6.13 Pharmaceuticals Production

6.13.1 Process Description

Thousands of individual products are categorized as pharmaceuticals. These products usually are produced in modest quantities in relatively small plants using batch processes. A typical pharmaceutical plant will use the same equipment to make several different products at different times. Rarely is equipment dedicated to the manufacture of a single product.

Organic chemicals are used as raw materials and as solvents, and some chemicals such as ethanol, acetone, isopropanol, and acetic anhydride are used in both ways. Solvents are almost always recovered and used many times.

In a typical batch process, solid reactants and solvent are charged to a reactor where they are held (and usually heated) until the desired product is formed. The solvent is distilled off, and the crude residue may be treated several times with additional solvents to purify it. The purified material is separated from the remaining solvent by centrifuge and finally is dried to remove the last traces of solvent. As a rule, solvent recovery is practiced for each step in the process where it is convenient and cost effective to do so. Some operations involve very small solvent losses, and the vapors are vented to the atmosphere through a fume hood. Generally, all operations are carried out inside buildings, so some vapors may be exhausted through the building ventilation system.

Certain pharmaceuticals — especially antibiotics — are produced by fermentation processes. In these instances, the reactor contains an aqueous nutrient mixture with living organisms such as fungi or bacteria. The crude antibiotic is recovered by solvent extraction and is purified by essentially the same methods described above for chemically synthesized pharmaceutical. Similarly, other pharmaceuticals are produced by extraction from natural plant or animal sources. The production of insulin from hog or beef pancreas is an example. The processes are not greatly different from those used to isolate antibiotics from fermentation broths.

6.13.2 Emissions And Controls

Emissions consist almost entirely of organic solvents that escape from dryers, reactors, distillation systems, storage tanks, and other operations. These emissions are exclusively nonmethane organic compounds. Emissions of other pollutants are negligible (except for particulates in unusual circumstances) and are not treated here. It is not practical to attempt to evaluate emissions from individual steps in the production process or to associate emissions with individual pieces of equipment because of the great variety of batch operations that may be carried out at a single production plant. It is more reasonable to obtain data on total solvent purchases by a plant and to assume that these represent replacements for solvents lost by evaporation. Estimates can be refined by subtracting the materials that do not enter the air because of being incinerated or incorporated into the pharmaceutical product by chemical reaction.

If plant-specific information is not available, industrywide data may be used instead. Table 6.13-1 lists annual purchases of solvents by U. S. pharmaceutical manufacturers and shows the ultimate disposition of each solvent. Disposal methods vary so widely with the type of solvent that it is not possible to recommend average factors for air emissions from generalized solvents. Specific information for individual solvents must be used. Emissions can be estimated by obtaining

Table 6.13-1. SOLVENT PURCHASES AND ULTIMATE DISPOSITION BY PHARMACEUTICAL MANUFACTURERS[a]

Solvent	Annual Purchase (megagrams)	Ultimate Disposition (%)					Liquid Density lb/gal @ 68 °F
		Air Emissions	Sewer	Incineration	Solid Waste or Contract Haul	Product	
Acetic Acid	930	1	82	—	—	17	8.7
Acetic Anhydride	1,265	1	57	—	—	42	9.0
Acetone	12,040	14	22	38	7	19	6.6
Acetonitrile	35	83	17	—	—	—	6.6
Amyl Acetate	285	42	58	—	—	—	7.3
Amyl Alcohol	1,430	99	—	—	—	1	6.8
Benzene	1,010	29	37	16	8	10	7.3
Blendan (AMOCO)	530	—	—	—	—	100	NA
Butanol	320	24	8	1	36	31	6.8
Carbon Tetrachloride	1,850	11	7	82	—	—	13.3
Chloroform	500	57	5	—	38	—	12.5
Cyclohexylamine	3,930	—	—	—	—	100	7.2
o-Dichlorobenzene	60	2	98	—	—	—	10.9
Diethylamine	50	94	6	—	—	—	5.9
Diethyl Carbonate	30	4	71	—	—	25	8.1
Dimethyl Acetamide	95	7	—	—	93	—	7.9
Dimethyl Formamide	1,630	71	3	20	6	—	7.9

Table 6.13-1 (cont.).

