Pharmaceuticals Manufacturing

Industry Description and Practices

The pharmaceutical industry includes the manufacture, extraction, processing, purification, and packaging of chemical materials to be used as medications for humans or animals. Pharmaceutical manufacturing is divided into two major stages: the production of the active ingredient or drug (primary processing, or manufacture) and secondary processing, the conversion of the active drugs into products suitable for administration. This document deals with the synthesis of the active ingredients and their usage in drug formulations to deliver the prescribed dosage. Formulation is also referred to as galenical production.

The main pharmaceutical groups manufactured include:

- Proprietary ethical products or prescription-only medicines (POM), which are usually patented products
- General ethical products, which are basically standard prescription-only medicines made to a recognized formula that may be specified in standard industry reference books
- Over-the counter (OTC), or nonprescription, products.

The products are available as tablets, capsules, liquids (in the form of solutions, suspensions, emulsions, gels, or injectables), creams (usually oil-in-water emulsions), ointments (usually water-in-oil emulsions), and aerosols, which contain inhalable products or products suitable for external use. Propellants used in aerosols include chlorofluorocarbons (CFCs), which are being phased out. Recently, butane has been used as a propellant in externally applied products.

The major manufactured groups include:

- Antibiotics such as penicillin, streptomycin, tetracyclines, chloramphenicol, and antifungals
- Other synthetic drugs, including sulfa drugs, antituberculosis drugs, antileprotic drugs, analgesics, anesthetics, and antimalarials
- Vitamins
- Synthetic hormones
- Glandular products
- Drugs of vegetable origin such as quinine, strychnine and brucine, emetine, and digitalis glycosides
- Vaccines and sera
- Other pharmaceutical chemicals such as calcium gluconate, ferrous salts, nikethamide, glycerophosphates, chloral hydrate, saccharin, antihistamines (including meclozine, and buclozine), tranquilizers (including meprobamate and chloropromoazine), antifilarials, diethyl carbamazine citrate, and oral antidiabetics, including tolbutamide and chloropropamide
- Surgical sutures and dressings.

The principal manufacturing steps are (a) preparation of process intermediates; (b) introduction of functional groups; (c) coupling and esterification; (d) separation processes such as washing and stripping; and (e) purification of the final product. Additional product preparation steps include granulation; drying; tablet pressing, printing, and coating; filling; and packaging. Each of these steps may generate air emissions, liquid effluents, and solid wastes.

The manufacture of penicillin, for example, involves the batch fermentation—using 100–200 cubic meter (m^3) batches—of maize steep liquor or a similar base, with organic precursors added to control the yield. Specific mold culture such

as *Penicillium chrysogenum* for Type II is inoculated into the fermentation medium. Penicillin is separated from the fermentation broth by solvent extraction. The product is further purified using acidic extraction. This is followed by treatment with a pyrogen-free distilled water solution containing the alkaline salt of the desired element. The purified aqueous concentrate is separated from the solvent in a supercentrifuge and pressurized through a biological filter to remove the final traces of bacteria and pyrogens. The solution can be concentrated by freeze drying or vacuum spray drying. Oil-soluble procaine penicillin is made by reacting a penicillin concentrate (20–30%) with a 50% aqueous solution of procaine hydrochloride. Procaine penicillin crystallizes from this mixture.

The manufacture of pharmaceuticals is controlled by Good Management Practices (GMP) in some countries. (See, for example, United Kingdom 1993.) Some countries require an environmental assessment (EA) report addressing the fate and toxicity of drugs and their metabolized by-products. The EA data relate to the parent drug, not to all metabolites, and include (a) physical and chemical properties; (b) biodegradability; (c) photolysis propensity; (d) aqueous toxicity to fish; (e) prediction of existing or planned treatment plant to treat wastes and wastewaters; and (f) treatment sequences that are capable of treating wastes and wastewaters.

Waste Characteristics

The principal air pollutants are volatile organic compounds (VOCs) and particulate matter (PM).

Liquid effluents resulting from equipment cleaning after batch operation contain toxic organic residues. Their composition varies, depending on the product manufactured, the materials used in the process, and other process details. Cooling waters are normally recirculated. Some wastewaters may contain mercury, in a range of 0.1–4 milligrams per liter (mg/l), cadmium (10–600 mg/l), isomers of hexachlorocyclohexane, 1,2-dichloroethane, and solvents. Typical amounts released with the wastewater are 25 kilograms of biochemical oxygen demand (BOD) per metric ton of product (kg/t), or 2,000 mg/l; 50 kg/t chemical oxygen demand (COD), or 4,000 mg/l; 3 kg/t of suspended solids; and up to 0.8 kg/t of phenol.

