Chapter 2
Waste Treatment in the Pharmaceutical Biotechnology Industry Using Green Environmental Technologies

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Nomenclature

k	Maximum substrate utilization rate
K_i	The partitioning coefficient, also called the vapor-liquid equilibrium constant
K_s	Half saturation constant
P	Total pressure
P_i	Vapor pressure of the pure substance at the operating temperature
r_i	Activity coefficient of organic compound i in the wastewater at a certain temperature
V_i	Mole fraction of organic compound i in the vapor phase
Wi	Mole fraction of organic compound i in the wastewater phase

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2.1 Introduction to Biotechnology

2.1.1 Pharmaceutical Industry and Biotechnology Terminologies

Pharmaceutical industry is an industry responsible for manufacturing of drugs, vaccines, antibiotics, etc. using chemical reactors, biological systems, or organisms. The chemical synthesis-based pharmaceutical industry is a part of chemical industry using chemical technology and chemical reactors, while the fermentation process-based pharmaceutical industry is a part of biotechnology industry using biological systems or organisms in biochemical reactors.

Biotechnology is an engineering science field involving the use of biological systems found in organisms or the use of the living organisms themselves to make scientific advances and adapt those knowledge to various application branches, such as medical biotechnology, agricultural biotechnology, industrial biotechnology, environmental biotechnology, computational biotechnology, and military biotechnology.

Medical biotechnology (including pharmaceutical biotechnology) involves the use of living cells and other cell materials to find cures for preventing diseases and bettering the health of humans; development of vaccines and antibiotics is a typical example. Specific pharmaceutical biotechnology related to medicine and veterinary products (vaccines, antibiotics, molecular diagnostics techniques, genetic engineering techniques, etc.) is also termed red biotechnology.

Agricultural biotechnology focuses on developing genetically modified plants to increase crop yields or introduce characteristics to those plants that provide them with an advantage growing in regions that place some kind of stress factor on the plant, namely, weather and pests. Development of pest-resistant crops and improvement of plant and animal breeding are typical examples. Green biotechnology refers to specific agricultural biotechnology that creates new plant varieties of agricultural interest, biopesticides, biofertilizers, etc. This area of agricultural biotechnology is based on transgenics (genetic modification), i.e., an extra gene or genes inserted into their DNA. The additional gene may come from the same species or a different species.

Industrial biotechnology (including industrial fermentation biotechnology) involves the utilization of cells, such as microorganisms, or components of cells, like enzymes, to generate products in sectors that are industrially useful, such as food and feed, chemicals, detergents, paper and pulp, textiles, biofuels, and biogas, or to create genetically modified organisms (GMOs) that enhance the diversity of applications and the economic viability of industrial biotechnology. Development of biocatalysts (such as enzymes, to synthesize chemicals), improvement of fermentation process, and production of new plastics/textiles, biofuels, etc. are typical examples. Specific industrial biotechnology related to production of wine, cheese, and beer by fermentation is also termed yellow biotechnology. Designing more energy-efficient, less polluting, and low resource-consuming processes and products that can beat traditional ones is also termed white biotechnology.

Environmental biotechnology is an interdisciplinary branch of biotechnology using biological systems and/or organisms for conservation of environment, resources, and energy and for protection of humans, animals, and plants on Earth and beyond. It can be of green biotechnology, gray biotechnology, blue biotechnology, gold biotechnology, or white biotechnology, depending on the applications or achievement goals. Modern green environmental biotechnology has a symbol of "green cross" that involves the construction of resource recovery facilities (RRF), bioreactor landfills, in-vessel or in-bin composting reactors, bioremediation sites, wildlife sanctuary areas, environmental protection parks, global warming control facilities, salmon ladders, etc. using the best available technologies (BAT) for reclamation of water, air, land, nutrients, methane gas, animals, plants, etc. and production of biofuels, bioplastics, waste-converted animal foods, etc. in turn, achieving environmental conservation, resource sustainability, biodiversity, climate control, ozone layer protection, etc. Gray biotechnology refers to an old traditional environmental biotechnology applications to maintain biodiversity and the partial removal of certain pollutants or contaminants using microorganisms and plants to isolate and dispose of many kinds of substances such as heavy metals and hydrocarbons, but without sustainability of natural resources. Typical examples are the old biological secondary wastewater treatment plants (WWTP) and old sanitary landfills. Modern environmental biotechnology is considered to be a green biotechnology. Blue biotechnology is based on the use of marine resources to produce goods, generate energy, or reduce pollution.

Computational biotechnology can be defined as "conceptualizing biotechnology" to address biotechnology problems using computational techniques and makes the rapid organization as well as analysis of biotechnological data possible. It can also be termed gold biotechnology or bioinformatics.

Military biotechnology is also termed dark biotechnology because it is associated with bioterrorism or biological weapons and bio-warfare using microorganisms and toxins to cause diseases and death in humans, domestic animals, and crops.

Biotechnology itself is an academic field of engineering science, while any other academic field dealing with the law and ethical and philosophical issues around the engineering science biotechnology is liberal art biotechnology or violet biotechnology. This publication emphasizes environmental biotechnology to be applied to environmental control of medical (pharmaceutical) and industrial biotechnology industry.

2.1.2 Historical Development of Biotechnology Industry

The biotechnology industry is still young, especially compared with the automotive, chemical, and steel industries. Despite its comparative youth, it is becoming an important influence on many other industry segments, as well as developing an impressive presence of its own. Its technology base continues to grow dynamically and is melding medical science with information technology in new and exciting

ways. While its relationship with capital markets has sometimes been stormy, that relationship now appears to be settling into maturity as its medically oriented companies bring growing numbers of new products to market.

The growth of the biotechnology industry is a unique story, and yet it rests on foundations common to other segments of industry. Years of research, both government-funded and privately funded, continue to provide an ever-expanding knowledge base. The capital market provides the ability to transform this knowledge into unique products and processes for markets around the world. While there is inevitable tension between the industry's desire to bring new products to market and the concerns of the industry's regulators, both sides have found new and innovative ways to work together.

