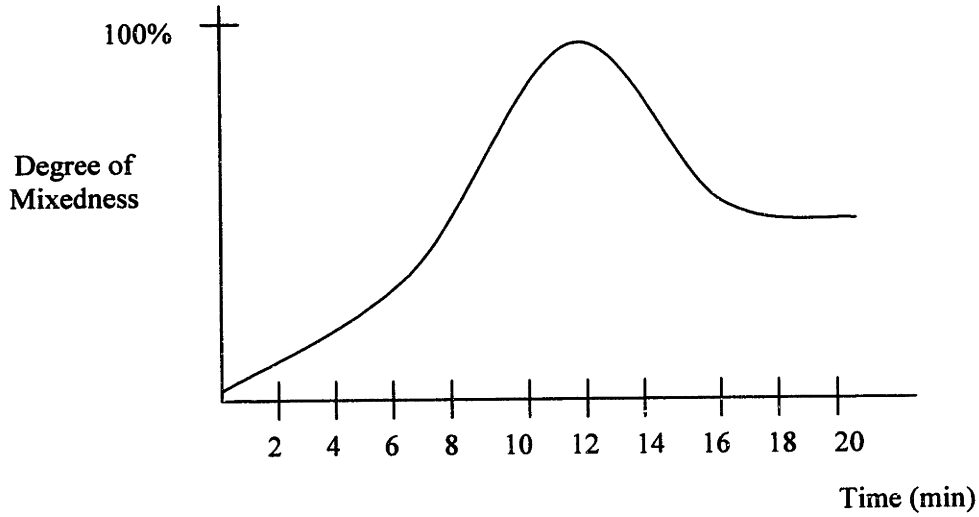


Figure 4.3
Determination of Blending Optimal Time

To assess the impact of the on-line homogeneity detection system in the process development stage, let's analyze a dry granulation (whose manufacturing process requires one blending operation) and a wet granulation (which requires two blending operations). The following assumptions are being made: **a)** 10 experiments are carried out to determine optimal blending time per blending operation (i.e., 10 samples are taken at 2 minute intervals for each operation); **b)** one shift days with 5 working days per week; **c)** the time spent in each sampling operation is 4 h (according to industry sources).

Then the total time spent on the experiment would be of over 40 h for the dry granulation and of over 80 h for the wet granulation. Transporting the samples to the analytical laboratory takes approximately 2 h (therefore, 4 h would be spent in transportation of samples in the wet proces). Analyzing each set of samples usually takes about 12 h, so the total amount of time spent on analysis would be 120 h and 240 h for the dry and wet granulations, respectively. Table 4.1 summarizes these findings.

TABLE 4.1

TIME SPENT IN DETERMINATION OF HOMOGENEITY DURING PROCESS DEVELOPMENT

	WET GRANULATION	DRY GRANULATION
Blending operations per process	2	1
Number of experiments per blending operation	10	10
Total number of sampling operations	20	10
Time taken in each sampling operation (h)	4	4
Total time taken on-line (h)	80 (10 Days)	40 (5 Days)
Time taken transporting the samples (h)	4	2
Time taken analyzing each set of samples (h)	12	12
Total time analyzing the samples (h)	240	120
Total time spent off-line (h)	244 (30.5 Days)	122 (15.25 Days)
Total time on-line and off-line (h)	324 (40.5 Days)	132 (20.25 Days)

The use of the LIF system eliminates the need to sample / transport / analyze. Therefore, the time spent on these operations disappears, yielding a reduction in the time to market of a new drug of 30 days, in average. Given that each day a drug is delayed in entering the market represents a lost opportunity cost of approximately 1 million dollars, then the potential cost savings amount 30 million dollars. The lost revenues that would be saved with the use of an on-line homogeneity detection technology, such as the LIF system, amount to 1 % of total development costs.

PROCESS VALIDATION

The Validation Guideline issued by the FDA in 1987 defines process validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes". A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the

process development phase and continuing through the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

The three components of this definition include documented evidence, consistency, and predetermined specifications. Documented evidence includes the experiments, data and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process. Validation protocols are developed from the information obtained during product development research. These protocols list the specific manufacturing process and specifications that will be tested during the demonstration runs. Validation protocols are not required for the Pre-Approval Inspection but are required for Post-Approval Inspections.

With regard to consistency, several batches have to be manufactured, using the full scale batch size, to demonstrate that a process meets the consistency test. At least three consecutive batches are needed to demonstrate consistency. In many of the post-approval, pre-marketing inspections, validation (and consistency) cannot be established. Failures of production size batches may include: dissolution, content uniformity and potency. Validation reports on batch scale-ups may also reflect selective reporting of data. The problems can only be identified through inspection and review of the facilities and raw data, which is an expensive and time consuming procedure.

Equipment and process validation can be split into two phases [16]:

1. Manufacture of active batches of product and determination of blending time to adequately distribute the drug substance.
2. Actual installation and validation of processes to allow routine manufacture to commence upon production schedules.

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full scale manufacturing process requires scientific judgement based on good scientific data. In-process control and product specifications should be established during the product

development process, with the test batch serving as the critical batch used for the establishment of specifications.

By examining the life-cycle of a drug it is possible to appreciate the importance of the validation process, which can take up to 3 months (Figure 4.3). Validation is involved at various stages of a drug's life-cycle. Mainly:

a) Development of the manufacturing process (pre-launch).

b) Stage of growth in sales of the drug, when improvement of the process takes place, including improvements in productivity, either through the selection and/or development of new technologies, or through better quality control systems.

c) Stage of maturity, when cost reduction becomes most important.

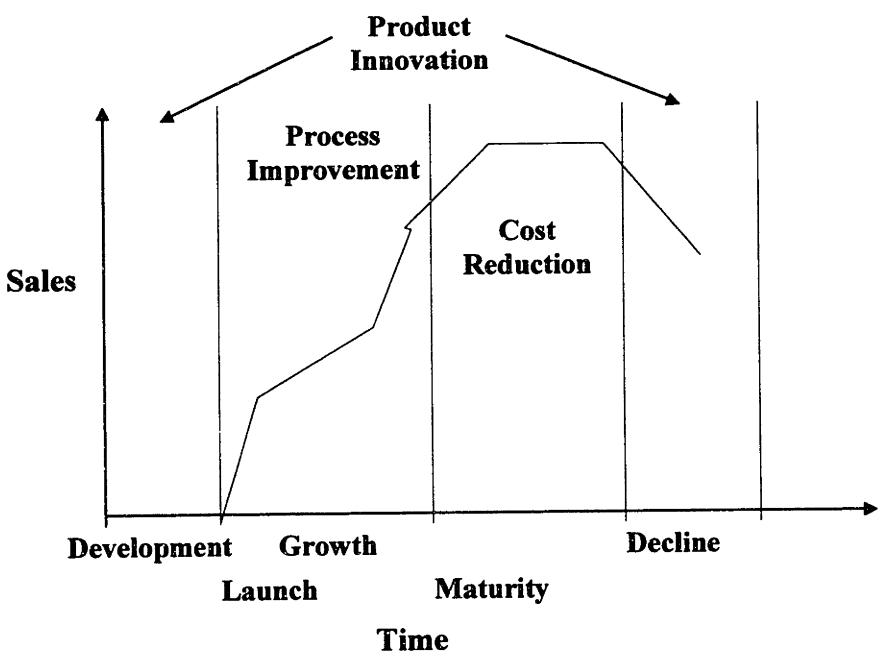


Figure 4.3
Innovation and a Drug's Life-Cycle

Several parameters must be considered when evaluating the validation of an oral solid dosage form:

- Bio-clinical / commercial batch relationship

- Raw materials

- Manufacturing procedures and equipment: A detailed master formula with specific manufacturing directions and specifications must have been developed before any validation protocol is prepared and before the validation process begins. The basic premise of validation of a process is that a detailed process already exists which hopefully will be shown to perform consistently

- Granulation / mix analysis: A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then some dosage units may not comply with uniformity requirements. One of the major. The acceptance criteria for granulation dose uniformity testing needs to be evaluated. Although many firms evaluate dose uniformity using the compendial dose uniformity specifications (85-115% with an RSD of 6 to 7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases compendial assay limits for the finished product (90 to 110% of label claim) are broad enough for this purpose, and most firms should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used. This key issue needs to be examined during the inspection.

- In-process controls: In-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. USP assay limits are 90 to 110%

- Test results with validated methods: Unusual or atypical results should be explained in the validation report.

- Investigations / Product Failures
- Site review

At the production stage, changes in the following factors may require validation:

- Components and composition of the drug product.
- Manufacturing site
- Batch size (scaling up or scaling down)
- Manufacturing equipment
- Manufacturing process

Analysis to determine blending performance is carried out during the validation stage. During "full validation", once the variables of the manufacturing process have been specified, 12 samples are taken (although sometimes the number of samples taken can go up to 36); the samples are taken from the top, medium and bottom of the blender, and from the front and back of the eyebar, respectively. Validation usually takes about 3 months. It must be performed for three consecutive batches, and three positive results in a row must be obtained (that is, three consecutive runs must yield the desired homogeneity of the mix in the time determined during the experimental phase). Otherwise, it is necessary to start all over again. In certain cases (as with revalidation because of a change of raw materials), it may be possible to validate for only one or two batches; this is called "comparative validation".

If during validation, an analysis shows negative results (that is, if the results show that the mix is not homogeneously blended), three steps can be taken:

1. The first thing to do is to reanalyze the sample. Normally, each sample taken comprises 3 times the unit dose, and then subsampling is done. It is important to determine whether the lack of uniformity was due to:

a) A sampling error
b) A subsampling error
c) An operator error
d) A problem associated with the blending operation itself.

2. Sometimes, reprocess (rework) can be done to correct an error attributed to the mixing time or some other variable associated with blending.

3. The last resort is to discard the lot.

Specifications, such as hardness and particle size, should be established prior to validation of the process; these specifications should be included in the validation protocol. The use of product development runs of the process to establish both specifications and demonstrate that the system is validated often causes problems. In these cases, more in-depth inspection and evaluation will be required; some of these process runs often produce failing product because the product specifications have not been fully established and tested.

The issue of retrospective validation, and its application to marketed products, is frequently encountered. This concept of using historical data (test results), along with process control and process specificity was of value until more scientific methods for demonstrating process validation evolved. It should be pointed out that retrospective validation is not merely the review of test results. It also requires that the manufacturing process be specific and the same each time a batch is manufactured. Thus, specific raw material specifications (including particle size when necessary), in-process specifications (tablet hardness, etc.), and specific manufacturing directions are required. Obviously, any failing batches attributed to the process would necessitate the conclusion that the process is not validated, not under control and, therefore, inadequate.

Prospective process validation is required, particularly for those products introduced since 1990, or those for which manufacturing changes have been made. However, in some cases where older products have been on the market without sufficient pre-market process validation, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

Uniformity of content is not only measured after sampling/analysis, but also in other stages of the process as well (Figure 4.4). A more detailed description of the

process that takes place during the validation of a model process can be found in Appendix II.