Solvent	Annual Purchase (megagrams)	Ultimate Disposition (%)					Liquid Density lb/gal @ 68°F
		Air Emissions	Sewer	Incineration	Solid Waste or Contract Haul	Product	
Dimethylsulfoxide	750	1	28	71	—	—	11.1
1,4-Dioxane	43	5	—	—	95	—	8.6
Ethanol	13,230	10	6	7	1	76	6.6
Ethyl Acetate	2,380	30	47	20	3	—	7.5
Ethyl Bromide	45	—	100	—	—	—	12.1
Ethylene Glycol	60	—	100	—	—	—	9.3
Ethyl Ether	280	85	4	—	11	—	6.0
Formaldehyde	30	19	77	—	—	4	—[b]
Formamide	440	—	67	—	26	7	9.5
Freons	7,150	0.1	—	—	—	99.9	—[c]
Hexane	530	17	—	15	68	—	5.5
Isobutyraldehyde	85	50	50	—	—	—	6.6
Isopropanol	3,850	14	17	17	7	45	6.6
Isopropyl Acetate	480	28	11	61	—	—	7.3
Isopropyl Ether	25	50	50	—	—	—	6.0
Methanol	7,960	31	45	14	6	4	6.6
Methyl Cellosolve	195	47	53	—	—	—	8.7

Table 6.13-1 (cont.).

Solvent	Annual Purchase (megagrams)	Ultimate Disposition (%)					Liquid Density lb/gal @ 68° F
		Air Emissions	Sewer	Incineration	Solid Waste or Contract Haul	Product	
Methylene Chloride	10,000	53	5	20	22	—	11.1
Methyl Ethyl Ketone	260	65	12	23	—	—	6.7
Methyl Formate	415	—	74	—	12	14	8.2
Methyl Isobutyl Ketone	260	80	—	—	—	20	6.7
Polyethylene Glycol 600	3	—	—	—	—	100	9.5
Pyridine	3	—	100	—	—	—	8.2
Skelly Solvent B (hexanes)	1,410	29	2	69	—	—	5.6
Tetrahydrofuran	4	—	—	100	—	—	7.4
Toluene	6,010	31	14	26	29	—	7.2
Trichloroethane	135	100	—	—	—	—	11.3
Xylene	3,090	6	19	70	5	—	7.2

[a] These data were reported by 26 member companies of the Pharmaceutical Manufacturers Association, accounting for 53% of pharmaceutical sales in 1975.
[b] Sold as aqueous solutions containing 37% to 50% formaldehyde by weight.
[c] Some Freons are gases, and others are liquids weighing 12-14 lb/gal.

plant-specific data on purchases of individual solvents and computing the quantity of each solvent that evaporates into the air, either from information in Table 6.13-1 or from information obtained for the specific plant under consideration. If solvent volumes are given, rather than weights, liquid densities in Table 6.13-1 can be used to compute weights.

Table 6.13-1 gives for each plant the percentage of each solvent that is evaporated into the air and the percentage that is flushed into the sewer. Ultimately, much of the volatile material from the sewer will evaporate and will reach the air somewhere other than the pharmaceutical plant. Thus, for certain applications it may be appropriate to include both the air emissions and the sewer disposal in an emissions inventory that covers a broad geographic area.

Since solvents are expensive and must be recovered and reused for economic reasons, solvent emissions are controlled as part of the normal operating procedures in a pharmaceutical industry. In addition, most manufacturing is carried out inside buildings, where solvent losses must be minimized to protect the health of the workers. Water- or brine-cooled condensers are the most common control devices, with carbon adsorbers in occasional use. With each of these methods, solvent can be recovered. Where the main objective is not solvent reuse but is the control of an odorous or toxic vapor, scrubbers or incinerators are used. These control systems are usually designed to remove a specific chemical vapor and will be used only when a batch of the corresponding drug is being produced. Usually, solvents are not recovered from scrubbers and reused and, of course, no solvent recovery is possible from an incinerator.

It is difficult to make a quantitative estimate of the efficiency of each control method because it depends on the process being controlled, and pharmaceutical manufacture involves hundreds of different processes. Incinerators, carbon adsorbers, and scrubbers have been reported to remove greater than 90 percent of the organics in the control equipment inlet stream. Condensers are limited in that they can only reduce the concentration in the gas stream to saturation at the condenser temperature, but not below that level. Lowering the temperature will, of course, lower the concentration at saturation, but it is not possible to operate at a temperature below the freezing point of one of the components of the gas stream.

Reference For Section 6.13

1. *Control Of Volatile Organic Emissions From Manufacture Of Synthesized Pharmaceutical Products*, EPA-450/2-78-029, U. S. Environmental Protection Agency, Research Triangle Park, NC, December 1978.