

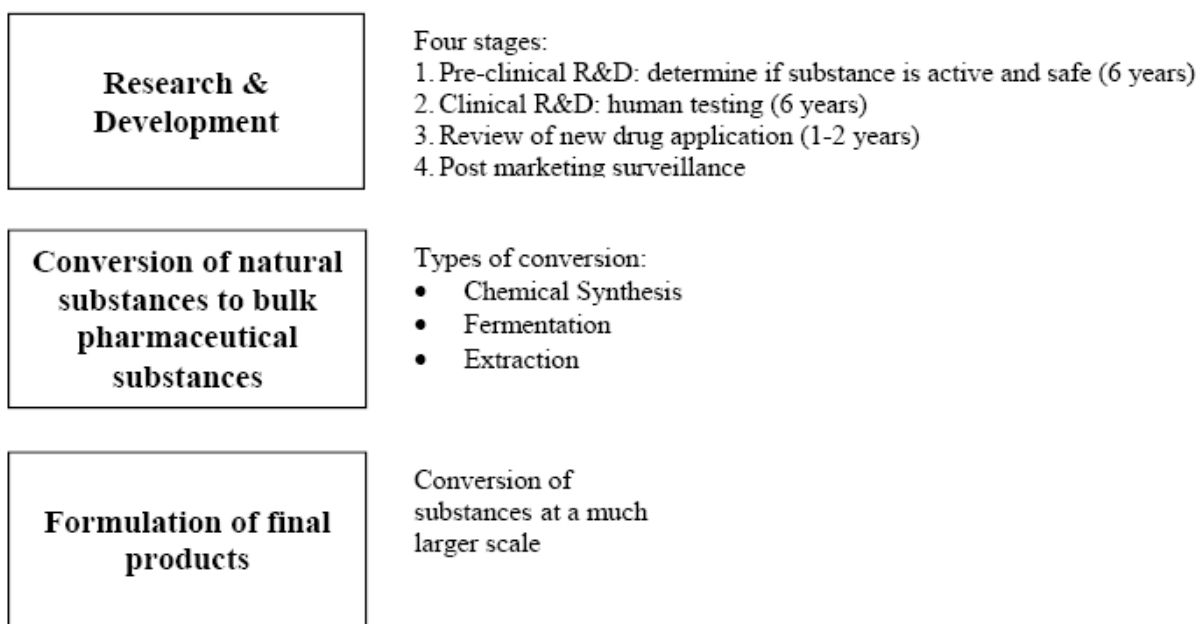
# Energy Efficiency Improvement and Cost Saving Opportunities for the Pharmaceutical Industry

## Process Description

There are three overall stages in the production of bulk pharmaceutical products: (1) R&D, (2) conversion of natural substances to bulk pharmaceuticals, and (3) formulation of final products. Figure 3 provides an overview of the main process steps in the manufacture of pharmaceuticals. Each of these stages is described in more detail below :

Main Process steps in the manufacture of pharmaceuticals :

**Figure 3. Main process steps in the manufacture of pharmaceuticals.**



## Research & Development

Because it is highly regulated, R&D is the longest stage in pharmaceutical product manufacturing. After identifying several thousands of compounds at the beginning stages of R&D, only one will be introduced as a new pharmaceutical drug. Many resources go into this stage of development. The four basic stages of R&D are listed above in Figure 3: (1) pre-clinical R&D, (2) clinical R&D, (3) review of new drug application, and (4) post marketing surveillance. In the pre-clinical R&D stage, compounds are tested on animals to determine biological activity and safety. This testing takes about six years on average to complete. After pre-clinical trials, an Investigational New Drug Application is filed with the U.S. Food and Drug Administration (FDA), the purpose of which is to provide data showing that it is reasonable to begin tests of a new drug on humans.