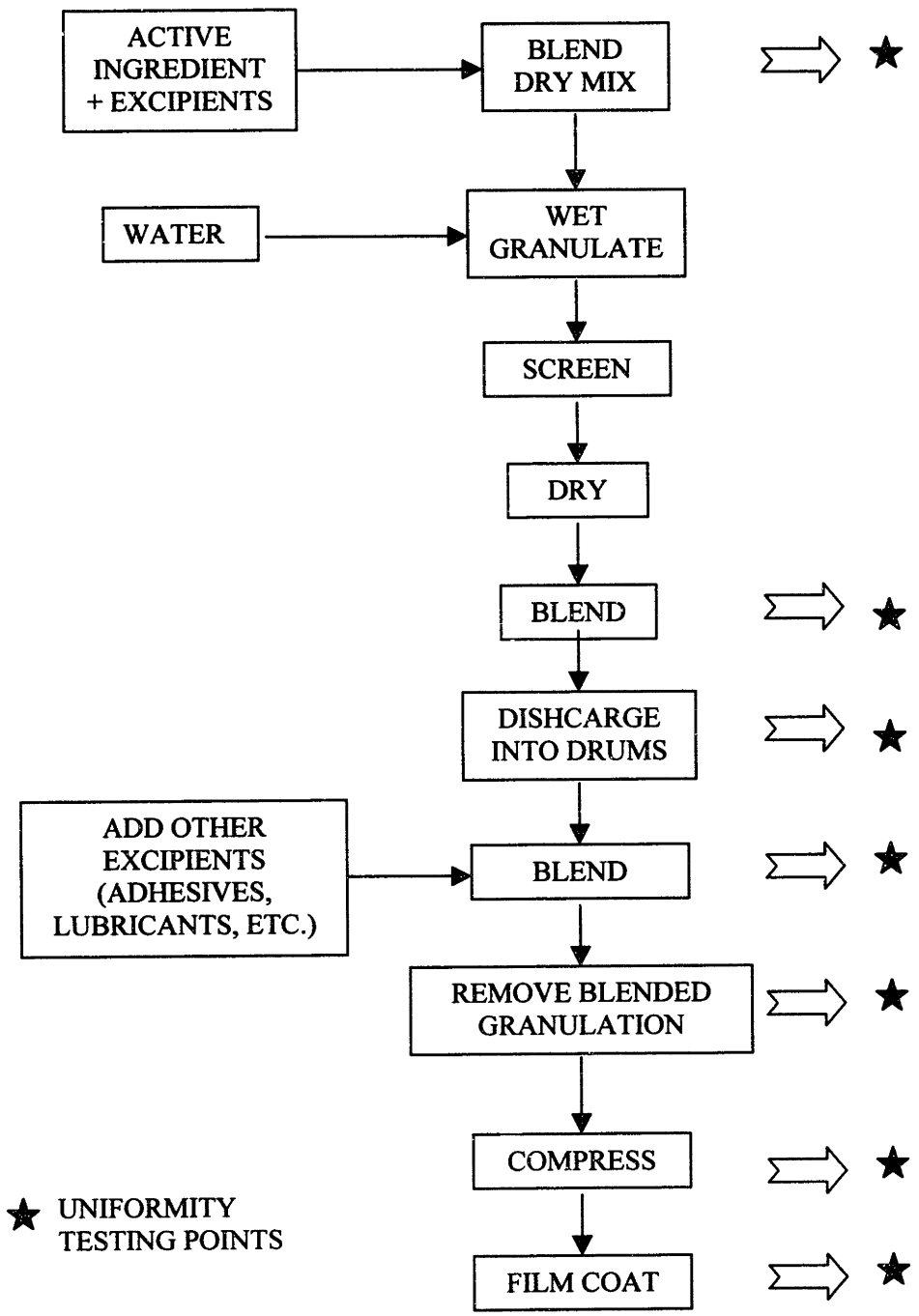


Figure 4.4
Model Validation Process

Analyzing every control point in the required three positive-result validations can take more than to 2 weeks of on-line work, as shown in Table 4.2.

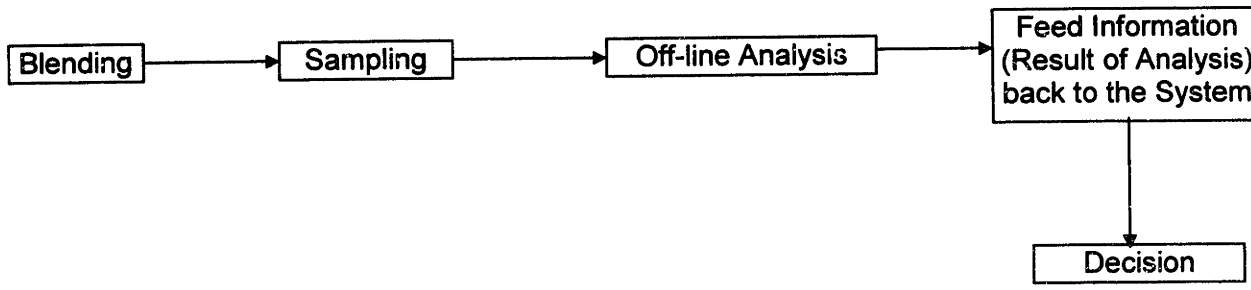
TABLE 4.2
TIME SPENT IN DETERMINATION OF HOMOGENEITY DURING VALIDATION

Number of control points sampled	7
Time taken per sampling operation (h)	4
Total time taken on-line (h)	28 (3-4 Days)
Time taken transporting the samples (h)	2
Time taken analyzing each set of samples (h)	12
Total time analyzing the samples (h)	94 (11.75 Days)
Total time spent off-line (h)	96 (12 Days)
Total time (on-line and off-line)	124 (15.5 Days)

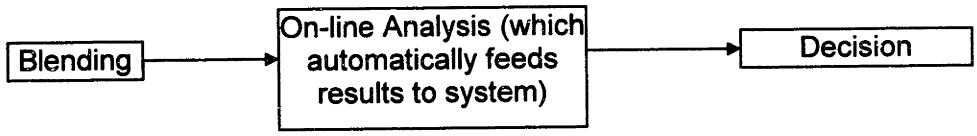
3 to 4 days are spent analyzing the samples taken in all the control points of the model validation process. Since this operation must be repeated for at least three batches, the total amount spent on sampling would amount to 12 to 16 days. As for transporting the samples and analyzing them, at least 36 days would be spent on these operations. During validation, the process is run as if it were a normal manufacturing run, so sample analysis is carried out at the same time as other operations in the process are being performed. Let's assume that 75 % of all the analysis are done while other operations in the process are still taking place; this means that there are 10 days when the validation process must stop to wait for the results of the analysis.

Focusing the analysis on the sub-process that takes place in the unit operation of blending (which is where the effect of the introduction of the device is directly felt) it is possible to appreciate that:

Without the LIF system, the process is as follows:



With the LIF system:



Thus, with the use of the LIF system, the total expected reduction in time (assuming three validation runs, each of which yields positive results) would be equal to the time currently being spent on sampling and analysis, that is, approximately 25 days. Again, assuming a product with sales of 1 million dollars per day, this implies cost savings of at least 25 million dollars.

Other cost reductions that have not been included in this analysis, but that may be significant as well, include:

- Overhead for testing
- Labor
- Equipment

MANUFACTURING

Technological innovations, such as the LIF probe, can have a systems effect on organizational functioning: they affect diverse aspects and functions of various operations, rather than just one particular activity.

The manufacturing process itself has few control points. No samples are taken, and the only stage at which the product Is analyzed is at the end, once the tablet is ready. Although sampling and analysis are only involved in critical points of the validation of a new product or the revalidation of an existing one, the use of the LIF device can also potentially have an impact on the production stage by reducing the possibility of obtaining non-homogeneous blends. This implies an improvement in the quality of the process and a reduction of the number of batches not meeting specifications and, therefore, reprocess and waste

The following model (Figure 4.5) depicts these dynamics; it has been simplified to assume that no reprocess is undertaken: if a batch fails to pass inspection, then it is thrown away.

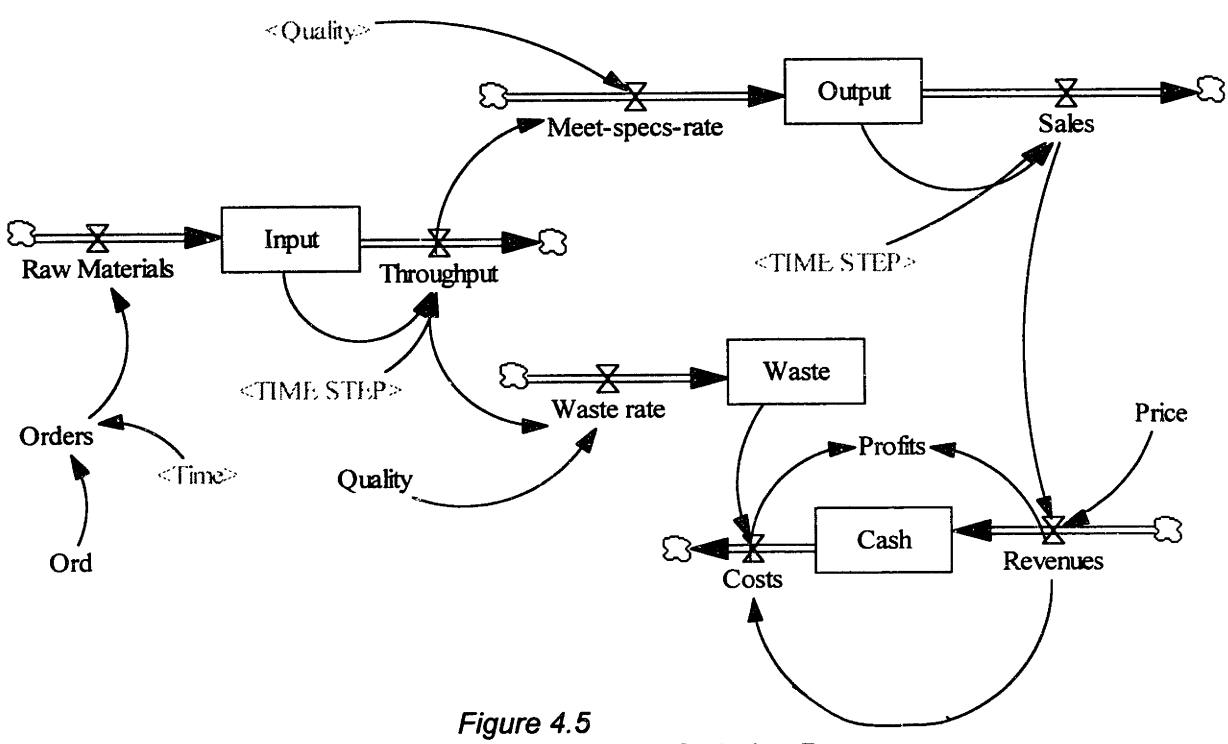


Figure 4.5
Dynamic Model of Pharmaceutical Manufacturing Process

The following assumptions were made:

	Current Practice	With LIF System
Quality	93 %	95 %
Costs	(0.21 * Revenues) + (5000 * Waste)	(0.21 * Revenues) + (5000 * Waste)
Raw Materials	Orders [1]	Same
Revenues	Sales * Price	Same
Profits	Revenues – Costs	Same
Price	100 000 $/Ton	Same

[1] See Table 4.3

TABLE 4.3

PRODUCT ORDERS

Time (Years)	Tons Ordered (t)
0	0
5	5500
10	5000
20	1000

- Quality represents the probability that a batch will meet specifications and pass inspection. Currently, it is estimated that 7 % of all batches fail to meet homogeneity requirements, therefore, the quality of the process is 93 %. It is assumed that with the use of the LIF system process quality can be improved about 2 % and, thus, go up to 95 %. The concept of improvement of quality in this context includes also the impact on overhead and inventory costs, which come as a result of the reduction in waste and the improvement on scheduling to meet the order rate.

- Costs are roughly estimated to be 21 % of total revenues [22]. For a formulation using 0.5 % of an active ingredient with a cost of 1000 $/kg, the cost of any material wasted would be of 5000 $/Ton.

- The price of the finished product has been estimated at 100 000 $/t.