Perhaps unique among industries, biotechnology is not defined by its products but by the technologies used to make those products [1]. Biotechnology refers to a set of enabling technologies used by a broad array of companies in their research, development, and manufacturing activities. To date, these technologies have been used primarily by the pharmaceutical industry, but they are being used increasingly by a variety of other industries, such as agriculture, mining, and waste treatment. Various US government publications have defined biotechnology as a set of techniques that use organisms or their cellular, subcellular, or molecular components to make products or modify plants, animals, and microorganisms to carry desired traits [1]. This broad definition includes methods of treating disease developed from recent research in molecular biology and other fields, as well as the century-old practices of animal and plant breeding and the use of microorganisms to make leavened bread and fermented beverages.

Advances in molecular biology over the past 25 years have led to the development of genetic engineering, monoclonal antibody technologies, DNA amplification, protein engineering, tissue engineering, and other methodologies with applications in the medical arena. These new techniques have enabled researchers to modify the genetic and biochemical makeup of organisms with far greater precision and speed.

In the roughly 25 years since the development of recombinant DNA technologies in research laboratories, more than 2000 firms have been founded in the USA alone to explore and to take advantage of these new technologies [2]. Approximately 30 new products have reached the medical market, and several hundred more are in human clinical trials. The market for such products has grown dramatically from $7.6 billion in 1996 to $24 billion in 2005. Similarly, the market for agricultural biotech products has increased from $295 million to $1.74 billion in the same period. Applications of the products will lead to enhanced pest resistance in food crops, improved methods of food preservation, and other advances. Table 2.1 shows the distribution of research activities and biotechnology firms in the USA.

It is clear that California and Massachusetts are the top leading biotechnology states followed by New Jersey, North Carolina, and Maryland [3, 4].

The biotechnology industry serves both medical and nonmedical markets. The medical market includes human therapeutics and human diagnostics as well as applications in veterinary medicine. Nonmedical markets encompass both

Table 2.1 Leading biotechnology states in the USA [3]

Rank	State	Number of companies
1	California	267
2	Massachusetts	130
3	New Jersey	80
4	North Carolina	71
5	Maryland	70
6	Pennsylvania	58
7	Wisconsin	56
8	New York	55
9	Texas	50
10	Washington	40

Table 2.2 Participation of biotechnology companies by primary focus [3]

Market area	Number of companies	Percentage of all companies
Therapeutics	315	29.4
Diagnostics	187	17.4
Reagents	84	7.8
Plant agriculture	68	6.3
Specially chemicals	54	5.0
Immunological products	36	3.4
Environmental testing/treatment	35	3.3
Testing/analytical services	32	3.0
Animal agriculture	29	2.7
Biotechnology equipment	26	2.4
Veterinary	26	2.4
Drug delivery systems	24	2.2
Vaccines	24	2.2

agriculture and industrial applications. Agricultural applications include making plants and crops pest resistant, providing improved seed quality, modulating growth and ripening times, enhancing nutrient content of foods, and providing simple and inexpensive diagnostics for use in field testing for contaminants and toxic materials. Industrial uses of biotechnology involve many different sectors and include industrial enzymes, waste management, bioremediation, energy biomass, cosmetic formulations, and diagnostics for toxicity determinations. Tables 2.2 and 2.3 show the distribution of biotechnology firms among the various medical and nonmedical markets by primary focus and in all areas, respectively [3, 4]. It is obvious that the pharmaceutical industry is by far the predominant and largest area of biotechnology [5–108].

Table 2.3 Participation of biotechnology companies in all areas [3]

Market area	Number of companies	Percentage of all Companies
Therapeutics	448	41.8
Diagnostics	346	32.3
Reagents	224	20.9
Specialty chemicals	159	14.8
Immunological products	146	13.6
Cell culture products	133	12.4
Fermentation/production	116	10.8
Plant agriculture	106	9.9
Vaccines	105	9.8
Drug delivery systems	94	8.8
Environmental treatment/testing	93	8.7

2.1.3 Core Technologies

The core technique of biotechnology is elegant in its simplicity. The cell is a miniature factory, containing a genetic material—DNA—that acts as a blueprint for its structure and function. Biotechnology allows researchers to isolate, copy, and rearrange this genetic blueprint at the molecular level to manipulate the quantity, structure, and function of the biomolecules that control cellular processes. As a result, researchers are expanding their abilities to identify, isolate, and modify those molecular agents.

Discoveries concerning the molecular bases of cellular processes will have a wide range of applications. For example, in the area of health, these mechanisms may lead to therapies that fight disease by regulating specific cellular processes. With the help of molecular biology, biochemistry, and biophysics, the search for molecular information is yielding an increasingly detailed guide to cell behavior and its disruption. This knowledge allows biotechnologists to develop new products, processes, and therapies of commercial interest.

2.1.4 Biotechnology Materials

The raw materials of biotechnology are cells and their constituent biomolecules. These materials may be used for a variety of purposes, including drug synthesis, food production, and the bioremediation of hazardous waste. Examples of biotechnology materials include the following [1]:

