

SYNTHESIZED PHARMACEUTICAL MANUFACTURING PLANTS

A. PROCESS DESCRIPTION

The synthesis of medicinal chemicals may be done in a very small facility producing only one chemical or in a large integrated facility producing many chemicals by various processes. Most pharmaceutical manufacturing plants are relatively small. Organic chemicals are used as raw materials and as solvents. Nearly all products are made using batch operations. In addition, several different products or intermediates are likely to be made in the same equipment at different times during the year; these products, then, are made in "campaigned" equipment. Equipment dedicated to the manufacture of a single product is rare, unless the product is made in large volume.

Production activities of the pharmaceutical industry can be divided into the following categories:

1. **Chemical Synthesis** - the manufacture of pharmaceutical products by chemical synthesis.
2. **Fermentation** - the production and separation of medicinal chemicals such as antibiotics and vitamins from microorganisms.
3. **Extraction** - the manufacture of botanical and biological products by the extraction of organic chemicals from vegetative materials or animal tissues.
4. **Formulation and Packaging** - the formulation of bulk pharmaceuticals into various dosage forms such as tablets, capsules, injectable solutions, ointments, etc., that can be taken by the patient immediately and in accurate amount.

Production of a synthesized drug consists of one or more chemical reactions followed by a series of purifying operations. Production lines may contain reactors, filters, centrifuges, stills, dryers, process tanks, and crystallizers piped together in a specific arrangement. Arrangements can be varied in some instances to accommodate production of several compounds. A very small plant may have only a few pieces of process equipment but a large plant can contain literally hundreds of pieces.

Exhibit 1 shows a typical flow diagram for a batch synthesis operation. To begin a production cycle, the reactor may be water washed and perhaps dried with a solvent. Air or nitrogen is usually used to purge the tank after it is cleaned. Following cleaning, solid reactants and solvent are charged to the glass batch reactor equipped with a condenser (which is usually water-cooled). Other volatile compounds may be produced as product or by-products. Any remaining unreacted volatile compounds are distilled off. After the reaction and solvent removal are complete, the pharmaceutical product is transferred to a holding tank. After each batch is placed in the holding tank, three to four washes of water or solvent may be used to remove any remaining reactants and by-products. The solvent used to wash may also be evaporated from the reaction product.

EXHIBIT 1: Typical Synthetic Organic Medicinal Chemical Process

The crude product may then be dissolved in another solvent and transferred to a crystallizer for purification. After crystallization, the solid material is separated from the remaining solvent by centrifugation. While in the centrifuge the product cake may be washed several times with

water or solvent. Tray, rotary, or fluid-bed dryers may then be employed for final product finishing.

B. SOURCES OF POLLUTION

Exhibit 2 identifies pollutants from a typical pharmaceutical process. Volatile organic compounds may be emitted from a variety of sources within plants synthesizing pharmaceutical products. The following process components have been identified as VOC sources and will be discussed further: reactors, distillation units, dryers, crystallizers, filters, centrifuges, extractors, and tanks.

1. Reactors

The typical batch reactor is glass lined or stainless steel and has a capacity of 2,000 to 11,000 liters (500-3000 gallons). For maximum utility the tanks are usually jacketed to permit temperature control of reactions. Generally, each tank is equipped with a vent which may discharge through a condenser. Batch reactors can be operated at atmospheric pressure, elevated pressure, or under vacuum, and may be used in a variety of ways. Besides hosting chemical reactions, they can act as mixers, heaters, holding tanks, crystallizers, and evaporators.