The following chart (Figure 4.6) represents the profits accrued per year, for a period of 20 years, for both current practice and use of LIF probe:

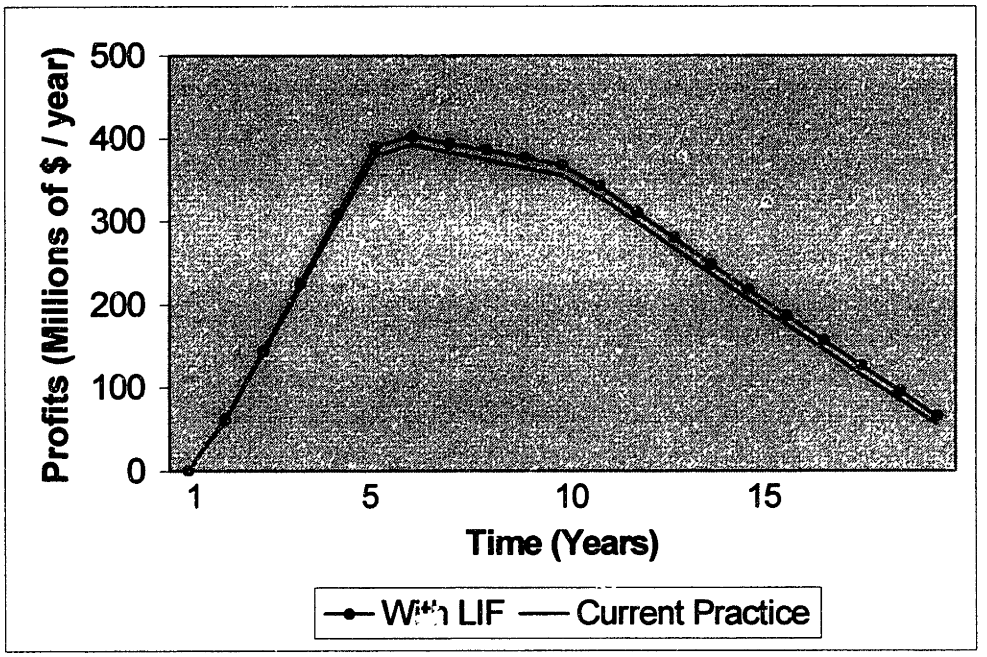


Figure 4.6

Profits Accrued With and Without LIF System

The use of the LIF system results in higher profits for the firm. Table 4.4 summarizes the net present value of the cumulative profits which the company may accrue in a period of 20 years. The discount rate used is 15 %.

TABLE 4.4

ACCRUED PROFITS FROM USE OF LIF

YEAR	EXTRA PROFITS (Millions of $)
1	1.6
5	17.6
10	36.8
15	46.7
20	51.0

SENSITIVITY ANALYSIS

Sensitivity tests were run modifying the original assumptions as follows (for each case, only one variable changes and the rest of the assumptions remain as originally stated):

1. Quality improves only 1 %: from 93 % to 94 %.
2. Reduction in overhead and inventory costs is considered separately from quality, as 500 000 $/Year.

The results are summarized in Table 4.5 (net present value of cumulative profits with a 15 % discount rate):

TABLE 4.5

EXTRA PROFITS ACCRUED FROM USE OF LIF (Millions of $)

Year	Base Case	Quality improvement of 1 %	Overhead / inventory cost reduction of 500 000 $/Year
1	1.6	0.6	2.9
5	17.6	8.0	22.7
10	36.8	17.2	44.4
15	46.7	21.9	55.5
20	51.0	23.9	60.4

From Table 4.5 it is possible to conclude that an acceptable range for the cost savings (or profit increase) resulting from the use of the LIF system would be of:

- 0.5 to 3 million dollars during the first year
- 8 to 25 million dollars in five years
- 25 to 60 million dollars by the twentieth year

Chapter 5
REGULATORY FRAMEWORK

ANALYSIS OF REGULATORY ENVIRONMENT

The main issue for the pharmaceutical industry in terms of the impact of the drugs they manufacture concerns patient safety. The patient, however, is usually unable to judge the safety, quality, and efficacy of a medicinal product and, thus, the State has overtaken this responsibility, together with the pharmaceutical manufacturers.

The legal control system can be divided in two main categories:

1. Government regulations.
2. Company guidelines and procedures.

Government Regulations

The government regulates the pharmaceutical industry with the purpose of:

1. Encouraging the marketing only of those drugs which can be demonstrated to be safe and efficacious and the use of only those processes which lead to such drugs.
2. Maximizing the value of the exports of pharmaceutical products.
3. Encouraging competition by the application of anti-trust legislation (monopolies and restrictive practices legislation).
4. Encouraging, by the provision of secure property rights (patents legislation) and consequent profits, a high level of research and development.

To ensure patient safety, the government analyzes, approves and monitors pharmaceutical facilities, processes and products. This process is legislatively mandated so that both the regulatory agency and the industry can meet the needs of the patient. The Federal agency in charge of regulating the pharmaceutical industry in the

United States is the Food and Drug Administration (FDA). The US has the most stringent and the tightest regulatory system regarding pharmaceuticals in the world. The adherence to the rules set forth by the FDA is legally supervised, and offenses, whether committed deliberately or by negligence, are punished by administrative fines and / or by imprisonment.

It is noteworthy that it has become an increasingly important issue for the FDA to accelerate or shorten the period required for evaluation and approval of new drug applications (NDA's) and, moreover, to make unbiased evaluations and sound judgments within the established regulatory and approval processes while providing the best possible products and techniques.

These two objectives may seem contradictory since, on the one hand, an extensive body of regulations is required to assure the quality of the product, including every step involved in its manufacture, and ensuring compliance with these rules is a time intensive process. In particular, the Barr Decision establishes closer monitoring of each control point of a drug's manufacturing process, as well as a smaller range in the size of samples taken from validation batches. On the other hand, the need to market potentially life-saving medicines exerts pressure from the public onto the regulatory agency to liberate NDA's and make them accessible to the patient.

The main set of rules established by the FDA are contained in the Food, Drug and Cosmetic Act, which specifies the requirements of safety and performance for pharmaceutical products, including processes and products.

The United States Pharmacopoeia (USP) contains a detailed description of the methods of analysis to which a finished product or a bulk formulation must be submitted, as well as the acceptable parameters for compliance. The Code of Federal Regulations establishes the policies to follow for the analysis of NDAs, the marketing of drugs and other issues, and the Regulatory Procedures Manual defines the various types of FDA samples.

Company Guidelines and Procedures

In order to facilitate compliance with FDA regulations, pharmaceutical companies follow specific procedures, which may or may not be directly enforced by the Federal Government. For instance, one set of procedures to which all pharmaceutical companies abide are those contained in the Good Manufacture Practice requirements (GMPs). GMPs are part of a quality system that establishes methods, specifications and controls for pharmaceutical processes and products.

GMPs usually exceed other requirements [28]. For instance, GMPs establish more stringent requirement than those set forth in the International Organization for Standards (ISO) as related to the concept of validation, the provisions regarding hygiene, and pharmaco-vigilance. GMPs are used for the application of validation guidelines (and other development and manufacturing guidelines), as well as for the development of a process report.

There is no statute or regulation that specifically requires a product development report, although companies are required to produce scientific data which justifies the formulation and the manufacturing and control processes. Industry practice dictates that the companies develop a product development SOP (Standard Operation Procedures) which describes the development process, the documentation requirements, and the individuals responsible for approving the filed process. The development data found in these reports is important to deal with potential liability issues that may arise at any stage of a product's life cycle and should include the following:

1. Drug substance characterization: chemical and physical properties, as well as the physical quality (e.g., particle size of raw materials) can sometimes have a significant impact on the availability and clinical effect of a drug. In most cases the manufacturing process for a new chemical entity is developed and scaled-up before the finished dosage form is obtained. Changes to the manufacturing process for the drug substance may change the purity profile or physical characteristics and thus cause problems with the finished dosage form. The finished dosage form manufacturer must perform the appropriate test to characterize the drug substance chemically and physically and establish appropriate specifications.

Variation in particle size, particle shape, and/or bulk density can also have an effect on the uniformity of dosage forms, particularly those manufactured by direct compression or direct encapsulation. Changes in particle size of some excipients, for example, may affect content uniformity.

The control of mixing times and physical characteristics of all ingredients is critical to successful validation of all formulations and processes.

2. Manufacturing Procedures: Procedures used to manufacture development batches must be specific and well documented. This is necessary for scale-up and subsequent comparison to the commercial process.

3. In-process Testing: Specifications required to control the manufacturing process must be established and justified. This requires granulation studies which include blend uniformity, sieve analysis, and moisture content.

4. Finished Product Testing: Testing for the monograph standards (USP, NF, etc.), including:

   - Dissolution Profile
   - Stability

Figure 5.1 depicts the process that takes place from the development of the first bio-clinical batch until the successful commercial process is achieved: once the bio-clinical batches and the development reports are completed, the company files for the approval of the NDA. The company must then scale-up the process, following GMP guidelines, and perform the three validation runs required to prove that the process performs according to specifications. Once the process is validated and final approval form the authorities is received, it is ready for commercial production.

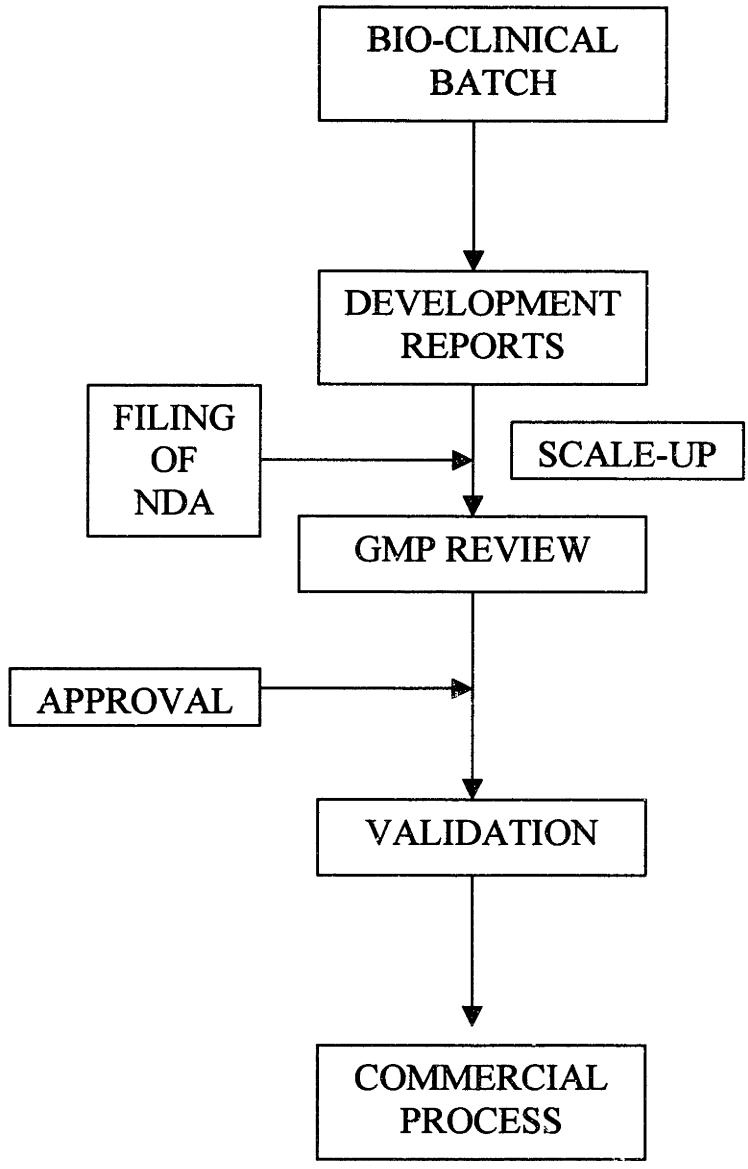


Figure 5.1

Documentation Link between Bio-clinical Batches and Commercial Process: Development Reports, GMP Reviews and Validation

Total Quality Management

In order to satisfy the safety and performance needs of pharmaceutical products, a total systems approach is needed, where the quality system is an integrated effort between manufacturers and regulatory agencies.

The quality assurance (QA) activities do not simply consist of inspection and testing. Quality should be considered at the earliest stages in every significant area that has an effect on the quality, safety, and effectiveness of the drug. These areas include product development, design verification and validation, component and/or supplier selection, documentation, development of labeling, design transfer, process development and validation, pilot production, routine manufacturing, test/inspection, distribution and complaints.

Figure 5.2 represents the interaction between the rules and guidelines set forth by the Federal Government and those developed by the firms themselves, within the context of a total quality management system.

Current GMP requirements have the most comprehensive coverage in terms of a firm's development and manufacturing practice. They supersede (but not invalidate) other more specific guidelines (since they may change over the drug's life cycle). These procedures allow the company to work from the creation of the process development report to the actual commercial process and its SOPs.

The FDA interacts with the firm mainly through the Food, Drug and Cosmetic Act, and the methods specified in the USP and the Regulatory Procedures Manual.

A properly functioning quality system results in increased safety and efficacy of the drug, reduced liability exposure, reduced regulatory exposure, increased customer satisfaction, less waste, lower costs, higher employee morale, and, as a result, higher profits.