1. *Cytokines.* Hormone-like proteins that stimulate the growth or regulate the function of various cell types. They include such agents as erythropoietin, which stimulates the production of red blood cells and can be used to treat severe ane-

mia associated with renal disease, and granulocyte colony-stimulating factor, which stimulates the production of white blood cells and is used to counter the loss of such cells in patients who have received anticancer therapy, which help regulate and target the body's immune response and can be used to treat certain cancers and selected viral infections.
2. *Antibodies.* Large protein molecules produced by the immune system that can bind specifically to discrete antigens; foreign substances are recognized and then attacked by the immune system.
3. *Enzymes.* Protein catalysts that facilitate specific chemical or metabolic reactions necessary for cell growth and function. Enzymes can be used in such activities as food processing, the bioremediation of hazardous waste, and the synthesis of certain drugs, vitamins, and fine chemicals.
4. *Restriction enzymes.* Enzymes that break DNA in specific locations, creating gaps into which new genes can be inserted. These enzymes play a vital role in genetic engineering.
5. *Viral vectors.* Modified, nonpathogenic viruses that deliver useful genetic information to host cells in gene therapy and genetic engineering. In gene therapy applications, such viruses are encoded with a specific gene, which, when incorporated into a host cell, confers a clinical benefit to the patient.
6. *Antisense oligonucleotides.* Strands of DNA that bind to targeted messenger RNA molecules (which tell cells what proteins to make) and block the synthesis of specific proteins. In therapeutic applications, the synthesis of disease-related proteins is inhibited. These compounds are used in drug development and in agricultural biotechnology.

2.1.5 Drug Development

The acceleration of the drug discovery process resulting from biotechnology research is contributing to US competitiveness in biotechnology. Many companies emerged in the past decade to become involved in this new approach to drug commercialization. Important areas of drug-related research include the following [1]:

1. *Rational drug design.* Scientists are using a combination of chemistry, biology, biophysics, and computer modeling to determine the structure of target proteins in molecular detail and to then design specific small-molecule drugs for those target proteins. Companies involved in rational drug design include Agouron, Arris, BioCryst, Chiron, Procept, and Vertex.
2. *Natural product screening.* New methods of screening materials extracted from animals and plants offer a rich source of potentially therapeutic compounds. NPS Pharmaceuticals, Magainin, Shaman, and Xenova are among the biotech firms that literally search the air, land, and sea for new drugs.
3. *Combinatorial chemistry.* This technology allows chemists to synthesize large, diverse collections of molecules quickly and efficiently and to then identify the

most active compound for a given application. Because combinatorial chemistry can identify promising compounds in a fraction of the time required by traditional methods of drug discovery, it can significantly reduce the cost of commercializing new drugs. Companies using such technology include Gilead Sciences, Isis, and Pharmacopeia.

2.1.6 Gene Sequencing and Bioinformatics

Mutations are alterations in DNA sequence that may be associated with disease-causing genes. Such modified genes, and the proteins for which they encode, represent targets for drug therapy. Genes are sequenced by cutting pieces of DNA into small segments and cloning and copying those segments millions of times over. The order of the nucleotides (subunits of DNA) contained in those segments is then determined. A computer program is used to analyze and correlate the nucleotide sequences of the individual segments to create a map of the entire gene. The genes identified by this computer analysis are then scrutinized as possible drug targets. Rapid advances in the speed and accuracy of sequencing will revolutionize the discovery of innovative drugs and diagnostics. Companies in the business of gene sequencing include Darwin Molecular, Human Genome Sciences, Mercator Genetics, and Sequana.

2.1.7 Applications of Biotechnology Information to Medicine

Biotechnology produces information that is used to alter and improve cell behavior. Many biotech companies specialize in finding ways to deliver and apply biotechnology information to cells to aid in identifying, preventing, and treating disease. Representative applications include the following [1]:

1. *Diagnostics.* Tests that use biotechnology materials to detect the presence or risk of disease or pollution of a cell or material.
2. *Vaccines.* Preparations of whole or significant structural portions of viruses, microbes, plants, or other entities that are intended for active immunological prophylaxis. Companies working in this area may specialize in the route of administration as well as in the disease that the vaccine targets.
3. *Gene therapy.* The process of replacing defective genes with healthy genes, either in vivo or ex vivo, to regulate cell replication or the production of proteins. Alternatively, gene function may be modulated by designing and delivering molecules to cells to inhibit or promote gene action.

2.1.8 Applications of Biotechnology Information to Nonmedical Markets

Biotechnology also offers significant applications in agriculture and industry. Industrial applications include specialty and fine chemicals and bioremediation. Biotechnology materials, specialized software packages, and equipment used in drug development and production are also important adjuncts to the core biotechnology markets.

In nonmedical areas, there are a number of potentially important developments under way. Genetic modification of food crops, increasing protein content or salt resistance, may help to reduce world hunger. In addition, biotechnology has the potential to shift the world's fish supply from an uncertain and threatened wild food source to an agricultural analog cultivated through mariculture and freshwater aquaculture. The exploration, study, and harvesting of marine genetic resources through biotechnology are expected to produce important commercial applications, including improved diagnostics and pharmaceuticals, increased production of ocean foods, novel energy sources, and the engineering of microorganisms to control and eliminate environmental contaminants.

2.1.9 The Regulatory Environment

Regulation has been and will continue to be a major factor influencing the development of the biotechnology industry and its international competitiveness, especially for products made from recombinant DNA technology. Health, safety, and environmental regulations are of critical importance, affecting the cost and time needed to get biotech products to market and the profits thereafter. At the same time, other federal regulations, such as those relating to the cleanup of waste sites and to air and water quality generally, can play an important role in the development of the markets served by the bioremediation portion of the biotech industry.

The US Environmental Protection Agency's (USEPA's) effect on the domestic industry is complex. On one hand, it has regulatory authorities that it intends to use to regulate aspects of the industry's activities and that industry fears may result in new regulatory burdens. On the other hand, the USEPA's responsibilities for overseeing the cleanup of polluted sites give it the power to create important new markets for the industry.

The USEPA's broad responsibilities for the cleanup of hazardous waste sites under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA) give rise to important market opportunities for companies offering bioremediation technologies and services, but industry has pointed to several aspects of these activities that may discourage the use of bioremediation technologies. The USEPA has initiated proceedings to reexamine its approaches to its cleanup responsibilities, and many

within the biotechnology industry hope this will create more opportunities for bioremediation technologies in both the RCRA and Superfund programs.