The principal solid wastes of concern include process and effluent treatment sludges, spent catalysts, and container residues. Approximately 200 kg wastes per ton of product of waste are generated. Some solid wastes contain significant concentrations of spent solvents and other toxic organics.

Pollution Prevention and Control

Every effort should be made to replace highly toxic and persistent ingredients with degradable and less toxic ones. Recommended pollution prevention measures are as follows:

- Meter and control the quantities of active ingredients to minimize wastage.
- Reuse by-products from the process as raw materials or as raw material substitutes in other processes.
- Recover solvents used in the process by distillation or other methods.
- Give preference to the use of nonhalogenated solvents.
- Use automated filling to minimize spillage.
- Use “closed” feed systems into batch reactors.
- Use equipment washdown waters and other process waters (such as leakages from pump seals) as makeup solutions for subsequent batches.
- Recirculate cooling water.
- Use dedicated dust collectors to recycle recovered materials.
- Vent equipment through a vapor recovery system.
- Use loss-free vacuum pumps.
- Return toxic materials packaging to the supplier for reuse, or incinerate/destroy it in an environmentally acceptable manner.
- Minimize storage time of off-specification products through regular reprocessing.
- Find productive uses for off-specification products to avoid disposal problems.
- Minimize raw material and product inventory to avoid degradation and wastage.
- Use high-pressure hoses for equipment cleaning to reduce wastewater.
- Provide stormwater drainage and avoid contamination of stormwater from process areas.

- Label and store toxic and hazardous materials in secure, bunded areas. Spillage should be collected and reused.

Where appropriate, a pharmaceutical manufacturing plant should prepare a hazard assessment and operability study and also prepare and implement an emergency plan that takes into account neighboring land uses and the potential consequences of an emergency. Measures to avoid the release of harmful substances should be incorporated in the design, operation, maintenance, and management of the plant.

Pollution Reduction Targets

Implementation of cleaner production processes and pollution prevention measures can yield both economic and environmental benefits.

Specific reduction targets for the different processes have not been determined. In the absence of specific pollution reduction targets, new plants should always achieve better than the industry averages quoted in the section on Waste Characteristics. Table 2, below, presents the maximum effluent levels after the addition of pollution control measures**.**

Vapor recovery systems should be installed to control air emissions. Wastewaters and treated effluents should be recycled to the extent feasible.

Treatment Technologies

Air Emissions

Stack gas scrubbing, carbon adsorption (for toxic organics), and baghouses (for particulate matter removal) are applicable and effective technologies for minimizing the release of significant pollutants to air. In some cases, biological filters are also used to reduce emissions of organics. Combustion is used for the destruction of toxic organics.

Liquid Effluents

Reverse osmosis or ultrafiltration is used to recover and concentrate active ingredients. Effluent treatment normally includes neutralization, flocculation, flotation, coagulation, filtration, settling, ion exchange, carbon adsorption, detoxification of active ingredients by oxidation (using ozone wet air oxidation ultraviolet systems or peroxide solutions), and biological treatment (using trickling filters, anaerobic, activated sludge, and rotating biological contactors). Exhausted carbon from adsorption processes may be sent for regeneration or combustion. In some cases, air or steam stripping is performed to remove organics. Toxic metals are precipitated and filtered out.

Solid Wastes

Contaminated solid wastes are generally incinerated, and the flue gases are scrubbed. Combustion devices should be operated at temperatures above 1,000° C, with a residence time of at least 1 second, to achieve acceptable destruction efficiency (over 99.99%) of toxics. However, temperatures of around 900° C are acceptable provided that at least 99.99% destruction / removal efficiency of toxics is achieved.

Emissions Guidelines

Emissions levels for the design and operation of each project must be established through the environmental assessment (EA) process on the basis of country legislation and the *Pollution Prevention and Abatement Handbook,* as applied to local conditions. The emissions levels selected must be justified in the EA and acceptable to the World Bank Group.

The following guidelines present emissions levels normally acceptable to the World Bank Group in making decisions regarding provision of World Bank Group assistance. Any deviations from these levels must be described in the World Bank Group project documentation. The emissions levels given here can be consistently achieved by well-designed, well-operated, and well-maintained pollution control systems.

The guidelines are expressed as concentrations to facilitate monitoring. Dilution of air emissions or effluents to achieve these guidelines is unacceptable.

All of the maximum levels should be achieved for at least 95% of the time that the plant or unit

is operating, to be calculated as a proportion of annual operating hours.