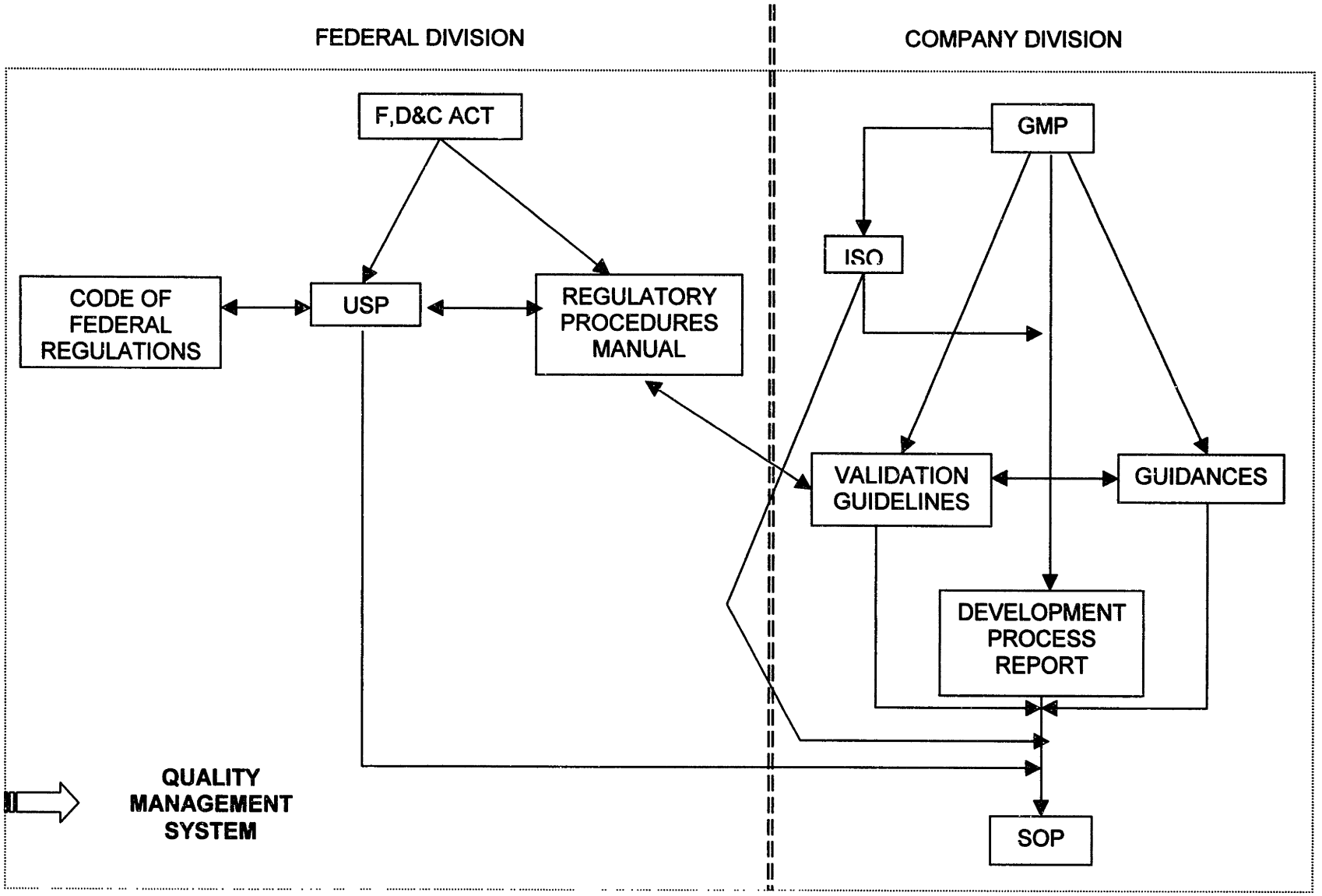


Figure 5.2
Government-Industry Regulatory Interaction within a Total Quality Management System

POLICY IMPLICATIONS

The introduction of a new technology must be analyzed, not only in terms of the technological feasibility of its implementation or its economic attractiveness, but also from the perspective of its impact on the regulatory structure in which it is embodied, as it relates both to established regulatory mechanisms and to potential policies likely to arise from its use.

First, it is important to recognize that there is a "network effect" regarding the regulatory context in which pharmaceutical companies operate: in the case of a new technology such as the LIF probe, the FDA must first familiarize itself with the way in which it operates, analyze its performance and approve its use. In order to do achieve this, companies must validate the new homogeneity detection technology and convince the agency that the use of the probe on-line yields the same degree of certainty in relation to a blend's homogeneity as the off-line analysis currently in practice.

Therefore, companies that decide to invest on the technology first, will also have to invest resources in the process of gaining approval from the FDA. With time, more companies will have adopted the technology and it will be easier for each subsequent firm to implement it as a function of FDA requirements. However, the potential increase in profits of over 30 million dollars that the innovation offers for NDAs seems to indicate that being first in adopting this innovation gives a "first-mover" advantage, especially considering that it is estimated that the process of validating a new technology and obtaining FDA approval for its use, would cost the companies less than 0.5 % of their profit increase (approximately 100 thousand dollars).

From the point of view of the regulatory agency, it is likely that in the context in which the FDA is currently operating, where there has been increasingly strong pressure from different sectors to facilitate and fasten the drug approval process, the adoption of a device such as the LIF probe might be seen as a technology with the potential of harmonizing the agency's goals: to diminish the time to market of a new drug without compromising its safety and efficacy. At the same time, the use of the LIF probe would allow for a closer control of the manufacturing process by monitoring blend's homogeneity on-line, in every critical step of the process.

Basic quality controls such as inspection and testing are important parts of a quality system because they provide information that should be fed back into the process where action can be taken to correct root causes of quality problems. The Barr Decision can be seen as a tool to achieve total quality assurance, which dictates that all production activities must be controlled, finished product specifications must be met and feedback must result in appropriate corrections [2].

Identifying and solving quality problems is a core requirement of the total quality management system. With the implementation of the LIF system, companies would be able to abide to the requirements of the Barr Decision without the costly and timely procedures of sampling and analyzing during manufacturing.

Additionally, if used in manufacturing, on-line monitoring of homogeneity would solve some of the quality problems encountered in a drug's life cycle.

For instance, at the early stages of a drug's development process it may be determined that particle size has no effect on drug absorption and dissolution and a wide range particle size specification may be established. However, in the GMP review, new information may be obtained and the results may establish that variation in particle size has a major effect on content uniformity. Therefore, a tighter particle size specification would have to be established. Since firms should validate the process using the specifications listed in the filing, it would become necessary to amend the filing and resubmit it (Figure 5.3).

With the introduction of the LIF detection system, the flow of activities would change as follows (Figure 5.4): The effect of particle size on homogeneity can be determined at the process development stage and, thus, the correct specifications can be set at the beginning of the process. The LIF device can then be used to monitor blending performance on-line at subsequent steps of the process, ensuring the quality of the process at every stage.