2.2 General Industrial Description and Classification

2.2.1 Industrial Classification of Biotechnology Industry's Pharmaceutical Manufacturing

The pharmaceutical industry is the biggest and most important biotech industry. This industry produces substances that are of value for humans and other living beings. According to the census by the US Department of Commerce (US DC), the industry employed about 170,000 people and produced goods which were valued at over 39 billion US dollars in 1987 [5].

The Standard Industrial Classification (SIC) has been developed and revised since the first major version in 1972, with the purpose of promoting the comparability of established data describing various facets of the US economy, such as management, budget, and data on production, sales, and cost for various industries.

While the pharmaceutical industry requires ultrapure water for their manufacturing processes [6], their process effluents contain highly toxic pollutants which must be properly treated before being discharged to a receiving water.

According to the Standard Industrial Classification Manual [7], the products of the pharmaceutical industry are segregated into four categories:

1. Medical chemicals and botanical products
2. Pharmaceutical preparations
3. In vitro and in vivo diagnostic substances
4. Biological products, except diagnostic substances

The pharmaceutical industry has steadily grown because of the need to market, develop, and discover a variety of drugs required throughout the world. This growth of the industry has also increased the amount of waste generation and in turn disposal problems. To control effluent discharge and to reduce the impact of waste from the pharmaceutical industry, the USEPA categorized pharmaceutical manufacturing processes according to the SIC standard and has developed effluent discharge limitation guidelines based on the production activities and wastes from this industry [8–15].

It should be noted that the pharmaceutical SIC in the USEPA's effluent discharge limitation guidelines [8, 9, 11, 13–15] was based on the older versions rather than the 1987 SIC codes cited above, although the 1987 SIC codes were used for the recent guidelines to pollution prevention in the pharmaceutical industry [15, 16]. To follow the effluent discharge limitation guidelines established by the USEPA, the following sections present those SIC codes for the pharmaceutical manufacturing quoted by the USEPA [11–15].

2.2.2 *Biotechnology Industry's Pharmaceutical SIC Subcategory Under the USEPA's Guidelines*

According to the USEPA's effluent discharge guidelines [11–15], pharmaceutical manufacturing includes those plants producing or utilizing the following products, processes, and activities:

1. Biological products
2. Medicinal chemicals and botanical products
3. Pharmaceutical products
4. All fermentation, biological and natural extraction, chemical synthesis, and formulation products which are considered as pharmaceutically active ingredients by the US Food and Drug Administration, but which are not covered by other categories
5. Cosmetic preparations which function as a skin treatment
6. The portion of a product with multiple end uses which is attributable to pharmaceutical manufacturing either as a final pharmaceutical product, component of a pharmaceutical formulation, or pharmaceutical intermediate
7. Pharmaceutical research which includes biological, microbiological, and chemical research, product development, and clinical and pilot plant activities

The pharmaceutical manufacturing under this categorization does not include all the activities producing the substances used in medical purposes, such as some medical instruments. Moreover, not all products containing pharmaceutical ingredients belong to pharmaceuticals, such as milk containing vitamin D. To clarify the confusion in the nature of pharmaceutical manufacturing, it is helpful to review the manufacturing which is similar to, but not included in, pharmaceutical manufacturing. The following lists the production or activities specifically excluded from the pharmaceutical manufacturing category [11]:

1. Surgical and medical instrument and apparatus
2. Orthopedic, prosthetic, and surgical appliances and supplies
3. Dental equipment and supplies
4. Medical laboratory
5. Dental laboratory
6. Outpatient care facilities
7. Health and allied sources, not elsewhere classified
8. Diagnostic devices not covered under other categories
9. Animal feeds which include pharmaceutically active ingredients such as vitamins and antibiotics
10. Foods and beverages which are fortified with vitamins or other pharmaceutically active ingredients

Note, again, that these SIC codes are cited according to the earlier versions of the Standard Industrial Classification Manual rather than the 1987 version [11, 13].

Because each of the pharmaceutical subcategories is involved in one or more particular processes, it is difficult to make any generalization regarding various effluents discharged from the pharmaceutical industry. The problem is even more complicated by the fact that pharmaceutical manufacturing uses both inorganic and organic raw materials. To better minimize and treat pharmaceutical wastes, the manufacturing processes must be first fully understood. This chapter will initially discuss the pharmaceutical manufacturing processes and waste generation, then discuss the waste characteristics and their environmental impact, and finally discuss waste minimization and treatment [15–108].

2.3 Manufacturing Processes and Waste Generation

While the preceding section itemizes the pharmaceutical manufacturing under the SIC subcategorization, it is better to generalize the pharmaceutical manufacturing with its main processes and the waste generation, so as to better understand how to control and treat the manufacturing wastes. The five common processes used in the manufacture of pharmaceutical products are as follows:

1. Fermentation (subcategory A)
2. Natural product extraction (subcategory B)
3. Chemical synthesis (subcategory C)
4. Formulation/mixing/compounding (subcategory D)
5. Research and development activities (subcategory E)

These five processes have been the basic pharmaceutical manufacturing processes, although the SIC subcategory codes for the pharmaceutical industry can be revised as stated in the preceding sections. The USEPA's guidelines to the point source category for pharmaceutical manufacturing (40 CFR Part 439) are established based on these five processes and their related wastes [11, 12, 14, 15]. These five processes are identified by the USEPA as the subcategories of pharmaceutical manufacturing and will be used throughout this chapter, instead of using the SIC subcategories.

The USEPA [13] has reported that subcategory D (formulation/mixing/compounding) is the most prevalent pharmaceutical manufacturing process, and about 80% of the plants in the industry are engaged in this activity. Furthermore, 58% of these plants conduct subcategory D operations only.