A typical reaction cycle takes place as follows. After the reactor is clean and dry, the appropriate raw materials, usually including some solvent(s), are charged for the next product run. Liquids are normally added first, then solid reactants are charged through the manhole. After charging is complete, the vessel is closed and the temperature raised, if necessary, via reactor jacket heating. The purpose of heating may be to increase the speed of reaction or to reflux the contents for a period which may vary from 15 minutes to 24 hours. During refluxing, the liquid phase may be "blanketed" by an inert gas, such as nitrogen, to prevent oxidation or other undesirable side reactions. Upon completion of the reaction, the vessel may be used as a distillation pot to vaporize the liquid phase (solvent), or the reaction products may be pumped out so the vessel can be cooled to begin the next cycle.

2. Distillation Operations

Distillation may be performed by either of two principal methods. In the first method, the liquid mixture to be separated is boiled and vapors produced are condensed and prevented from returning to the still. In the second method, part of the condensate is allowed to return to the still so that the returning liquid is brought into intimate contact with the vapors on the way to the condenser. Either of these methods may be conducted as a batch or continuous operation.

Exhibit 2: Major Pollutants From Solvent Use in Pharmaceutical Production^a

(Solvent)	Pollutant			
	Ultimate Disposition (%)			
	Air Emissions	Sewer	Incineration	Solid

Waste	Product			
Acetic anhydride	1	57		42
Acetone	14	22	38	719
Amyl alcohol	42	58		
Benzene	29	37	16	810
Carbon tetrachloride	11	7	82	
Dimethyl formamide	71	3	20	6
Ethanol	10	6	7	176
Ethyl acetate	30	47	20	3
Isopropanol	14	17	17	745
Methanol	31	45	14	64
Methylene chloride	53	5	20	22
Solvent B (hexanes)	29	2	69	
Toluene	31	14	26	29
Xylene	6	19	70	5

^a Numbers are based on a survey of 26 U.S. manufacturers

3. Separation Operations

Several separation mechanisms employed by the industry are extraction, centrifugation, filtration, and crystallization.

Extraction is used to separate components of liquid mixtures or solutions. This process utilizes differences in solubilities of the components rather than differences in volatilities (as in distillation); i.e., solvent is used that will preferentially combine with one of the components. The resulting mixture to be separated is made up of the extract which contains the preferentially dissolved material and the raffinate which is the residual phase.

Centrifuges are used to remove intermediate or product solids from a liquid stream. Center-slung, stainless steel basket centrifuges are most commonly used in the industry. To begin the process, the centrifuge is started and the liquid slurry is pumped into it. An inert gas, such as nitrogen, is sometimes introduced into the centrifuge to avoid the buildup of an explosive atmosphere. The spinning centrifuge strains the liquid through small basket perforations. Solids retained in the basket are then scraped from the sides of the basket and unloaded by scooping them out from a hatch on the top of the centrifuge or by dropping them through the centrifuge bottom into receiving carts.

Filtration is used to remove solids from a liquid; these solids may be product, process intermediates, catalysts, or carbon particles (e.g., from a decoloring step). Pressure filters, such as shell and leaf filters, cartridge filters, and plate and frame filters are usually used. Atmospheric and vacuum filters have their applications too. The normal filtration procedure is simply to force or draw the mother liquor through a filtering medium. Following filtration, the retained solids are removed from the filter medium for further processing.

Crystallization is a means of separating an intermediate or final product from a liquid solution. This is done by creating a supersaturated solution, one in which the desired compound will form crystals. If performed properly and in the absence of competing crystals, crystallization can produce a highly purified product.

4. Dryers

Dryers are used to remove most of the remaining solvent in a centrifuged or filtered product. This is done by evaporating solvent until an acceptable level of “dryness” is reached. Evaporation is accelerated by applying heat and/or vacuum to the solvent-laden product or by blowing warm air around or through it. Because a product may degrade under severe drying conditions, the amount of heat, vacuum, or warm air flow is carefully controlled. Several types of dryers are used in synthetic drug manufacture. Some of the most widely used are tray dryers, rotary dryers, and fluid bed dryers.