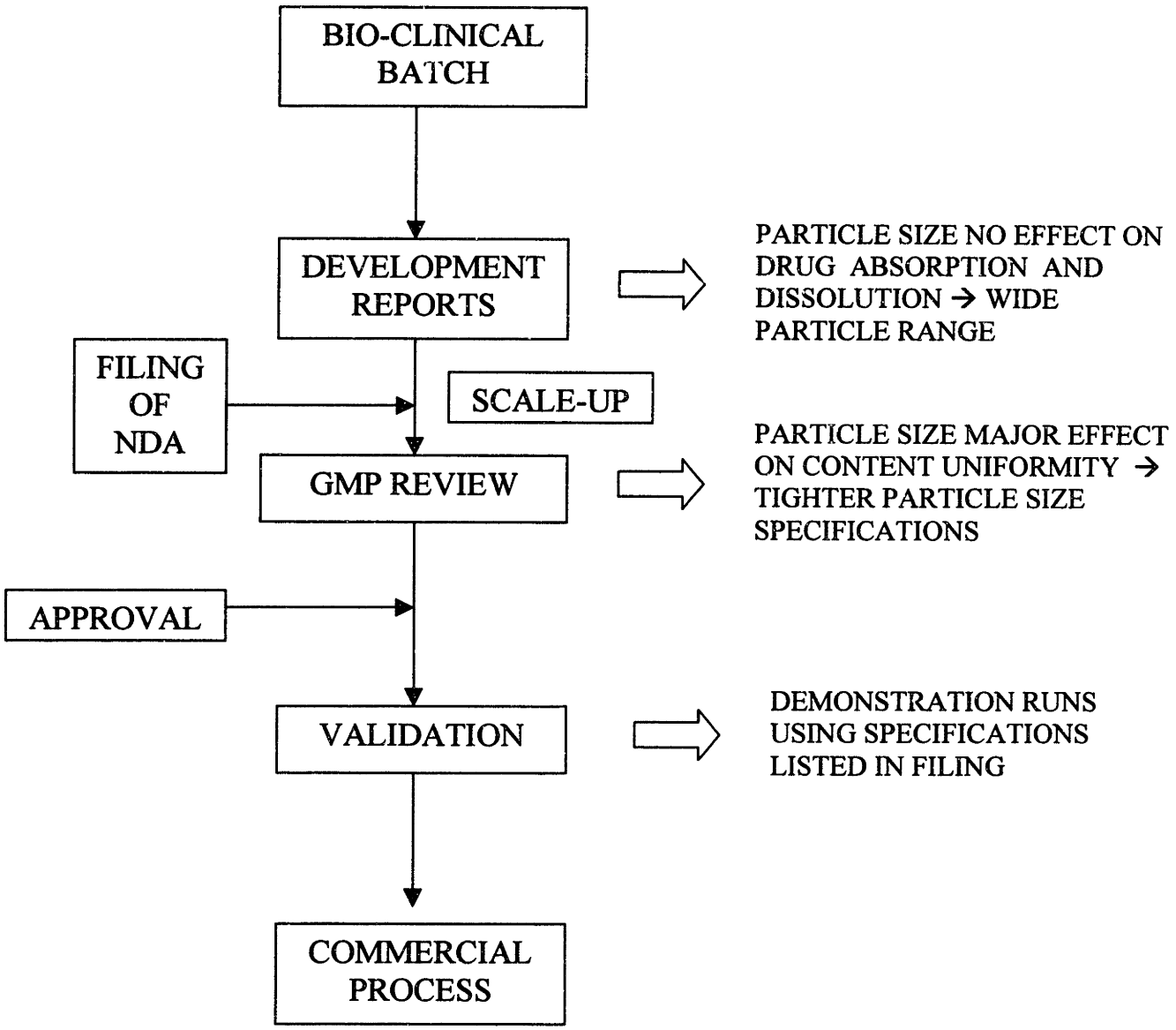


Figure 5.2

Interaction Between Stages of the Process: Current Practice

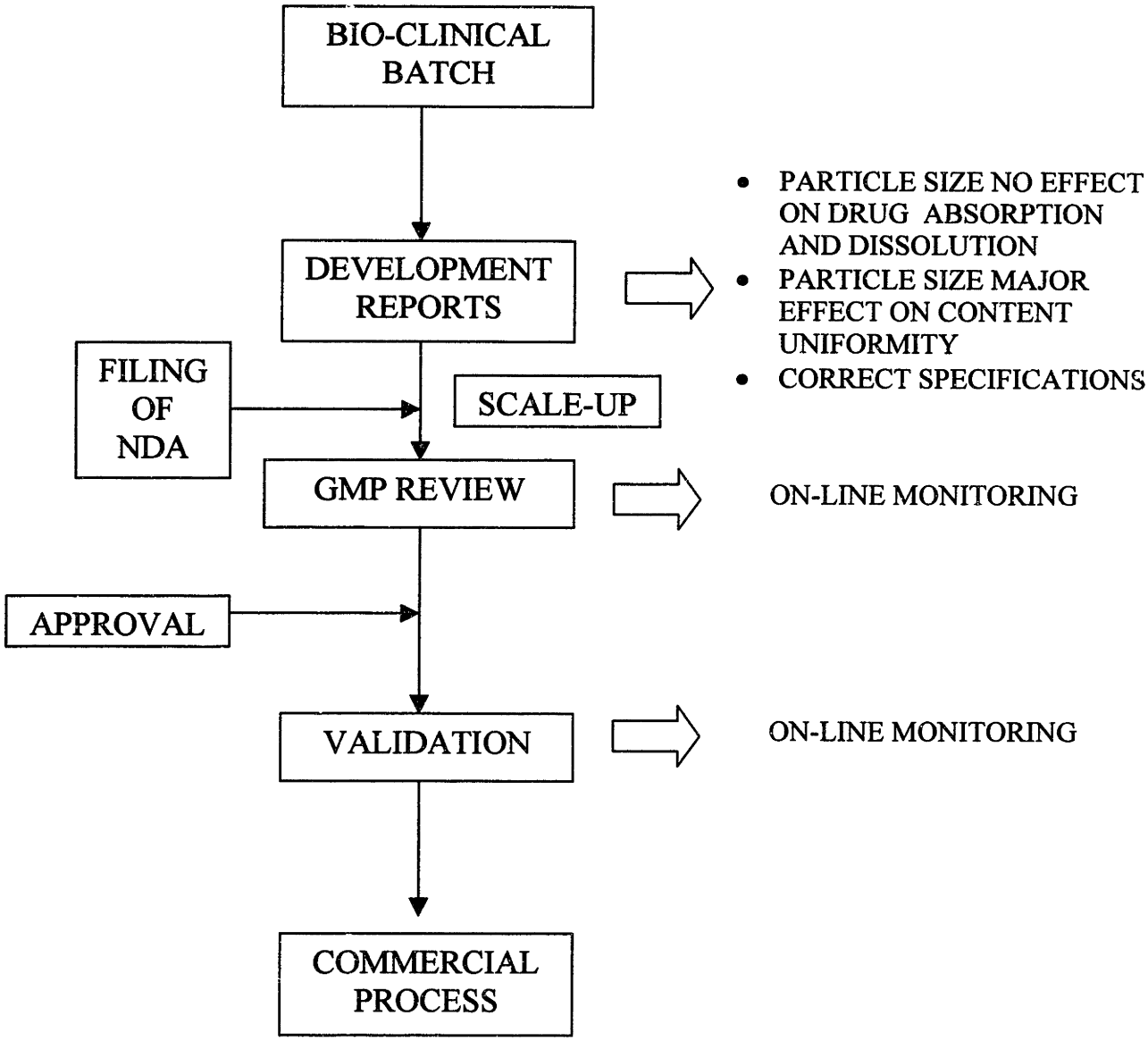


Figure 5.4

Interaction Between Stages of the Process: With Use of LIF

An i;) f 'Ч-Ч iqq k Ч Mf Hpi k' iq uz k Hkk Ч f (k'Mf ; k 'kqiqЧ-Mk Ч uz k · qk f l the new technology by operators, quality assurance departments, regulators and the industry itself. The pharmaceutical industry produces established, high-volume products, whose markets are well defined. The product characteristics are well understood, unit profit margins are typically low, production technology is efficient, equipment-intensive, and specialized to a particular product. Change is therefore costly, because an alteration in any one attribute or process has ramifications for many others.

However, although breaking the inertia and overcoming the resistance posed by the aforementioned entities may be difficult for established processes, and although it would require some effort from management, it is an essential task to improve the current drug development and validation processes; since it is expected that the new technology will solve some of the problems associated with sampling and off-line analysis and, thus, help reduce the time to market of a new drug, it is reasonable to think that pharmaceutical companies will have the incentive to implement the innovation, at least for the drugs currently on an investigational stage (that is, the LIF device could be used for the process development and validation of New Drug Applications - NDAs -).

In order to accomplish this purpose, it is important to consider the absorptive capacity required to implement the new technology and to make the adoption of the process innovation successful. The ability of a firm to recognize the value of new, external information, assimilate it and apply it to commercial ends is critical to its innovative capabilities.

Management of the pharmaceutical companies should evaluate the potential of the new technology and assimilate and exploit the process innovation. Given that pharmaceutical firms have prior knowledge in the area of blending technology, assimilation of the process innovation in relation to the creation and dissemination of knowledge and learning should not represent a barrier to implementation. The following diagram (Figure 5.5) depicts some of the company's incentives to adopt the innovation, as they relate to the firm's absorptive capacity:

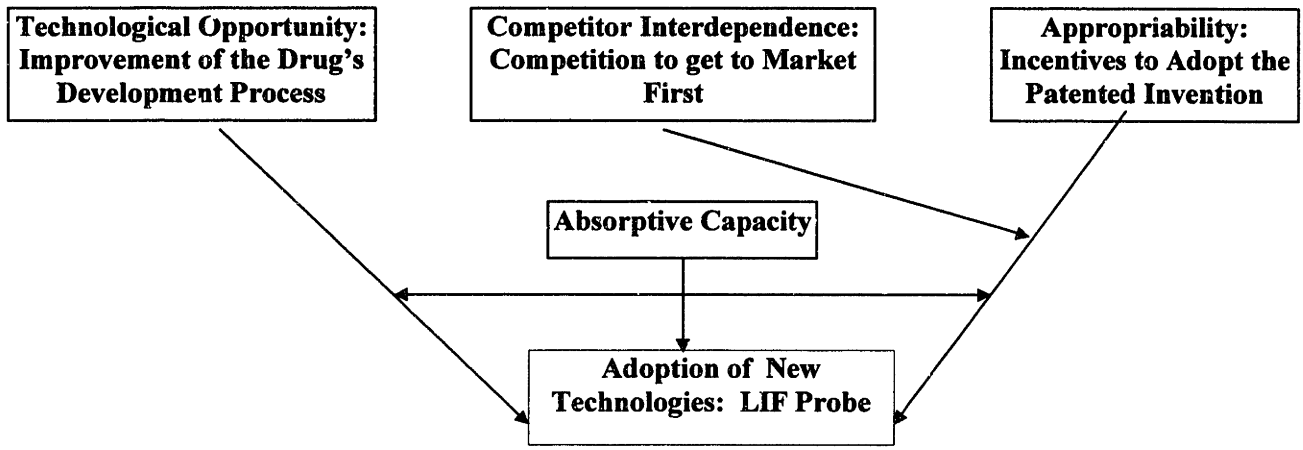


Figure 5.5

Model of Absorptive Capacity and Adoption of Innovations

Another approach to analyze the competencies needed to achieve a successful implementation of the innovation involves the complementary capabilities of the firm (Figure 5.6).

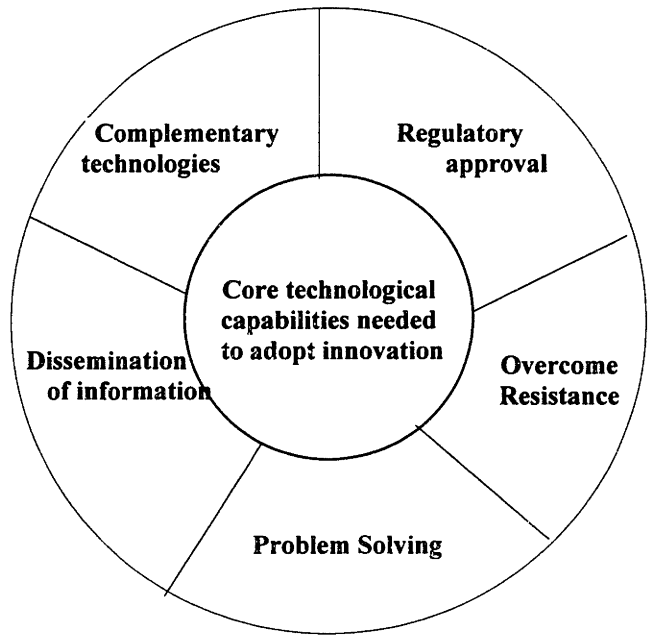


Figure 5.6

Complementary Capabilities Needed to Successful Implementation of the Innovation

In the case of the adoption of the LIF probe, the firm's capabilities neeed for successful implementation comprise a combination of complementary technologies and know-how (including the timely dissemination of information regarding the technology among operators and quality analysts), approval from the FDA of the new process and its incorporation in the practices of the firm (GMP, SOP), and the ability to solve problems effectively (accurate homogeneity analysis).

RECOMMENDATIONS

Any kind of change is always associated with risk, especially in the pharmaceutical industry, where the technical risks inherent in the implementation of new process technologies come with other regulatory and managerial implications.

However, an innovation is an opportunity. In this case, the technical advantages of the innovation in terms of its capability to produce considerable time and cost savings and to improve the overall quality of the manufacturing process, are compounded with regulatory, managerial and policy issues.

It has been noted that the regulatory authorities could clearly benefit from on-line homogeneity detection technologies, since they would be able to ensure a total quality management process control approach, without lengthening manufacturing times. Thus, the FDA can fulfill its duty of monitoring products' quality at the different stages of their manufacture, ensure patients' safety and shorten the time for regulatory approval, which is critical for the time to market of a new drug and its accessibility to patients in need.

Pharmaceutical companies, on their side, can greatly benefit from the introduction of a system like the LIF device, since it would allow them to fasten their process development and validation processes as well as to improve the quality of their manufacturing process and achieve a considerable increase in profits (a gross 60 million dollars during the pre-launch phase of the life-cycle of a drug, and over 500 million dollars during its after-launch phase).

Pharmaceutical firms must be capable of sustaining a consensus about long-term goals through investments in new technology and innovation. Their task is to focus the new technical alternatives toward the improvement of their unit operations and, consequently, toward the improvement of a tablet's development process. In order to achieve this goal, they will need to redirect financial resources to make the adoption of the new technology possible, and foster close collaboration between operators, quality analysts and regulators.

Companies which adopt the LIF system (or other on-line homogeneity detection technologies) first, will likely have a competitive advantage over their competitors because they will be able to shorten their new drug's development process and increase their profits. Given that investment in research and development is usually given as a fraction of a firm's profits (approximately 10 %), then the more profits a firm accrues, the more research it will be able to undertake and the more products it will be able to take to the market - and in the shorter time – (Figure 5.7).

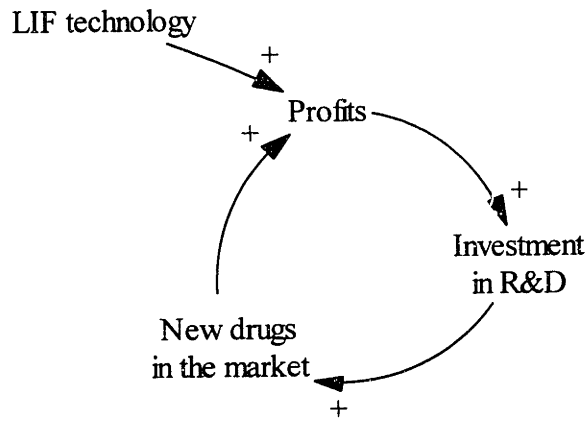


Figure 5.7

Profit Reinforcing Loop Resulting from Implementation of LIF

In order to better meet consumers needs, and meet both safety requirements and product availability, it is necessary to improve the interaction between the regulatory authorities and the private sector, especially in an industry where product quality control is not only a concern of the manufacturing companies, but of the government and

society at large. Total quality management calls for monitoring of every stage of the development and marketing of a drug, but this type of control is expensive and time consuming. The determination of an operation's performance by on-line technology appears as a viable alternative to meet these ends, without either compromising returns on the investment for the developing firm, or jeopardizing the role of the FDA in assuring products' and process' quality and performance. Only through the close collaboration between these entities will the full potential of the new technology will be reached.

Chapter 6
OTHER APPLICATIONS

DRYING

Drying in the pharmaceutical industry usually deals with the drying of granulations. Wet granulation is a step in the production of many oral solid dosage forms, which can be made by: 1) Mixing dry powders. 2) Adding a paste containing the binder. 3) Mixing to form granules. 4) Drying the wet granules.

In order to dry it, the granulation is exposed to a stream of air. The lower the absolute humidity of an air sample (that is, the lower its moisture content) at a given temperature, the more rapidly it will dry a given granulation.

The three most common pharmaceutical drying methods are tray drying, fluid-bed drying, and vacuum drying. Somewhat less common is rotary current drying. Occasional operations call for truck drying and tunnel drying.