Pharmaceutical manufacturing plants generate a variety of wastes during manufacturing, maintenance, and housekeeping operations. While maintenance and housekeeping activities are similar from one plant to the next, actual processes used in pharmaceutical manufacturing vary widely. With this diversity of processes comes a similarly diverse set of waste streams. Typical waste streams include spent fermentation broths, process liquors, solvents, equipment washwaters, spilled materials, off-spec products, and used processing aids [16].

The following subsections discuss those five main manufacturing processes and their associated wastes.

2.3.1 Fermentation

Although only about 6% of pharmaceutical products and their wastes are generated by fermentation processes, fermentation is considered an important production process for the industry [14, 16]. Most antibiotics (penicillin, streptomycin), steroids (such as cortisone), and vitamin B12 are produced using fermentation processes.

Fermentation processes consist of three major steps:

1. Inoculum and seed preparation
2. Fermentation
3. Product recovery and purification

Figure 2.1 shows a flow diagram for a fermentation process [16]. Sterile inoculum preparation begins with a carefully maintained population of a microbial strain. A few cells from this culture are matured into a dense suspension through a series of test tubes, agar slants, and shaker flasks. The cells are then transferred to a seed tank for further propagation into a culture of sufficient quantity to function as a seed. While tailored to a specific fermentation, the volume of the final seed tank occupies from 1 to 20% of the volume used in full-scale production.

In the fermentation step, the material from the seed tank, along with selected raw materials, is introduced, through a series of sterilized lines and valves, into a sterilized fermentor (batch vessel). Once these sterilized nutrient materials are added to the vessel, fermentation commences. Dissolved oxygen content, pH, temperature, and several other parameters are carefully monitored throughout the fermentation cycle.

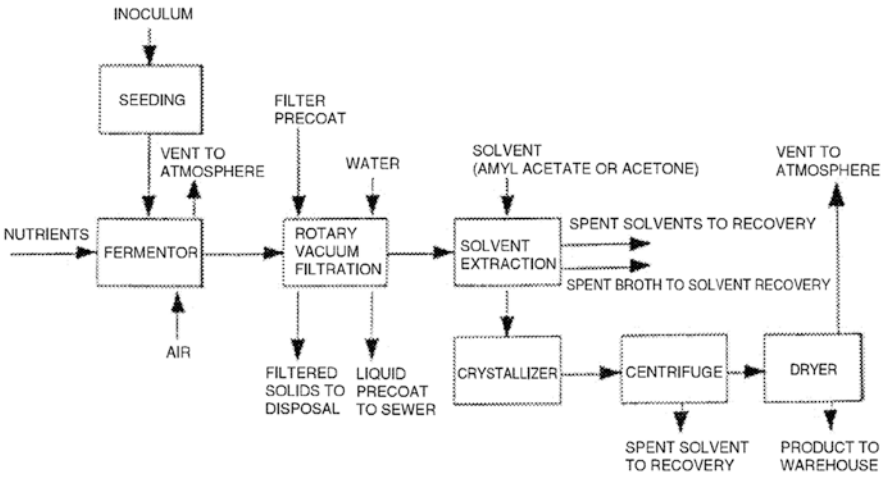

Fig. 2.1 Fermentation process diagram [16]

Following cell maturation, the fermentor broth from the batch vessel is often filtered to remove the solid residues resulting from the fermentation process; the filtrate is then processed to recover the desired product.

There are three commonly used schemes for product recovery, i.e., solvent extraction, direct precipitation or solvent evaporation, and ion exchange or adsorption [17].

In the solvent extraction process [18], an organic solvent is used to separate a pharmaceutical product from an aqueous filtrate and to form a more concentrated solution. With subsequent extractions, the product is purified, especially from contaminants. Finally, the product is further recovered, specifically removed from the solvent, by precipitation or crystallization or solvent evaporation.

Normally, solvents used for product recovery are recovered and reused. However, small portions left in the aqueous phase during the solvent extraction can appear in the plant's wastewater stream. Typical processing solvents used in fermentation operations are methylene chloride, benzene, chloroform, butyl acetate, 1,1-dichloroethylene, and 1,2-transdichloroethylene [11, 12, 15, 16].

In precipitation or evaporation processes, product is recovered directly from a treated broth. In an ion-exchange process, a product is removed from a treated broth using ion-exchange resin and then proceeded for an additional purification and a final isolation.

The waste characteristics of fermentation processes may vary depending on the production. For example, the antibiotic wastes can generally be divided into four groups [19]:

1. Group A: spent fermentation mash
2. Group B: wastes containing acids, bases, and solvents (used in the purification of the product)
3. Group C: condensate from barometric condensers in evaporation and drying
4. Group D: washing water (used for cleaning equipment and floors)

The waste of Group A has a 5-day biological oxygen demand (5-day BOD or $BOD_{5)}$ of 4000–13,000 mg/L [20] if the end product is totally absent from the effluent. For example, in the production of streptomycin, the average 5-day BOD or the spent mash is approximately 2500 mg/L, and for aureomycin, it is in the range of 4000–7000 mg/L. When the fermentation does not proceed satisfactorily, a batch of the mash has to be discharged to waste together with the mycelium, which results in the 5-day BOD of the waste rising to 20,000 mg/L or even 30,000 mg/L, while the permanganate value increases to more than 15,000 mg/L. If the mycelium is very carefully separated from the mash, the waste liquors are fairly clear, and the combined content of organic and inorganic suspended solids in a filtered penicillin mash is about 400 mg/L. However, the waste is commonly milky-yellow in color and cannot be clarified easily. The waste directly from the fermentation tanks has a pH of 2–3 units. The pH may rise to 7.5–8.0 units when it is mixed with the effluents from Group D.

Group B waste consists of the tailings from distillation apparatus used for the recovery of organic solvents. The concentration of these components depends on their solubility in water.

Group C waste consists of condensates from barometric condensers which are only slightly polluted. Those wastes from the manufacturer of aureomycin, however, have a 5-day BOD of 60–120 mg/L.

