Multilateral Investment Guarantee Agency

Environmental Guidelines for

Pharmaceutical Manufacturing

Industry Description and Practices

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

Major pharmaceutical groups manufactured include:

- proprietary ethical products or prescription only medicines (POM) and usually are patented products;
- general ethical products which are basically standard prescription only medicines made to a recognized formula, which may be specified in standard industry reference books; and
- over-the counter (OTC) or non-prescription products.

The products are available as tablets; capsules; liquids (which may be in the form of solutions, suspensions, emulsions, gels, or injectables); creams and ointments (which usually consist of an oil-in-water emulsion (cream) or water-in-oil emulsion (ointment)); and aerosols (which contain inhalable products or products suitable for external use). Propellants used in aerosols include chlorofluorocarbons—CFCs—(which are being phased out) and more recently butane has been used in externally applied products.

Major manufactured groups include: (a) antibiotics (such as penicillin, streptomycin, tetracyclines, chloramphenicol, and antifungals); (b) other synthetic drugs including sulfa drugs, anti-tuberculosis drugs, antileprotic drugs, analgesics, anaesthetics, and antimalarials; (c) vitamins; (d) synthetic hormones; (e) glandular products; (f) drugs of vegetable origin such as quinine, strychnine and brucine, emetine, and *digitalis* glycosides:; (g) vaccines and sera; (h) other pharmaceutical chemicals such as calcium gluconate, ferrous salts, nikethamide, glycerophosphates, chloral hydrate, saccharine, antihistamines (including meclozine, and buclozine), tranquilizers (including meprobamate and chloropromoazine), antifilarials, diethyl carbamazine citrate, and oral antidiabetics (including tolbutamide and chloropropamide); and (i) 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. In addition, other 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—100 to 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 to the fermentation medium. Separation of penicillin from fermentation broth is accomplished using solvent extraction and the product is further purified using acidic extraction. This is followed by treatment with 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 then 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. The oil-soluble procaine penicillin is made by reacting a penicillin concentrate (20 to 30 percent) with a 50 percent 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 (for example, refer to Her Majesty's Inspectorate of Pollution, 1993) and 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 all metabolites, and includes: (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 and are variable in their composition depending on the product manufactured, materials used in the process, and other process details. Cooling waters are normally recirculated. Some wastewaters may contain mercury—0.1 to 4 milligrams per liter (mg/L), cadmium (10-600 mg/L), isomers of hexachlorocyclohexane, 1,2-dichloroethane, and solvents. Typically 25 kilograms kg of biochemical oxygen demand (BOD_5) per metric ton of product (kg/t) (or 2000 mg/L); 50 kg chemical oxygen demand (COD) per metric ton of products (or 4,000 mg/L), together with 3 kg of suspended solids per metric ton, and up to 0.8 kg of phenol per metric ton are released with the wastewater. However, in some cases, BOD is not to be considered when the pollutants are toxic to the micro-organisms in the test.

Major solid wastes of concern include process and effluent treatment sludges, spent catalysts, and container residues. Approximately 200 kg of waste is generated per metric ton of active ingredient manufactured. Some solid wastes contain spent solvents and other toxic organics at significant concentrations.

Pollution Prevention and Control

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

- 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 non-halogenated 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 make-up 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 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 storm water drainage and avoid its contamination from process areas.
- Label and store toxic and hazardous materials in secure bunded areas. Spillage should be collected and re-used.

Where appropriate, a pharmaceutical manufacturing plant should prepare a hazard assessment and operability study and also prepare and implement an Emergency Plan which 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 provide 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 and should approach the effluent levels. The table in the Emissions Requirements section presents the maximum effluent levels after the addition of pollution control measures**.**

For controlling air emissions, install vapor recovery systems. Recycle wastewaters and treated effluents 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 ultra-filtration 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 $1,000^0$C with a residence time of at least one second to achieve acceptable destruction efficiency (of over 99.99 percent) of toxics. However, temperatures of around 900^0C are acceptable provided at least 99.99 percent destruction/removal efficiency of toxics is achieved.

Emissions Requirements

Emission levels for the design and operation of each project must be established through the Environmental Assessment (EA) process, based on country legislation and the *Pollution*

Prevention and Abatement Handbook as applied to local conditions. The emission levels selected must be justified in the EA and acceptable to MIGA.

The following guidelines present emission levels normally acceptable to the World Bank Group in making decisions regarding provision of World Bank Group assistance, including MIGA guarantees; any deviations from these levels must be described in the project documentation.

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 following emissions levels should be achieved:

Emissions from Pharmaceutical Manufacturing

Parameter	*Maximum value milligrams per normal cubic meter (mg/Nm^3)*
Active ingredient *(each)	0.15
Particulate matter	20
Total Class A[1]	20
Total Class B[2]	80
Benzene, vinyl chloride, dichloroethane (each)	5

[1] Applicable when Total Class A compounds exceed 100g/hr.

[2] Applicable when Total Class B compounds (expressed as toluene) exceed the lower of 5 t/year or 2 kg/hr.

* Releases below these mass emission limits may not be trivial, and so may still require controls and setting of appropriate release limits.

Class A compounds: Class A compounds are those that may cause significant harm to human health and the environment. These include Montreal Protocol substances together with others identified from a review of the Group B compounds in the proposed EU Directive on '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: Class B compounds are organic compounds of lower environmental impact than Class A compounds. Examples of this class include toluene, acetone, and propylene. Odors should be acceptable at the plant boundary.

Liquid Effluents

The following effluent levels should be achieved:

Effluents from Pharmaceutical Manufacturing

Parameter	*Maximum value milligrams per liter (mg/L)*
pH	6-9
BOD_5*	30
COD	150
AOX	1
Total suspended solids	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

*BOD test is to be performed only in cases where the effluent does not contain any substance toxic to the micro-organisms used in the test.

Bioassay testing should be performed to ensure that toxicity of the effluent is acceptable. Toxicity to Fish, TF=2; Toxicity to Daphnia, TD=8; Toxicity to Algae, TA=16; and Toxicity to Bacteria, TB=8.

Solid Wastes

Contaminated solid wastes should be incinerated under controlled conditions at a minimum temperature of 1,000°C and a residence time of one second for liquid feed, so as to achieve over 99.99 percent 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 following levels or a maximum increase in background levels of 3 dB(A). Measurements are to be taken at noise receptors located outside the project property boundary.

Ambient Noise

	Maximum Allowable L_{eq} (hourly), in dB(A)	
Receptor	Daytime 07:00 – 22:00	Nighttime 22:00 - 07:00
Residential; institutional; educational	55	45
Industrial; commercial	70	70

The emissions requirements given here can be consistently achieved by well-designed, well-operated and well-maintained pollution control systems.

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 above should be as detailed 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 on a daily basis.

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. These should be reported to the responsible authorities and relevant parties, as required, and provided to MIGA if requested.

Key Issues

The following box summarizes the key production and control practices that will lead to compliance with emissions requirements:

- Substitute highly toxic and persistent ingredients with less toxic and 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 make-up solutions for subsequent batches.
- Minimize wastage by inventory control and find uses for off-specification products.

Further Information

The following are suggested as sources of additional information (these sources are provided for guidance and are not intended to be comprehensive):

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. HMSO, London.