Truck dryers are basically trucks upon which trays can be placed. They are placed in a room and the gentle movement of air across the trays (which contain the substance to be dried) causes the drying. The unit that dries the air may consist of two towers: one contains dry desiccant (the air to be dried passes through this unit) and the other contains "used" desiccant (the redrying of this is accomplished by passing hot air through it). When the desiccant in use becomes too high in moisture content, the air stream is shifted to the regenerated tower, and the tower containing the moist desiccant is subjected to regeneration by hot air.

Tunnel drying is not a common pharmaceutical drying method in terms of the number of times it is encountered; however, some of the operations to be described produce a sizeable number of products. In this type of drying operation the wet unit

moves through a tunnel in which drying takes place gradually , so that the exiting unit has de desired (low) moisture content. The source of heat is either infrared light or hot air.

Countercurrent drying is carried out in rotary dryers. These are long cylinders with internal baffles (sometimes helical) that direct the product in the direction opposite to that of the air flow. Because of the rotation, the granules continuously cascade down through the air stream. The drier the product, the drier the air it encounters, because of the countercurrent nature of the flow. Countercurrent drying is usually applied only to large-volume products, and only in automated or semiautomated processes. In an automated setup, rotary and tunnel dryers have the advantage of defining input and output points without manual operation (a point that does not hold for truck or tray dryers, and hold only with modifications in fluid-bed or vacuum dryers)

In tray drying, wet granulation is placed on trays which are either placed in an oven, or placed on a truck which in turn is placed in an individual oven(as opposed to truck drying). The drying air enters from one wall of the oven, passes over the trays, and exits at the other wall. Although tray drying is not in the forefront of technology (being both slow and inefficient), it is still a widely used method of drying, and because of the considerable capital investment that would be required for an alternative, it is not likely to be replaced by more efficient means in the near future.

In fluid-bed drying, moist granules are placed in a slightly conical pot with a retaining screen on the bottom, which is placed in an air stream. The drying rate is a function of granule diameter. Particle size distributions do not change much on drying, so that in spite of the apparent vivid motion in the dryer, the relative velocities of the particles are small and the attrition is not great. It is of significance that the important parameter in the drying is the moisture content (not so much the temperature) of the incoming air. Also, the temperature falls very abruptly to the temperature of the bed as the incoming air crosses the distributor plate. Fluid-bed dryers are also excellent mixers.

Vacuum drying is not widely used in the pharmaceutical industry although it allows for safe drying of heat-sensitive products. It is also more rapid than tray, truck, or countercurrent drying but is not as rapid as fluid-bed drying. The temperature effect in

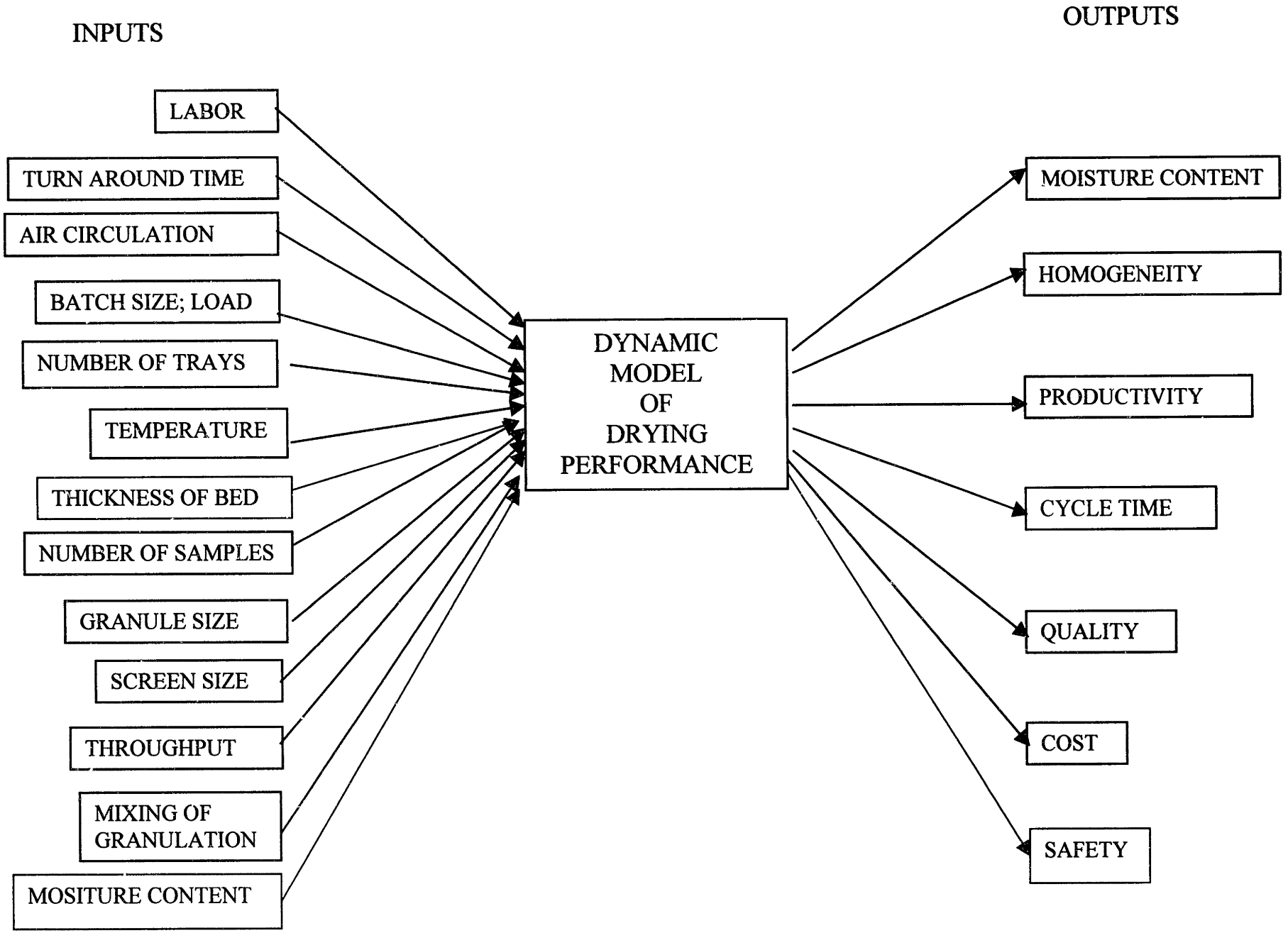
drying can be an overriding factor prompting consideration of a vacuum drying system. Others advantages also exist, such as the fact that oxidation is minimized in vacuum drying. The fact that air movement is minimized reduces the potential for particulate loss.

Other methods of drying include spray-drying and spray congealing. Spray-drying consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed (which may be a paste) is sprayed into a current of warm filtered air. The air supplies the heat for evaporation and conveys the dried product to the collector; the air is then exhausted with the moisture.

The spray-dried particles are homogeneous and have good flowability. Another application of the process in tableting is spray-drying the combination of table additives, which are then blended with the active ingredient or drug, lubricated and compressed directly to tablets. Since automization of the feed results in rapid evaporation of the moisture, the products is kept cool, and as a result, the method is applicable for drying heat-sensitive materials.

Spray-congealing consists of melting solids and reducing them to beads or powder by spraying the molten feed into a steam of air or other gas. No source of heat is required: either ambient or cooled air is used depending on the freezing point of the product.

The following model depicts the various variables that affect the process of drying and the performance metrics of the operation.


INPUTS
OUTPUTS
LABOR
TURN AROUND TIME
AIR CIRCULATION
BATCH SIZE; LOAD
NUMBER OF TRAYS
TEMPERATURE
THICKNESS OF BED
NUMBER OF SAMPLES
GRANULE SIZE
SCREEN SIZE
THROUGHPUT
MIXING OF GRANULATION
MOSITURE CONTENT
DYNAMIC MODEL OF DRYING PERFORMANCE
MOISTURE CONTENT
HOMOGENEITY
PRODUCTIVITY
CYCLE TIME
QUALITY
COST
SAFETY

MICROBIAL MONITORING

Many pharmaceutical preparations are filled as sterile liquid solutions (for instance, parenteral medications). To insure sterility, samples are taken and analyzed off-line for the occurrence of microbial contamination. The level of contamination can sometimes be very low and it therefore becomes necessary to process the samples for the recovery of cells and to cultivate them, waiting long periods of time for the contaminants to grow to a number that can be measured. The determination of sterility is, thus, a problem of sensitivity and time.

The United States Pharmacopoeia describes the methods currently being used to detect the presence of microbial growth. The two most common techniques include the Plate Method and the Multiple-tube Method. They both consist on taking samples from the sterile fluid, mixing them with appropriate growth mediums and incubating them. Following the incubation period, which for some microorganisms can take more than 48 hours, the dishes/tubes are examined for the detection of microbe colonies.

New developments in determining the presence of contaminants in pharmaceutical products include detection technologies and techniques for speeding up the rate of microbial growth. These comprise methods for fluorescent in situ hybridization labeling of cells on membrane filters with high-speed laser scanning, such as: Laser Induced Fluorescence, Micro-Drop Technology or Image Analysis.

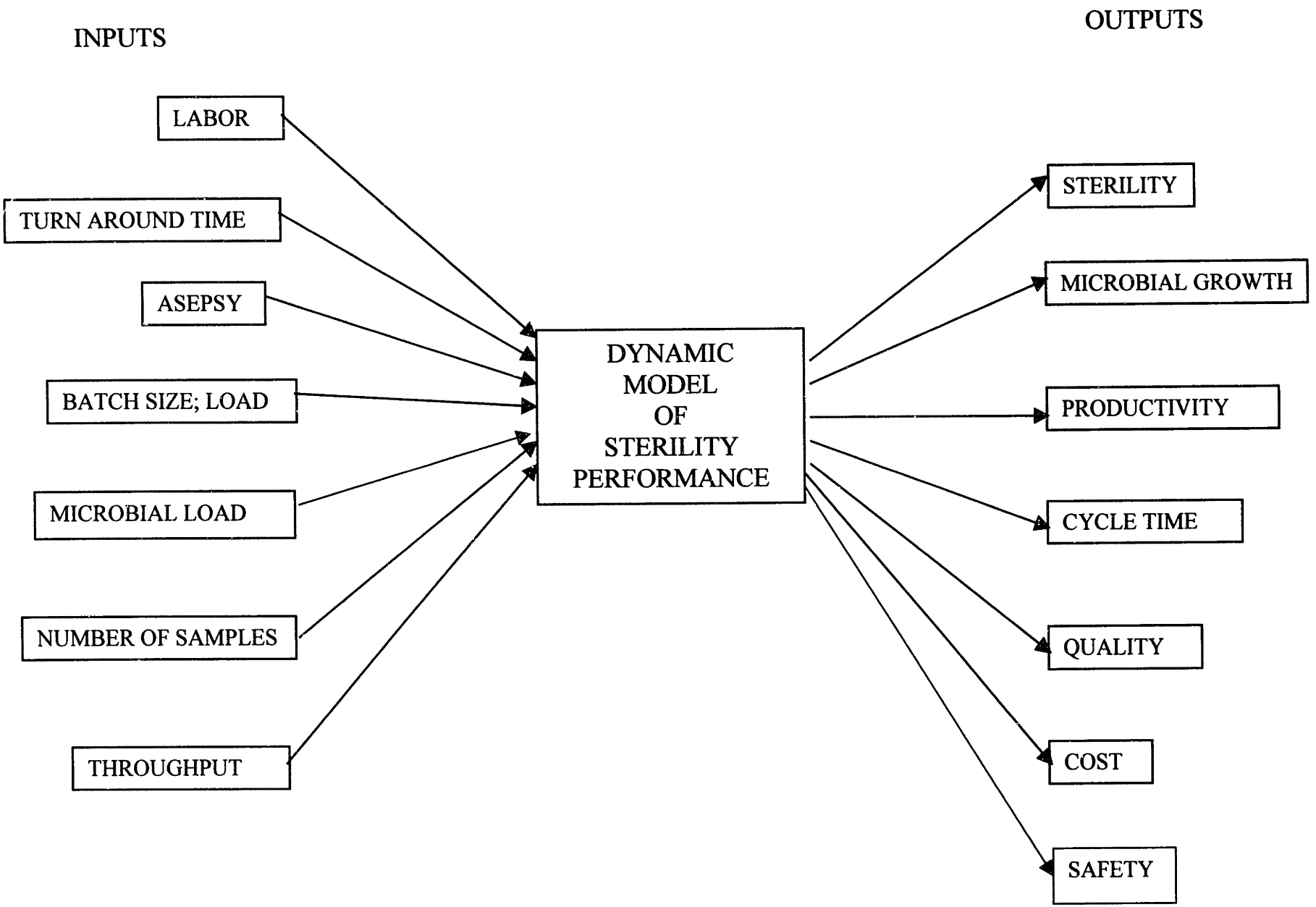
a) Laser Induced Fluorescence: This technique involves irradiating samples on-line with a laser and determining the wavelength absorption and reflection. Presently available instrumentation would yield measurements of the ingredients' concentrations on the surfaces at a sample rate of 10 million per hour, with an accuracy of over 1 part per million. The ability to quickly and accurately measure process and product characteristics, as in the case of the homogeneity of blending preparations, can facilitate the development and validation of processes and products. Microbial monitoring is potentially a suitable applications because many microbes fluoresce.