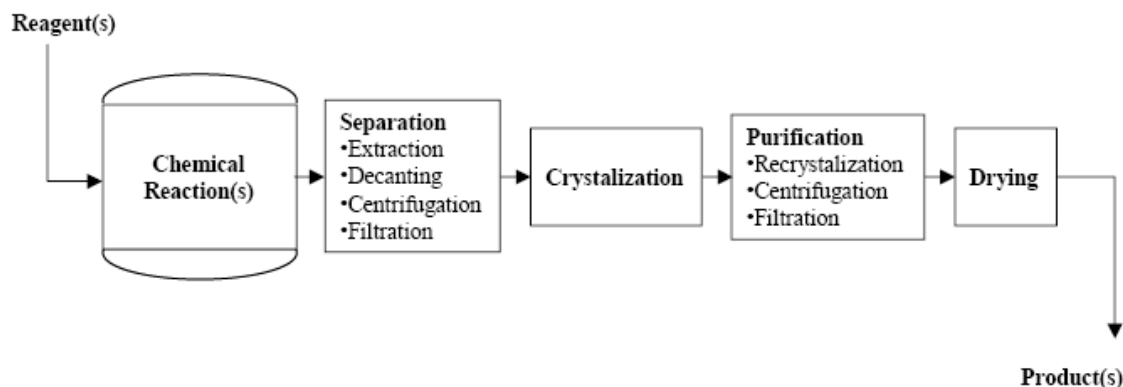
The next stage, clinical R&D, is typically conducted in three phases, each with progressively more human participants. The first phase of clinical R&D determines the safety of a new drug, the second phase determines a new drug's effectiveness, and the third phase provides further confirmation of safety and effectiveness along with determination of any adverse reactions. The clinical R&D stage altogether takes, on average, about six years to complete. The pharmaceutical manufacturer will evaluate various ways of formulating the drug on a larger scale for optimum delivery.

## Conversion to Bulk Pharmaceutical Substances

Bulk pharmaceutical substances are produced via chemical synthesis, extraction, fermentation, or a combination of these processes. Antihistamines, cardiovascular agents, central nervous system stimulants, and hormones are produced by chemical synthesis. Enzymes and digestive aids, allergy relief medicines, hematological agents, insulin, anti-cancer drugs, and vaccines are extracted from naturally-occurring substances. Most steroids, antibiotics, and some food additives, like vitamins, are produced by fermentation. Antibiotics, antineoplastic agents, central nervous system depressants, and vitamins are typically produced by more than one of these three processes.

## Chemical Synthesis

A simplified diagram below is the chemical synthesis process for pharmaceuticals. There are five primary stages in chemical synthesis: (i) reaction, (ii) separation, (iii) crystallization, (iv) purification, and (v) drying. Each of these five stages is described below.



### **(i) Reaction.**

In the reaction process, raw materials are fed into a reactor vessel, where reactions such as alkylations, hydrogenations, or brominations are performed. The most common type of reactor vessel is the kettle-type reactor. These reactors, which are generally made of stainless steel or glass-lined carbon steel, range from 50 to several thousand gallons in capacity. The reactors may be heated or cooled, and reactions may be performed at atmospheric pressure, at elevated pressure, or in a vacuum. Generally, both reaction temperature and pressure are monitored and controlled. Nitrogen may be required for purging the reactor, and some intermediates may be recycled back into the feed. Some reactions are aided via mixing action provided by an agitator. A condenser system may be required to control vent losses. Reactors are often attached to pollution control devices to remove volatile organics or other compounds from vented gases.

### **(ii) Separation.**

The main types of separation processes are extraction, decanting, centrifugation, filtration, and crystallization. Crystallization is used by many plants and is discussed separately below.

The extraction process is used to separate liquid mixtures. Extraction takes advantage of the differences in the solubility of mixture components. A solvent that preferentially combines with only one of the mixture components is added to the mixture. Two streams result from this process: the extract, which is the solvent-rich solution containing the desired mixture component, and the raffinate, which is the residual feed solution containing the non-desired mixture component(s).

Decanting is a simple process that removes liquids from insoluble solids that have settled to the bottom of a reactor or settling vessel. The liquid is either pumped out of the vessel or poured from the vessel, leaving only the solid and a small amount of liquid in the vessel.

Centrifugation is a process that removes solids from a liquid stream using the principle of centrifugal force. A liquid-solid mixture is added to a rotating vessel—or centrifuge—and an outward force pushes the liquid through a filter that retains the solid phase. The solids are manually scraped off the sides of the vessel or with an internal scraper. To avoid air infiltration, centrifuges are usually operated under a nitrogen atmosphere and kept sealed during operation.

Filtration separates fluid/solid mixtures by flowing fluid through a porous media, which filters out the solid particulates. Batch filtration systems widely used by the pharmaceutical industry include plate and frame filters, cartridge filters, nutsche filters, and filter/dryer combinations.

### **(iii) Crystallization.**

Crystallization is a widely used separation technique that is often used alone or in combination with one or more of the separation processes described above. Crystallization refers to the formation of solid crystals from a supersaturated solution. The most common methods of super saturation in practice are cooling, solvent evaporation, and chemical reaction. The solute that has crystallized is subsequently removed from the solution by centrifugation or filtration.

#### **(iv) Purification.**

Purification follows separation, and typically uses the separation methods described above. Several steps are often required to achieve the desired purity level. Recrystallization is a common technique employed in purification. Another common approach is washing with additional solvents, followed by filtration.