Air Emissions

The emissions levels presented in Table 1 should be achieved.

Class A compounds are those that may cause significant harm to human health and the environment. They include Montreal Protocol substances, as well as others identified from a review of the Group B compounds in the proposed EU directive "The Limitation of Organic Solvents from Certain Processes and Industrial Installations" and other international standards. Examples of Class A compounds include acetaldehyde, acrylic acid, benzyl chloride, carbon tetrachloride, chlorofluorocarbons (being phased out), ethyl acrylate, halons (being phased out), maleic anhydride, 1,1,1 trichlorethane, tichloromethane, trichloroethylene, and trichlorotoluene.

Class B compounds are organic compounds of with less environmental impact than Class A compounds. Examples include toluene, acetone, and propylene. Odors should be acceptable at the plant boundary.

Liquid Effluents

The effluent levels presented in Table 2 should be achieved.

Table 1. Emissions from Pharmaceutical Manufacturing

(milligrams per normal cubic meter)

Parameter	*Maximum value*
Active ingredient (each)[a]	0.15
PM	20
Total Class A[b]	20
Total Class B[c]	80
Benzene, vinyl chloride, dichloroethane (each)	5

a. Releases below these mass emissions limits may not be trivial and so may still require controls and setting of appropriate release limits.

b. Applicable when total Class A compounds (see text) exceed 100g/hr.

b. Applicable when total Class B compounds (see text), expressed as toluene, exceed the lower of 5 t/year or 2 kg/hr.

Table 2. Effluents from Pharmaceutical Manufacturing

(milligrams per liter, except for pH)

Parameter	*Maximum value*
pH	6–9
BOD[a]	30
COD	150
AOX	1
TSS	10
Oil and grease	10
Phenol	0.5
Arsenic	0.1
Cadmium	0.1
Chromium (hexavalent)	0.1
Mercury	0.01
Active ingredient (each)	0.05

a. A BOD test is to be performed only in cases where the effluent does not contain any substance toxic to the microorganisms used in the test.

Bioassay testing should be performed to ensure that toxicity of the effluent is acceptable (toxicity to fish = 2; toxicity to *Daphnia* = 8; toxicity to algae = 16; and toxicity to bacteria = 8).

Solid Wastes

Contaminated solid wastes should be incinerated under controlled conditions at a minimum temperature of 1,000^{o}C and a residence time of 1 second for liquid feed, so as to achieve over 99.99% reduction in toxic organics. Halogenated organics should not normally be incinerated. Where incineration of such organics is required, the release of dioxins and furans is restricted to levels below 1 nanogram per normal cubic meter (ng/Nm^3), as measured using a toxicity equivalent factor for 2, 3, 7, 8-TCDD.

Ambient Noise

Noise abatement measures should achieve either the levels given below or a maximum increase in background levels of 3 decibels (measured on the A scale) [dB(A)]. Measurements are to be taken at noise receptors located outside the project property boundary.

Receptor	Maximum allowable log equivalent (hourly measurements), in dB(A)	
	Day (07:00–22:00)	Night (22:00–07:00)
Residential, institutional, educational	55	45
Industrial, commercial	70	70

Monitoring and Reporting

Frequent sampling may be required during start-up and upset conditions. Once a record of consistent performance has been established, sampling for the parameters listed in this document should be as described below.

Monitoring of air emissions should be on a continuous basis. Liquid effluents should be monitored for active ingredients at least once every shift. The remaining parameters should be monitored at least daily.

Monitoring data should be analyzed and reviewed at regular intervals and compared with the operating standards so that any necessary corrective actions can be taken. Records of monitoring results should be kept in an acceptable format. The results should be reported to the responsible authorities and relevant parties, as required.

Key Issues

The key production and control practices that will lead to compliance with emissions requirements can be summarized as follows:

- Replace highly toxic and persistent ingredients with less toxic, degradable ones.
- Control loss and wastage of active ingredients.
- Return packaging for refilling.
- Use vapor recovery systems to prevent the release of toxic organics into air.
- Recover solvents and avoid the use of halogenated solvents.
- Use equipment washdown waters as makeup solutions for subsequent batches.
- Minimize wastage by inventory control, and find uses for off-specification products.

Reference

United Kingdom, Her Majesty's Inspectorate of Pollution. 1993. "Chief Inspector's Guidance to Inspectors, Environment Protection Act 1990, Process Guidance Note IPR 4/9: Pharmaceutical Processes." Her Majesty's Stationery Office, London.