b) Micro-Drop Technology: This technique detects and counts microorganisms by microencapsulating a small sample in such a way as to create a large number of gel micro-drops (for instance, a million). Initial colony forming units with the gel micro-drops lead to micro-colonies that can be optically measured within 2 to 3 cell division times. Gel micro-drops are 20-40 μ in diameter and are highly permeable; this allows nutrients to readily reach the cells, wastes to be eliminated, and fluorescent stains to be quickly introduced. Therefore, fluorescence labeling of micro-colonies with gel micro-drops provides the basis for rapid detection of the early stages of microbial growth. Optical measurements and assessment of gel micro-drops can be carried out using flow cytometry or imaging systems; for detection of a small number of contaminants, 2 or 3 fluorescent colors can be used.

c) Image Analysis: This technique can be applied to characterize and count gel micro-drops containing micro-colonies, without necessarily having to use high resolution, because micro-colonies are larger than individual cells. Fluorescence tecnologies can then be used to obtain a fluorescence signal, which is proportional to the micro-colony size.

One strategy to follow would consist of using micro-drop technology in combination with image analysis and/or fluorescence techniques to identify particulates in the micro-drops. By creating and analyzing micro-drops from samples, it is possible to isolate individual cells, allow for their replication as micro-colonies and then screen each micro-drop for its contents. Drops suspected of containing contaminants can be isolated and further analyzed.

One milliliter of liquid will form about one thousand micro-drops, and approximately one thousand drops per second can be scanned. Therefore, in 10-20 minutes, an entire 1 ml sample can be screened. By simultaneously using image analysis and fluorescence it is possible to separate biological from non-biological samples. Suspected drops can be separated and further analyzed. Potential time savings from the use of the new technologies can therefore be very significant, reducing the time needed to perform the operation from one week (including the time needed to prepare the sterile growth media, take samples, incubate the samples and analyze them) to less than half an hour.


INPUTS
OUTPUTS
LABOR
TURN AROUND TIME
ASEPSY
BATCH SIZE; LOAD
MICROBIAL LOAD
NUMBER OF SAMPLES
THROUGHPUT
DYNAMIC MODEL OF STERILITY PERFORMANCE
STERILITY
MICROBIAL GROWTH
PRODUCTIVITY
CYCLE TIME
QUALITY
COST
SAFETY

Chapter 7
CONCLUSIONS

1. On-line homogeneity detection technologies, such as the LIF system, are advantageous to pharmaceutical firms because they can:
   - Reduce a drug's time to market by approximately two months.
   - Improve manufacturing process quality.
   - Allow for important cost savings in the process development and validation stages, in the order of 60 million dollars per project.
   - Allow for extra profits during the manufacturing stage, in the order of 2 million dollars per year per product.
   - Eliminate the need to reprocess and / or waste due to problems in homogeneity.
   - Decrease worker exposure.
   - Optimize equipment usage.

2. In terms of the impact of the new technology in the regulatory process, it can be concluded that the innovation may:
   - Facilitate the implementation of the Barr Decision, without damaging the relationship between the FDA and the pharmaceutical companies, since it would allow the firms to monitor each critical step of their manufacturing processes, without increasing manufacturing time and costs.
   - Potentially improve the relationship between regulatory agencies and the private sector, by assuring product and process quality at every stage of a drug's life-cycle and increasing, thus, the degree of confidence in the operation, since homogeneity results of each critical step are monitored and recorded in adherence with total quality management guidelines.

3. The economic and dynamic models presented in this work have been used to assess the impact of the new technology for only one project / product. In reality, pharmaceutical companies manage in the order of ten approved projects (in the development and validation stages) and about 10 products at a time. Therefore, the

actual cost savings that would result from the use of an on-line homogeneity detection system would be:

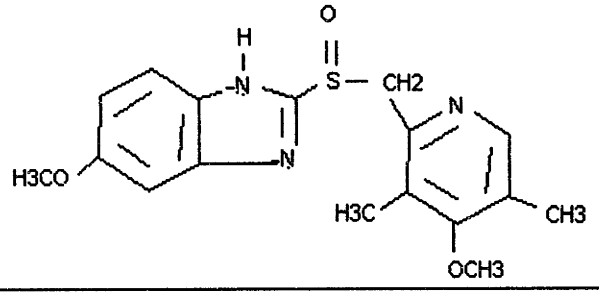
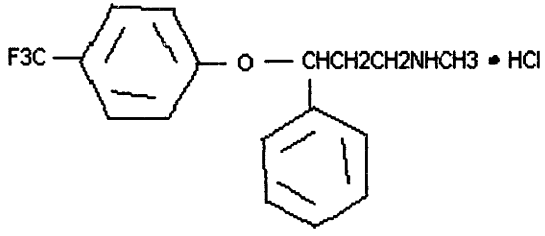
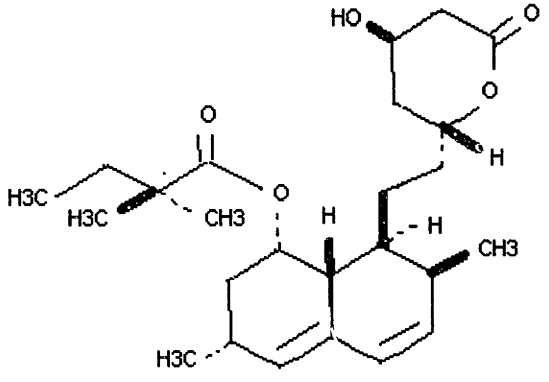
- Process development: 300 million dollars.
- Validation: 300 million dollars.
- Manufacturing: 20 million dollars per year.
- Total savings (or extra profits) in one year: 620 million dollars.
- It is also important to mention that the cost of the LIF system is marginal (60 – 100 thousand dollars), compared to the savings that can be achieved through its use, as is the cost of validating the new methodology with the FDA (approximately 100 thousand dollars).

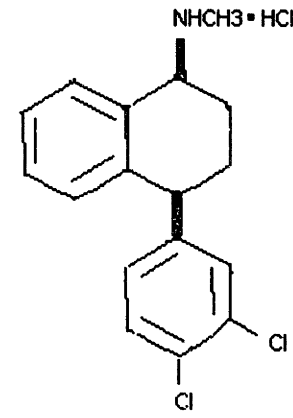
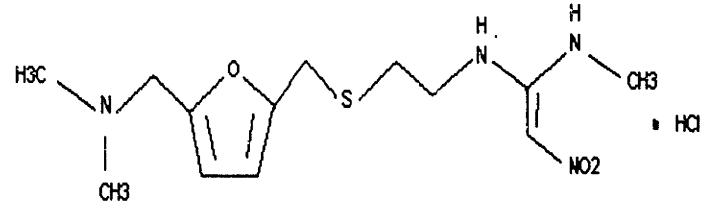
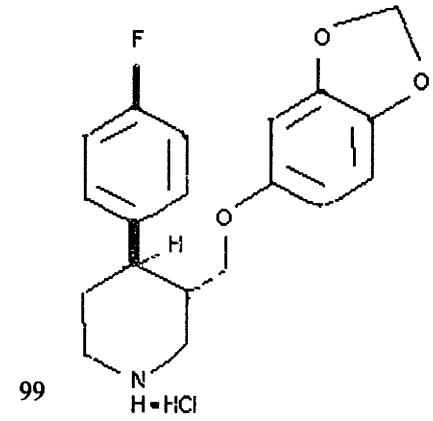
4. Firms which implement the system will have a competitive advantage over those which do not, because they will be able to diversify their product portfolio and reach the market it shorter times.

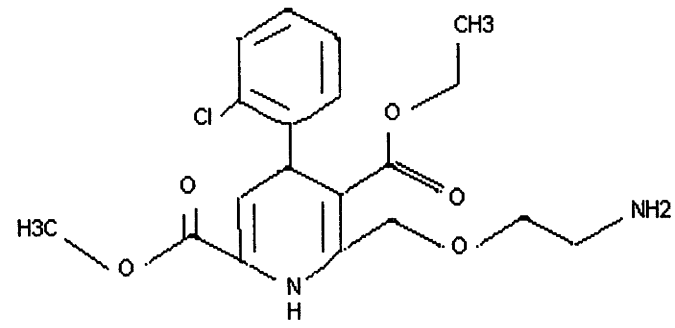
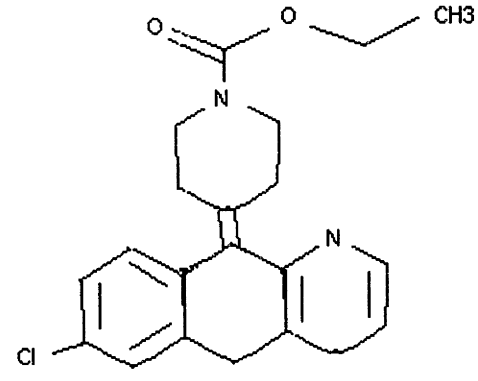
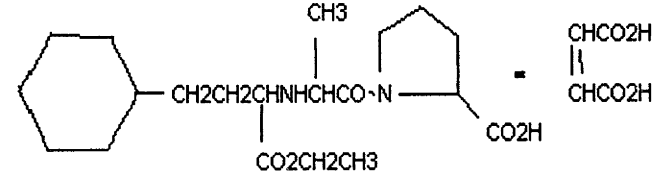
5. The use of on-line technology to monitor blending performance is consistent with the current paradigm which places quality assurance emphasis on the process rather than the final product. The ability to monitor blending processes in real time is part of the understanding of the relationship between final product specification and the critical variables during the manufacturing process, which may eventually lead towards the goal of parametric release.