#### **(v) Drying.**

The final step in chemical synthesis is drying the product (or intermediates). Drying is done by evaporating solvents from solids. Solvents are then condensed for reuse or disposal. The pharmaceutical industry uses several different types of dryers, including tray dryers, rotary dryers, drum or tumble dryers, or pressure filter dryers. Prior to 1980, the most common type of dryer used by the pharmaceutical industry was the vacuum tray dryer. Today, however, the most common dryers are tumble dryers or combination filter/dryers. In the combination filter/dryer, an input slurry is first filtered into a cake, after which a hot gaseous medium is blown up through the filter cake until the desired level of dryness is achieved. Tumble dryers typically range in capacity from 20 to 100 gallons. In tumble dryers, a rotating conical shell enhances solvent evaporation while blending the contents of the dryer. Tumble dryers utilize hot air circulation or a vacuum combined with conduction from heated surfaces.

### **Product Extraction**

Active ingredients that are extracted from natural sources are often present in very low concentrations. The volume of finished product is often an order of magnitude smaller than the raw materials, making product extraction an inherently expensive process.

Precipitation, purification, and solvent extraction methods are used to recover active ingredients in the extraction process. Solubility can be changed by pH adjustment, by salt formation, or by the addition of an anti-solvent to isolate desired components in precipitation. Solvents can be used to remove active ingredients from solid components like plant or animal tissues, or to remove fats and oils from the desired product. Ammonia is often used in natural extraction as a means of controlling pH.

### **Fermentation**

In fermentation, microorganisms are typically introduced into a liquid to produce pharmaceuticals as by-products of normal microorganism metabolism. The fermentation process is typically controlled at a particular temperature and pH level under a set of aerobic or anaerobic conditions that are conducive to rapid microorganism growth. The process involves three main steps: (i) seed preparation, (ii) fermentation, and (iii) product recovery.

*(i) Seed preparation.* The fermentation process begins with seed preparation, where inoculum (a medium containing microorganisms) is produced in small batches within seed tanks. Seed tanks are typically 1-10% of the size of production fermentation tanks.

*(ii) Fermentation.* After creating the inoculum at the seed preparation stage, the inoculum is introduced into production fermentors. In general, the fermentor is agitated, aerated, and controlled for pH, temperature, and dissolved oxygen levels to optimize the fermentation process. The fermentation process lasts from hours to weeks, depending on the product and process.

*(iii) Product Recovery.* When fermentation is complete, the desired pharmaceutical by-products need to be recovered from the fermented liquid mixture. Solvent extraction, direct precipitation, and ion exchange may be used to recover the product. Additionally, if the product is contained within the microorganism used in fermentation, heating or ultrasound may be required to break the microorganism's cell wall. In solvent extraction, organic solvents are employed to separate the product from the aqueous solution. The product can then be removed from the solvent by crystallization. In direct precipitation, products are precipitated out of solution using precipitating agents like metal salts. In ion exchange, the product adsorbs onto an ion exchange resin and is later recovered from the resin using solvents, acids, or bases.

### **Formulation of Final Products**

The final stage of pharmaceutical manufacturing is the conversion of manufactured bulk substances into final, usable forms. Common forms of pharmaceutical products include tablets, capsules, liquids, creams and ointments, aerosols, patches, and injectable dosages.

To prepare a tablet, the active ingredient is combined with a filler (such as sugar or starch), a binder (such as corn syrup or starch), and sometimes a lubricant (such as magnesium stearate or polyethylene glycol). The filler ensures the proper concentration of the active ingredient; the purpose of the binder is to bond tablet particles together. The lubricant may facilitate equipment operation during tablet manufacture and can also help to slow the disintegration of active ingredients.

Tablets are produced via the compression of powders. Wet granulation or dry granulation processes may be used. In wet granulation, the active ingredient is powdered and mixed with the filler, wetted and blended with the binder in solution, mixed with lubricants, and finally compressed into tablets. Dry granulation is used when tablet ingredients are sensitive to moisture or drying temperatures. Coatings, if used, are applied to tablets in a rotary drum, into which the coating solution is poured. Once coated, the tablets are dried in the rotary drum; they may also be sent to another drum for polishing.

Capsules are first constructed using a mold to form the outer shell of the capsule, which is typically made of gelatin. Temperature controls during the molding process control the viscosity of the gelatin, which in turn determines the thickness of the capsule walls. The capsule's ingredients are then poured (hard capsules) or injected (soft capsules) into the mold.