5. Storage and Transfer

Volatile organic compounds are stored in tank farms, 233-liter (55 gallon) drums, and sometimes in process holding tanks. Storage tanks in tank farms range in size from about 2,000-20,000 liters (500-5,000 gallons). In-plant transfer of VOCs is done mainly by pipeline, but also may be done manually (e.g. loading or unloading drums). Raw materials are delivered to the plant by tank truck, rail car, or in drums.

C. POLLUTANTS AND THEIR CONTROL

1. Air Emissions

Solvents constitute the predominant VOC emission from production. Plants differ in the amount of organics used; this results in widely varying VOC emission rates. Therefore, some plants may be negligible VOC sources while others are highly significant. In addition, all types of equipment previously described have the potential to emit air pollutants.

a. Reactors

Reactor emissions stem from the following causes: (a) displacement of air containing VOC during reactor charging, (b) solvent evaporation during the reaction cycle (often VOC's are emitted along with reaction by-product gases which act as carriers), (c) overhead condenser venting uncondensed VOC during refluxing, (d) purging vaporized VOC remaining from a solvent wash, and (e) opening reactors during a reaction cycle to take samples, determine reaction end-points, etc.

Equipment options available to control emissions from reactors include surface condensers, carbon adsorbers, liquid scrubbers, and vapor incinerators (under certain conditions). Condensers are often included on reactor systems as normal process control equipment.

b. Distillation Operations

Volatile organic compounds may be emitted from the distillation condensers used to recover evaporated solvents. The magnitude of emissions depends on the operating parameters of the condenser, the type and quantity of organic being condensed, and the quantity of inerts entrained in the organic.

Emissions from distillation condensers can be controlled through the use of aftercondensers, scrubbers, and carbon adsorbers.

c. Separation Operations

1. Emissions from **batch extraction** stem mainly from displacement of vapor while pumping solvent into the extractor and while purging or cleaning the vessel after extraction. Some VOCs also may be emitted while the liquids are being agitated. A column extractor may emit VOCs while the column is being filled, during extraction, or when it is emptied after extraction. Emissions occur not only at the extractor itself, but also at associated surge tanks. These tanks may emit significant amounts of solvent due to working losses as the tank is repeatedly filled and emptied during the extraction process.
2. A large potential source of emissions is the open-type **centrifuge** which permits large quantities of air to contact and evaporate solvents. The industry trend is toward completely enclosed centrifuges and, in fact, many plants have no open-type centrifuges. If an inert gas blanket is used, it can act as a transport vehicle for solvent vapor. This vapor may be vented directly from the centrifuge or from a process tank receiving the mother liquor. However, this emission source is likely to be small because the inert gas flow is only a few cubic feet per minute.
3. If **crystallization** is done mainly through cooling of a solution, there will be little VOC emission. In fact, the equipment may be completely enclosed. However, when the crystallization is done by solvent evaporation, there is greater potential for emissions. Emissions will be significant if evaporated solvent is vented directly to the atmosphere. It is more likely, however, that the solvent will be passed through a condenser or from a vacuum jet (if the crystallization is done under vacuum), thereby minimizing emissions.

Several add-on control technologies may be used on the separation equipment described above. Condensers, which can be applied to individual systems, are effective and may be the least costly option. Water scrubbers also have found wide usage in the industry. They are versatile and capable of handling a variety of VOCs which have appreciable water solubility. Scrubbers can be either small or quite large; thus, they can be designed to handle emissions from a single source or from many sources (via a manifold system). Carbon adsorbers can be and have been employed on vents from separation operations. Several vents may be ducted to an adsorber because it is likely that emissions from a single source would not warrant the expense of a carbon adsorption unit. Finally, in some instances, incinerators may be applicable. They may not be a good choice, however, since the expected variability from these emission sources might make continuous incinerator operation difficult.