Group D wastewater from washing of floor and equipment is similar to that of the waste in Group A, with 5-day BOD from 500 to 1500 mg/L. But in penicillin production, the washing wastewater contains alkaline, due to the use of basic substances for removing unwanted matter from equipment tanks and fermentors.

The fermentation process generates a large volume of waste such as the spent aqueous fermentation medium and solid cell, debris. The aqueous medium is very impure, containing unconsumed raw materials such as corn steep liquor, fish meal, and molasses. Filtration processes result in large quantities of solids in the form of spent filter cake including solid remains of the cells, filter aid, and some residual product. After product recovery, spent filtrate is discharged as wastewater (known as the "spent beers"), which contributes the most significant waste load in the fermentation process. That is, this filtrate still contains a large amount of organic material, protein, and other nutrients. Some wastewater may also come from the use of washwater and gas and dust scrubbers. While solvent extraction contributes relatively small amounts of organic solvents, direct precipitation results in increased metallic ion (particularly copper and zinc) concentration.

In general, the wastewaters from fermentation operations typically have high 5-day BOD, COD (chemical oxygen demand), and TSS (total suspended solids) levels with a pH value in the range of 4–8 units [11, 12].

Sometimes a fermentation batch can be infested with a phage, a virus that attacks microorganism [13]. In such a case, very large wastewater discharges may be necessary in a short period of time, which causes a higher nutrient and 5-day BOD concentration than that of the spent broth during normal production. Some fermentation plants use heavy-metalbearing chemicals as biocides (such as organomercury) which will introduce heavy-metal contamination.

Volatile solvents used in product recovery operations may release vapors to the air. Some factories may generate acid and solvent vapors such as methanol and butyl acetate, causing air emission problems.

2.3.2 Biological Product Extraction

Biological product extraction is the production of pharmaceuticals from natural biological material sources such as roots, leaves, animal glands, and fungi. Such pharmaceutical, which typically exhibit unique pharmacological properties, includes allergy relief medicines, insulin, morphine, alkaloids, and papaverine [16]. Despite their diversity, all extractive pharmaceuticals have a common characteristic: they are too complex to synthesize commercially.

The extraction process requires very large volumes of specialized plant or animal matter to produce very small quantities of products. In other words, these extraction techniques basically consist of methods to concentrate particular compounds from either plant or animal tissue [21].

The extraction process consists of a series of subsequent extraction operations. In almost every step, the volume of material can greatly diminish. To that end, the volume on the final product may be less than one-thousandth of the initial volume. Therefore, another characteristic of natural product extraction is that the amount of finished drug product is small compared with the amount of source material used. Because of these volume reductions, conventional batch method and continuous processing method are not suitable for biological product extraction operations [11, 13]. Therefore, a unique assembly-line, small-scale batch processing method has been developed. The material is transported in portable containers through the plant in batches of 75–100 gallons (283.9–378.SL). In this method, a continuous line of these containers is sent past a series of operating stations where technicians perform specific tasks on each batch in turn.

An extraction plant may make one product for a few weeks and then may convert to produce a different product after changing and redefining the tasks to be conducted at each station.

Due to the nature of the extraction process, the waste material generated is practically equal to the amount of raw material processed, and most of the waste appears in the solid or semisolid form. Wastes from biological product extraction include spent raw materials such as leaves and roots, water-soluble solvents, solvent vapors, and wastewaters. The wastewater is mainly from the aqueous part of the spent natural materials and from the product recovery and purification processes. The wastewater also comprises organic solvents, heavy metals, and ammonia.

Organic solvents are used in product recovery to dissolve fats and oils which would contaminate the product; solvents are also used to extract the product itself. While ketones and alcohols are common extraction agents, other organic solvents, such as benzene, chloroform, and 1,2-dichloroethane, may be used to extract the alkali-treated plant alkaloids.

Common heavy metals are lead and zinc, which are used as precipitating agents. Ammonia (in solution or anhydrous forms) is often used for pH control, as are the hydroxides of various cations and also, more importantly, as a common extraction solvent.

In general, the extraction wastewater is characterized by small flows and low pollutant concentrations. The wastewaters typically have low $BOD_{5,}$ COD, and TSS levels and a pH in the range of 6–8 [13].

Similar to the fermentation process, volatile solvents used in product recovery operations may release vapors to the air.

2.3.3 *Chemical Synthesis*

Most drugs are produced by chemical synthesis. In a typical manufacturing plant, batch processing is a standard method of operation for chemical synthesis facilities, including a series of reaction, separation, and purification steps to make a desired product.

Chemicals used in chemical synthesis operations range widely and include organic and inorganic reactants and catalysts. In addition, manufacturers use a wide variety of solvents for product recovery, purification, or process reaction, which are listed as priority pollutants [13, 15]. A large number of toxic substances are used in chemical synthesis plants, and a correspondingly high incidence of toxic pollutants in the plant's wastewater has been observed.

Figure 2.2 is a process flow diagram of chemical synthesis for an anti-convulsive drug plant [16, 22]. Raw materials, potassium permanganate, and water are mixed in a 3000-gallon (11,355-L) reactor. A manganese dioxide precipitate is formed and is removed from solution by a rotary drum filter coated with Celite. The wet filter cake (manganese dioxide precipitate and Celite) is deposited into trash bins for disposal at a municipal landfill. The filtrate is neutralized with sulfuric acid and sent to a climbing film evaporator. Overhead water is collected and discharged into the sewer. The enriched product solution is then sent to an 800-gallon (3028-L) Pfaudler vessel where a final pH adjustment is made with sulfuric acid. As the mixture is agitated and cooled, potassium sulfate is crystallized. The potassium sulfate crystals are removed from the reaction mixture by centrifugation dissolved in water and then discharged to the sewer. Butyl acetate is added to the concentrate, and the mixture is azeotropically dehydrated.