For liquid pharmaceutical formulations, the active ingredients are weighed and dissolved into a liquid base. The resulting solutions are then mixed in glass-lined or stainless steel vessels and tanks. Preservatives may be added to the solution to prevent mold and bacterial growth. If the liquid is to be used orally or for injection, sterilization is required.

Ointments are made by blending active ingredients with a petroleum derivative or wax base. The mixture is cooled, rolled out, poured into tubes, and packaged.

Creams are semisolid emulsions of oil-in-water or water-in-oil; each phase is heated separately and then mixed together to form the final product.

Table below also shows that R&D and bulk manufacturing are typically the most important energy consuming activities in the pharmaceutical industry.

**Table 3. Distribution of energy use in the pharmaceutical industry.**

	Overall	Plug loads and processes	Lighting	Heating, ventilation and air conditioning (HVAC)
<b>Total</b>	<b>100%</b>	<b>25%</b>	<b>10%</b>	<b>65%</b>
<b>R&amp;D</b>	<b>30%</b>	Microscopes Centrifuges Electric mixers Analysis equipment Sterilization processes Incubators Walk in/reach in areas (refrigeration)	Task and overhead lighting	Ventilation for clean rooms and fume hoods Areas requiring 100% make-up air Chilled water Hot water and steam
<b>Offices</b>	<b>10%</b>	Office equipment including computers, fax machines, photocopiers, printers Water heating (9%)*	Task, overhead, and outdoor lighting	Space heating (25%)* Cooling (9%)* Ventilation (5%)*
<b>Bulk Manufacturing</b>	<b>35%</b>	Centrifuges Sterilization processes Incubators Dryers Separation processes	Task and overhead lighting	Ventilation for clean rooms and fume hoods Areas requiring 100% make-up air Chilled water Hot water and steam
<b>Formulation, Packaging &amp; Filling</b>	<b>15%</b>	Mixers Motors	Mostly overhead, some task	Particle control ventilation
<b>Warehouses</b>	<b>5%</b>	Forklifts Water heating (5%)*	Mostly overhead lighting	Space heating (41%)* Refrigeration (4%)*
<b>Miscellaneous</b>	<b>5%</b>		Overhead	

## Energy Efficiency Opportunities for the Pharmaceutical Industry

A variety of opportunities exist within pharmaceutical laboratories, manufacturing facilities, and other buildings to reduce energy consumption while maintaining or enhancing productivity. Table 4 categorizes available energy efficiency opportunities by the six major activity areas listed above: (1) R&D, (2) bulk manufacturing, (3) formulation, packaging and filling, (4) warehouses, (5) offices, and (6) miscellaneous.

Although technological changes in equipment conserve energy, changes in staff behavior and attitude can also have a great impact. Energy efficiency training programs can help a company's staff incorporate energy efficiency practices into their day-to-day work routines. Personnel at all levels should be aware of energy use and company objectives for energy efficiency improvement. Often such information is acquired by lower-level managers but neither passed up to higher-level management nor passed down to staff. Energy efficiency programs with regular feedback on staff behavior, such as reward systems, have had the best results. Though changes in staff behavior (such as switching off lights or closing windows and doors) often save only small amounts of energy at one time, taken continuously over longer periods they can have a much greater effect than more costly technological improvements. Other staff actions such as the closing of fume hood sashes could result in significant and immediate improvement.

Establishing formal management structures and systems for managing energy that focus on continuous improvement are important strategies for helping companies manage energy use and implement energy efficiency measures.

### Cogeneration:

For industries like pharmaceutical manufacturing that have requirements for process heat, steam, and electricity, the use of combined heat and power (CHP) systems may be able to save energy and reduce pollution. Cogeneration plants are significantly more efficient than standard power plants because they take advantage of waste heat. In addition, transmission losses are minimized when CHP systems are located at or near the plant.

Often, utility companies will work with individual companies to develop CHP systems for their plants. In this scenario, the utility company owns and operates the plant's CHP system; therefore, the company avoids the capital expenditures associated with CHP projects, but gains the benefits of a more energy efficient source of heat and electricity.

In addition to energy savings, CHP systems also have comparable or better availability of service than utility generation. In the automobile industry, for example, typical CHP units are reported to function successfully for 95-98% of planned operating hours. For installations where initial investment is large, potential multiple small-scale CHP units distributed to points of need could be used cost effectively.