4. Enclosed **pressure filters** normally do not emit VOCs during a filtering operation. Emissions can occur, however, when a filter is opened to remove collected solids. Emissions can also occur if the filter is purged (possibly with nitrogen or steam) before cleaning. The purge gas will entrain evaporated solvent and probably be vented through the receiving tank for the filtered liquid. The largest VOC emissions are from vacuum drum filters which are operated by

pulling solvent through a precoated filter drum. Potential emissions are significant both at or near the surface of the drum and from the ensuing waste stream. These filters can be shrouded or enclosed for control purposes.

d. Dryers

Dryers are potentially large emission sources. Emission rates vary during a drying cycle and are greatest at the beginning of the cycle and least at the end of the cycle. Drying cycle times can range from several hours to several days. Control options used for dryers include condensation, wet scrubbing, adsorption, and incineration.

1. Condensers are often the first control devices selected when dealing with air pollution from vacuum dryers. They can also be used by themselves or in series with another device. Condensers are not typically used on air dryers because the emissions are dilute.
2. Wet scrubbers have also been used to control many plant sources, including dryers. They can also remove particulates generated during drying. For water soluble compounds, VOC absorption efficiencies can be quite high (i.e. 98-99%).
3. Carbon adsorbers may also be used, especially following a condenser. Not only will overall efficiency increase but a longer regeneration cycle can be used in the adsorber.
4. Vapor incinerators might be viable controls although varying VOC flows to the incinerator may present operating problems.

e. Tanks

The vapor space in a tank will in time become saturated with the stored organics. During tank filling vapors are displaced, causing an emission or a "working loss." Some vapors are also displaced as the temperature of the stored VOC rises, such as from solar radiation, or as atmospheric pressure drops; these are "breathing losses." The amount of loss depends on type of VOC stored, size of tank, type of tank, diurnal temperature changes, and tank throughput.

Emissions from storage or process holding vessels may be reduced with varying efficacy through the use of vapor balance systems, conservation vents, vent condensers, pressurized tanks, and carbon adsorption.

2. Solid and Liquid Wastes

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The manufacture of the following types of pharmaceutical products can generate hazardous wastes:

- Organic medicinal chemicals
- Medicinals from animal glands
- Inorganic medicinal chemicals
- Antibiotics

- Biological products
- Botanicals
- Miscellaneous products

The largest quantities of hazardous waste are from the production of organic medicinal chemicals and antibiotics. Exhibit 3 identifies potential hazardous wastes from pharmaceutical production:

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Exhibit 3: Potential Hazardous Wastes from Pharmaceutical Production

Product or Operation (dry metric tons/yr) ¹	Potential Hazardous Wastes	Estimated U.S. Generation
• Organic medicinal chemicals	• Heavy metals	
• Terpenes, steroids, vitamins, tranquilizers		
• Ethylene dichloride		
• Acetone, toluene, xylene, benzene isopropyl alcohol, methanol, acetonitrile		
• Zinc, arsenic, chromium, copper, mercury		1,700
13,600		
3,400		
23,800		
2,700		
• Inorganic medicinal chemicals	• Selenium	200
• Antibiotics	• Amyl acetate, butanol, butyl acetate, MIBK, acetone, ethylene glycol, monomethyl ether	12,000
• Botanicals	• Ethylene dichloride, methylene chloride	
• Methanol, acetone, ethanol, chloroform, heptane, naphtha, benzene		
• Misc. organics	100	
100		
700		
• Medicinals from animal glands	• Misc. organics	800
• Biological products	• Vaccines, toxoids, serum, etc.	
• Ethanol	500	
300		
Misc. sources	Misc. solvents	63,900

¹Hazardous waste amounts are for 1973 estimated total U.S. generation.

D. REFERENCES

1. Control of Organic Emissions from the Manufacture of Synthesized Pharmaceutical Products, Environmental Protection Agency, Research Triangle Park, NC, December 1978.
2. The Handbook of Hazardous Waste Management, Metry, Amir A., Ph.D., P.E., Technomic Publication, January, 1980.

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