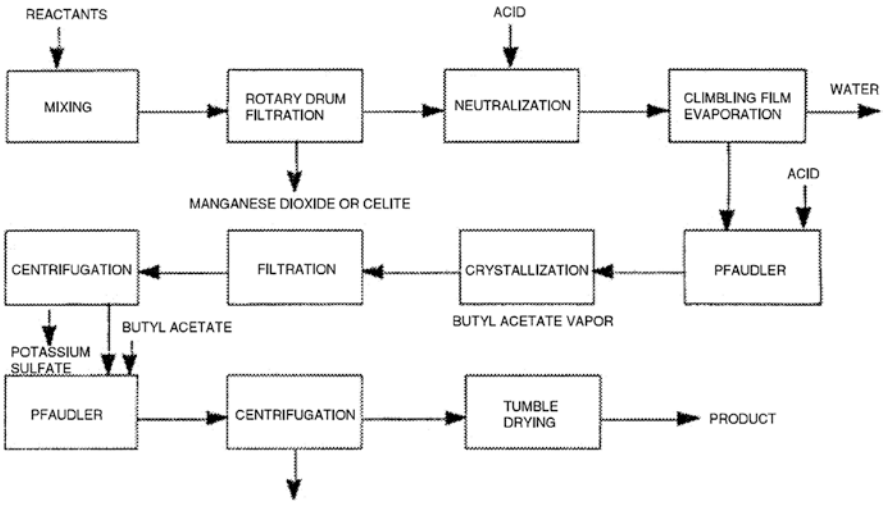

Fig. 2.2 Process flow diagram of chemical synthesis for an anti-convulsive drug plant [16]

In a continuous process, the overhead azeotropic mixture is condensed and sent to a decanter where the lower water layer is discharged to the sewer and butyl acetate is taken off the top and returned to the product mixture. This process procedure is continued until all the water (which contains some butyl acetate) is removed. The butyl acetate product mixture is then filtered to remove any remaining salt. The filtered solution is then cooled, allowing product to crystallize and be separated by centrifugation. Butyl acetate is recovered and stored for reuse. The product is sent to a tumble dryer prior to packaging. Butyl acetate vapor is vented from the dryer, condensed, and recovered for reuse [16].

Solvents serve several functions in a chemical synthesis process [11, 13]. They dissolve gaseous, solid, or viscous reactants to bring all reactants into close molecular proximity. They also serve to transmit heat to or from the reacting molecules. Benzene and toluene are widely used organic solvents since they are stable compounds that do not easily take part in chemical reactions.

Waste streams from chemical synthesis operations are complex due to the various operations and reactions employed. Virtually every step of an organic synthesis generates liquor that contains unconverted reactants, reaction byproducts, and residual products in the organic solvent base. Acids, bases, cyanides, and metals may also be generated. Typically, the spent solvents are recovered on-site by distillation or extraction [23], which also generate solvent recovery wastes such as still bottom tars.

Aqueous waste streams from synthesis processes may result from miscible solvents, filtrates, concentrates, equipment cleaning, wet scrubbers, and spills. Wastewaters typically have high 5-day BOD, COD, and TSS levels and have a pH value in the range of 1–11 units. Solid wastes may result from filter cakes. The use of volatile solvents can also result in air emissions.

2.3.4 Formulation, Mixing, and Compounding

Pharmaceutical formulation is a process for preparation of dosage forms such as tablets, capsules, liquids, parenterals, and creams and ointments for consumer use.

Tablets account for over 90% of all medications taken orally [24] and are produced in three varieties: plain compressed, coated, and molded. The form of tablet depends on the desired characteristics of active ingredient, which can be slow, fast, or sustained, for example, spraying or tumbling the tablets with a coating material is one of the ways controlling the release characteristics. Tablets are produced by blending the active ingredient with fillers, such as starch or sugar, followed by compressing using either wet granulation, or direct compression, or slugging.

Capsules prepared in hard or soft form are the next most widely used oral dosage form for solid drugs. Hard capsules consist of two separate pieces which are formed by dipping pins into a solution of gelatin maintained at a specified temperature. When removed, a gelatin film is deposited on the pins. Unlike hard capsules, soft

capsules are prepared by placing two continuous gelatin films between rotary die plates and then injecting in the drug.

The third type of pharmaceutical formulation is a liquid dosage form prepared for injection or oral use, which includes solutions, syrups, elixirs, suspensions, and tinctures, all of which are usually prepared by mixing the solutes with a selected solvent in a glass-lined or stainless steel vessel. Suspensions and emulsions are frequently prepared using colloid mills and homogenizers.

Parenteral dosage forms are injected into the body either intramuscularly, intravenously, or subcutaneously. Parenterals are prepared as solutions, as dry solids which are dissolved immediately before injection, as suspensions, as dry insoluble solids which are suspended before injection, and as emulsions.

Ointments and creams are semisolid dosage forms prepared for topical use. Ointments are usually prepared by melting a base, which is typically the petroleum derivative petrolatum. This base is then blended with the drug, and the cooled mixture is passed through a colloid or roller pill. Creams are oil-in-water or water-in-oil emulsions, rather than being petrolatum based, and are manufactured in a similar manner [16].

Most water used in the formulation process is as cooling water, which generates no contact wastewater. Wastewater is generally originated from cleanup, spills, and breakage of packaged products. Some wastewaters may come from the dust scrubbers, which are sometimes used to control dust from tablet and capsule production.

Most wastes are nontoxic, have relatively small flows, and have low 5-day BOD, COD, and TSS concentrations, with near neutral pH (6.0–8.0).

Air emissions may result from the use of volatile solvents in the formulation processes.

2.3.5 Research and Development

Research and development (R & D) processes in the pharmaceutical industry involve chemical research, microbiological research, and pharmacological research to provide information for pharmaceutical production related in the above. The development of a new drug with less environmental pollution requires cooperative efforts in several fields, such as medicinal, chemical engineering, biomedical engineering, environmental engineering, biology, biochemistry, pharmacology, and toxicology.