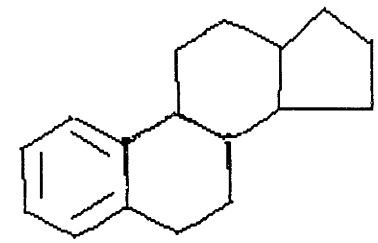
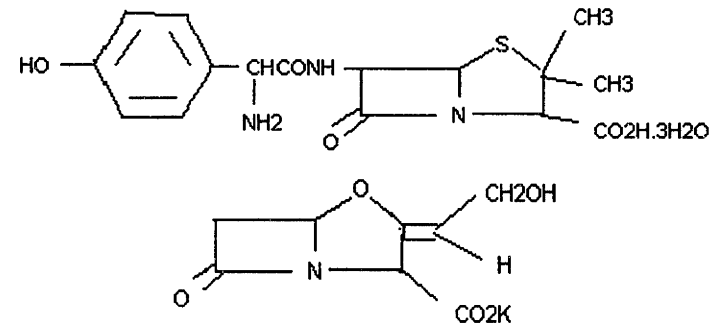
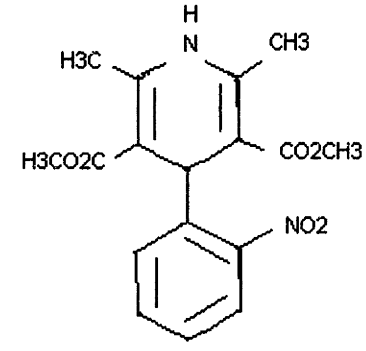
Appendix I

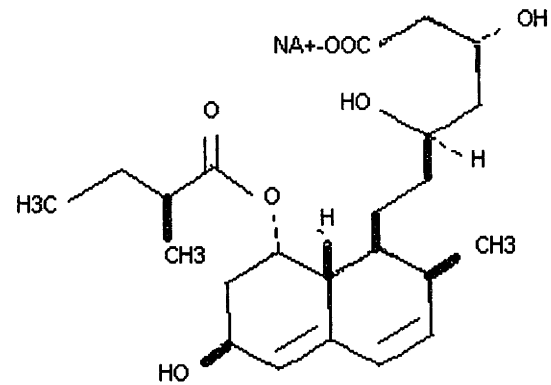
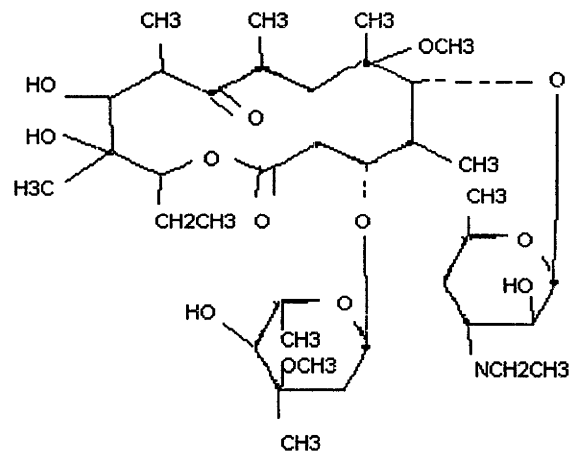
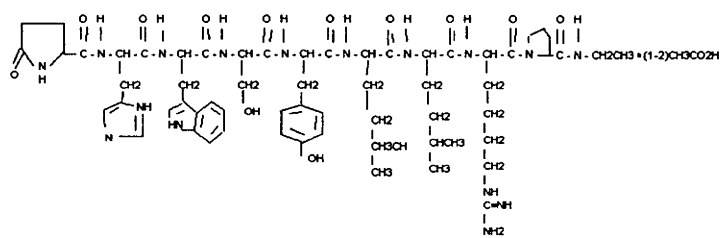
30 LEADING PHARMACEUTICALS IN THE US MARKET

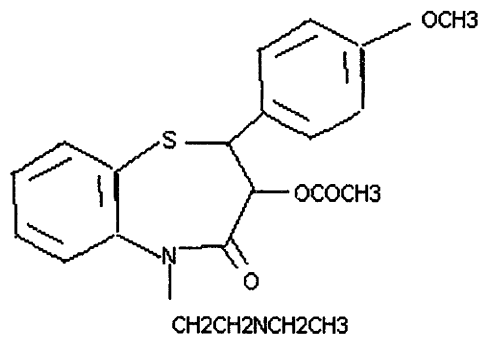
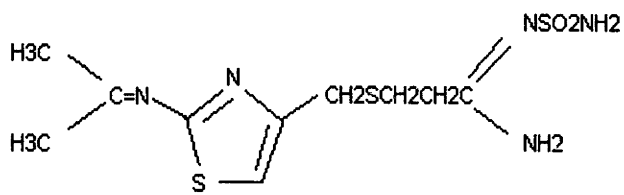
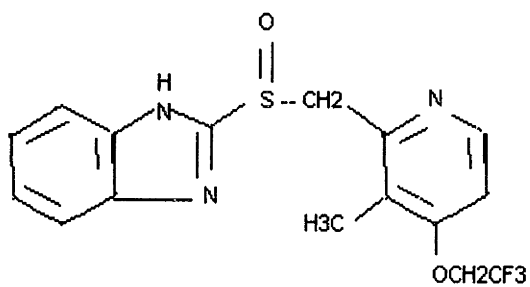
NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Prilosec	Capsule	Omeprazole		YES
Prozac	Capsule	Fluoxetine Hydochloride		(*)
Zocor	Tablet	Simvastatin		YES

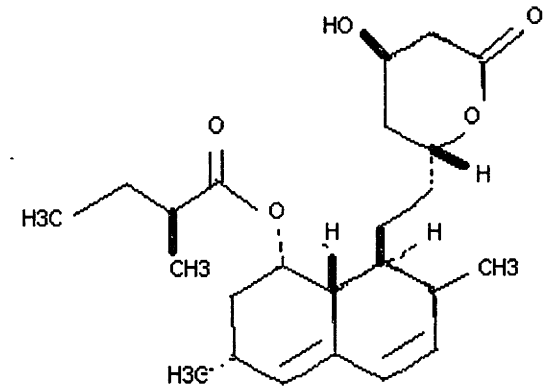
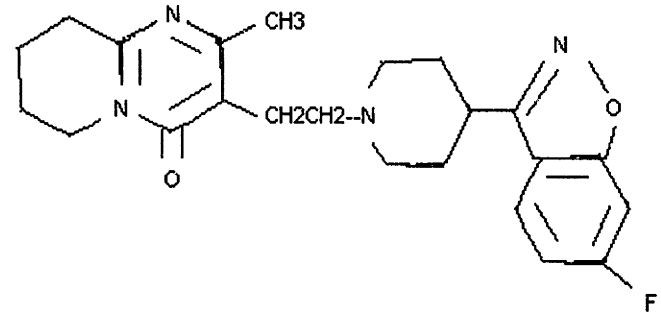
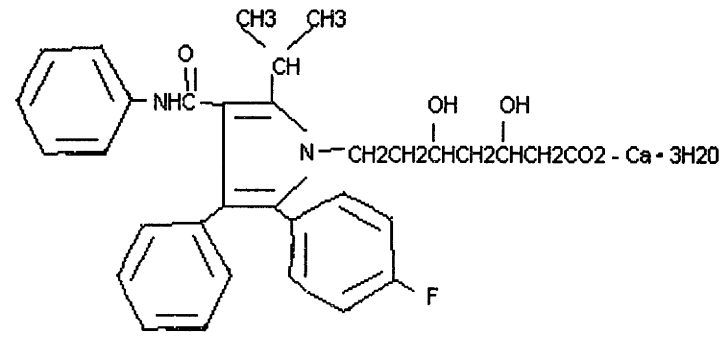
NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Epogen	Injection	---	---	---
Zoloft	Tablet	Sertraline Hydrochloride		YES
Zantac	Tablet	Rantidine Hydrochloride		(*)
Paxil	Tablet	Paroxetine Hydrochloride		YES

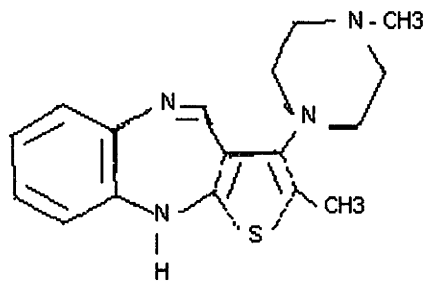
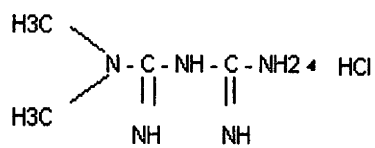
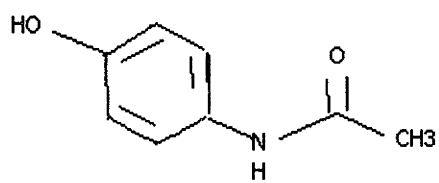
NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Norvasc	Tablet	Besylate salt of amilodipine		(*)
Claritin	Tablet	Loratidiene		YES
Vasotec	Tablet	Enelapril Maleate		

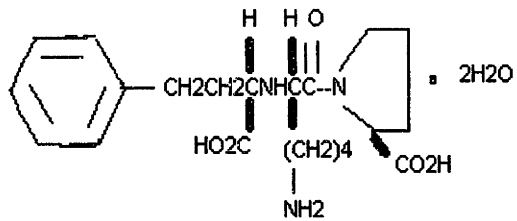
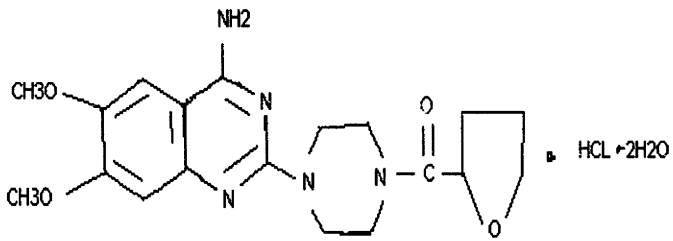
NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Premarin	Tablets	Conjugated Estrogens		YES
Augmentin	Tablet	Amoxicillin and Clavulanate Potassium		YES
Imitrex	Injection	---	---	---
Procardia XL	Tablet	Nifidipine		YES

NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Pravachol	Tablets	Pravastatin Sodium		YES
Biaxin	Tablet	Clarithromycin		YES
Lupron Depot	Powder	Leuprolide Acetate		YES

NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Cipro	Injection	---	---	---
Cardizem	Capsule	Diltiazem Hydrochloride		YES
Pepcid	Tablet	Famotidine		(*)
Prevacid	Capsule	Lansoprazole		YES

NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Mevacor	Tablet	Lovastatin		YES
Risperdal	Tablet	Risperidone		YES
Lipitor	Tablet	Atorvastatin Calcium		YES

NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Zyprexa	Tablet	Olanzapine		YES
Taxol	Injection	---	---	---
Glucophage	Tablet	Metformin Hydrochloride		(*)
Tylenol	Tablet	Acetaminophen		(*)

NAME	DOSAGE FORM	ACTIVE INGREDIENT	STRUCTURAL FORMULA	FLUORESCES?
Zestril	Tablet	Lisinopril		YES
Hytrin	Tablet	Terazosin Hydrochloride		YES

(*) Needs to be determined experimentally.

Appendix II

MANUFACTURING MODEL EQUATIONS

(1) Cash = INTEG (Revenues-Costs, 0)
Units: $
Amount of cash at any given time.

(2) Costs = 0.21*Revenues+Waste*5000('Overhead)
Units: $/Year
Direct and indirect costs associated with the manufacturing process.

(3) FINAL TIME = 20
Units: Year
The final time for the simulation.

(4) INITIAL TIME = 0
Units: Year
The initial time for the simulation.

(5) Input = INTEG (Raw Materials-Throughput, 0)
Units: Tons
Stock of ingredients at any given point in time.

(6) "Meet-specs-rate" = Throughput * Quality
Units: Tons/Year
Amount of finished product that has been proved to meet specifications per unit time.

(7) Ord ([(0,0)-(20,6000)],(0,0),(5,5500),(10,5000),(20,1000))
Units: Tons/Year
Finished product orders per year.

(8) Orders = Ord (Time)
Units: Tons/Year
Finished product orders as a function of time.

(9) Output = INTEG ("Meet-specs-rate"-Sales, 0)
Units: Tons
Stock of finished product.

(10) Overhead = 500000
Units: $/Year
Overhead costs.

(11) Price = 100000
Units: $/Tons
Price of the finished product per ton.

(12) Profits = Revenues-Costs
Units: $/Year
Company's profits per year.

(13) Quality = 0.93 or 0.95
Units: dimensionless
Process quality. Represents the likelihood that a batch will meet specifications.

(14) Raw Materials = Orders
Units: Tons/Year
Flow of formulation's ingredients, including active substance and excipients.

(15) Revenues = Price * Sales
Units: $/Year
Money entering the company as a result of sales.

(16) Sales = Output/TIME STEP
Units: Tons/Year
Rate of finished product sold.

(17) SAVEPER = TIME STEP
Units: Year
The frequency with which output is stored.

(18) Throughput = Input/TIME STEP
Units: Tons/Year
Rate at which materials are processed.

(19) TIME STEP = 0.125
Units: Year
The time step for the simulation.

(20) Waste = INTEG (Waste rate, 0)
Units: Tons
Stock of wasted product.

(21) Waste rate = Throughput * (1-Quality)
Units: Tons/Year
Amount of finished product that does not meet specifications and is therefore wasted.

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