Currently, most large-scale CHP systems use steam turbines. Switching to natural gas-based systems will improve the power output and efficiency of the CHP system, due to increased power production capability. Although the overall system efficiency of a steam turbine-based CHP system (80%, HHV) is higher than that of a gas turbine-based CHP system (74%, HHV), the electrical efficiency of a gas turbine-based CHP system is much higher (27-37% for typical industrial scale gas turbines). The power-to-heat ratio of a steam turbine-based CHP system is very low (limited to about 0.2), limiting the output of electricity. The power-to-heat ratio of a gas turbine-based CHP system is much higher (between 0.5 and 1.0), producing more power for the same amount of fuel. This may improve the profitability of a gas-based CHP unit, depending on the price of power to the plant. Modern gas-based CHP systems have low maintenance costs and will reduce emissions of NO<sub>x</sub>, sulfur dioxide, CO<sub>2</sub>, and particulate matter from power generation considerably, especially when replacing a coal-fired boiler.

In general, the energy savings of replacing a traditional system (i.e., a system using boiler-based steam and grid-based electricity) with a standard gas turbine-based CHP unit is estimated at 20%-30%. The efficiency gain will be higher when replacing older or less maintained boilers.

Combined cycles (combining a gas turbine and a back-pressure steam turbine) offer flexibility for power and steam production at larger sites, and potentially at smaller sites as well. Steam-injected gas turbines (STIG) can absorb excess steam (e.g., due to seasonal reduced heating needs) to boost power production by injecting steam into the turbine. The size of typical STIGs starts around 5 MW. This type of turbine uses the exhaust heat from a combustion turbine to turn water into high-pressure steam. This steam is then fed back into the combustion chamber to mix with the combustion gas. The advantages of this system are:

- The added mass flow of steam through the turbine increases power by about 33%.

- The machinery involved is simplified by eliminating the additional turbine and equipment used in combined cycle gas turbine.
- The steam is cool compared to combustion gases helping to cool the turbine interior.
- The system reaches full output more quickly than combined-cycle unit (30 minutes versus 120 minutes).

Additional advantages are that the amounts of power and thermal energy produced by the turbine can be adjusted to meet current power and thermal energy (steam) loads. If steam loads are reduced, the steam can then be used for power generation, increasing output and efficiency. Drawbacks include the additional complexity of the turbine's design. Additional attention to the details of the turbine's design and materials are needed during the design phase. This may result in a higher capital cost for the turbine compared to traditional models.

The economics of a cogeneration system depend strongly on the local situation, including power demand, heat demand, power purchasing and selling prices, natural gas prices, as well as interconnection standards and charges, and utility charges for backup power (backup charges).

### **Trigeneration:**

Furthermore, new CHP systems offer the option of trigeneration, which provides cooling in addition to electricity and heat. Cooling can be provided using either absorption or adsorption technologies, which both operate using recovered heat from the cogeneration process.

Absorption cooling systems take advantage of the fact that ammonia is extremely soluble in cold water and much less so in hot water. Thus, if a water-ammonia solution is heated, it expels its ammonia. In the first stage of the absorption process, a water-ammonia solution is exposed to waste heat from the cogeneration process, whereby ammonia gas is expelled. After dissipating the heat, the ammonia gas—still under high pressure—liquefies. The liquid ammonia flows into a section of the absorption unit where it comes into contact with hydrogen gas. The hydrogen gas absorbs the ammonia gas with a cooling effect. The hydrogen-ammonia mixture then meets a surface of cold water, which absorbs the ammonia again, closing the cycle. Absorption coolers are produced by a number of suppliers.

In contrast, adsorption cooling utilizes the capacity of certain substances to adsorb water on their surface, from where it can be separated again with the application of heat. Adsorption units use hot water from the cogeneration unit. These systems do not use ammonia or corrosive salts, but use silica gel (which also helps to reduce maintenance costs).

The thermal performance of absorption and adsorption systems is similar, with a COP between 0.68 and 0.75. The capital costs of both systems are also comparable. However, the reliability of an adsorption unit is expected to be better and maintenance cost is expected to be lower.

### **Power recovery turbines:**

Steam is often generated at high pressures (typically at 120-150 psig), but often the pressure is reduced (to as low as 10-15 psig) to allow the steam to be used by different process. Typically, pressure reduction is accomplished through a pressure reduction valve, which does not recover the energy embodied in the pressure drop. This energy could be recovered by using a micro scale-back pressure steam turbine, which is produced by several manufacturers. Applications of this technology have been commercially demonstrated for campus facilities and in the pulp & paper, food, and lumber industries. Power recovery turbines are capable of producing 13.5kWh/MBtu steam. The actual power generation on a particular site will vary depending on steam pressures and steam uses.

Reference:

<http://www.osti.gov/bridge/servlets/purl/860227-mj5IR5/860227.PDF>