An example is the R & D section [16] in a plant producing a wide range of dermatological products (such as shampoos, creams, and itch soothing preparations) and ophthalmic products (such as contact lens cleaners, eye drops, and disinfecting solutions). These pharmaceutical compounds are formulated in the production section after having been thoroughly researched by the R & D section. The R & D section involved two major groups: the synthetic chemistry division and the product development division. Halogenated and nonhalogenated solvents, such as chloroform, methylene chloride, acetone, methanol, acetonitrile, acetone, ethyl ether,

xylene, and hexane, are commonly used for extraction and analyses. Acetonitrile and methanol are extensively used as carrier liquid in high-performance liquid chromatography (HPLC). The plant consumed 400 gal (1514 L) of acetonitrile and 990 gal (3747 L) of methanol annually. Other chemical wastes, including photographic chemicals, radionuclides, bases, and oxidizers, can be produced from some pharmaceutical research and development sections. Sulfuric acid is the most widely used acid at an annual consumption of 450 gal (1703 L). In addition, a large quantity of sulfuric acid is used in glassware washing at an annual acid consumption of approximately 1080 gal (4088 L).

The wastes from the research and development processes can be similar to those wastes generated from one or more or all of the above four processes, chemical synthesis, fermentation, biological product extraction, and formulation, and can be even more complicated, because various attempts should be made to develop a new drug or a new pharmaceutical instrument. Radioactive wastes may also be generated.

As a result of the diverse nature of pharmaceutical research and development, a wide range of chemical and biological laboratory wastes are produced. However, the quantity, quality, and time schedule of discharging research and development wastes are usually erratic, and the problem cannot be measured entirely. The quantities of materials discharged by research and development operations are in general [25] relatively small as compared with the volumes generated by production facilities.

Pharmaceutical production can be batch, continuous, and semi-continuous operations. Batch-type production is the most common type of manufacturing technique for each of the subcategories. Table 2.1 summarizes the typical wastes and the associated process origins in pharmaceutical industry. Note that most of the process origins in the table can exist in all the five main processes but with varied qualities (i.e., having various kinds of materials and wastes) and quantities of wastes.

2.4 Waste Characterization and Options for Waste Disposal

2.4.1 Waste Characteristics

The preceding discussions show that numerous process wastes are generated by the pharmaceutical industry. The pharmaceutical wastes vary greatly depending upon the manufacturing processes. The very nature of the pharmaceutical industry determines the composition of each plant effluent, which varies considerably from plant to plant.

There are pharmaceutical plants which discharge only solid wastes, and no waste liquors in the sense of production process. However, these plants still have to deal with certain amounts of wastewater from washing of equipment and floors, etc.

A distinguishing feature of pharmaceutical fermentation and the biological product extraction manufacturing is that a large proportion of the material input to the

manufacturing process ends up as process wastes. The wastes from such a low product-yield process may be in either solid or liquid form.

Many plants generate wastewaters with COD concentration ranging from 500 to 1500 mg/L, whereas the wastewaters from fermentation and chemical synthesis products may have COD concentrations reaching 10,000 mg/L or even higher [26].

Generally, fermentation processes and chemical synthesis processes produce large flows and have high levels of 5-day BOD and COD, with high TSS for the fermentation processes, although they vary greatly from factory to factory, while the biological product extraction, formulation, and research and development tend to produce low flows with low levels of 5-day BOD, COD, and TSS [13]. Table 2.2 lists average waste flow and traditional pollutants from four manufacturing processes: chemical synthesis, fermentation, biological product extraction, and formulation/manufacturing.

Toxic pollutants can exist in the wastewaters. Especially, the waste from the chemical synthesis plant usually contains significant levels of a large number of toxic pollutants. Table 2.3 lists toxic organic pollutants associated with pharmaceutical industry according to the list of organic priority pollutants by the 1977 amendment to the US Clean Water Act.

Besides cyanide, many inorganic priority pollutants are commonly found in the waste streams from pharmaceutical industry, such as arsenic, beryllium, cadmium, chromium, copper, lead, mercury, nickel, selenium, silver, thallium, and zinc. Only a few of these priority pollutants are widespread in their occurrence or high in concentration. The significance of these facts affecting the regulation of these pollutants will be discussed later.

2.4.2 Options for Waste Disposal

There are three options of wastewater discharge for pharmaceutical manufacturing: direct discharge after treatment, indirect discharge (i.e., discharging to publicly owned treatment works, or POTW), and zero discharge. Many pharmaceutical manufacturers treat their wastes and directly discharge their treated wastewaters to the navigable waters. Some of pharmaceutical plants are so located that POTW are adequate to solve their, at least a part of, waste disposal problem. Some industrial plants generate basically no wastewater, or trade out waste, or limit the treated wastewater on-site, resulting in zero discharge. The numbers of the three types of wastewaters discharge by pharmaceutical industrial plants in the USA are listed in Table 2.4.

Deep well injection [27] generates no discharge to waterways. However, most of the deep well injections that were permitted in the early times, and at least some of them, may not be allowed for such operation sooner or later especially if the injected material has a great potential threat to the environment.

Datta Gupta et al. [28] described disposal of effluent by irrigation and application of dry waste biosolids as fertilizer [29], which may generate no wastewater

Table 2.4 Pharmaceutical process wastes [16]

Waste description	Process origin	Composition
Process liquors	Organic syntheses	Contaminated solvents
Spent fermentation broth	Fermentation processes	Contaminated water
Spent natural product raw materials	Natural product extraction processes	Leaves, tissues
Spent aqueous solutions	Solvent extraction processes	Contaminated water
Leftover raw material containers	Unloading of materials into process equipment	Bags, drums (liber, plastic, metal), plastic bottles
Scrubber water from pollution control equipment	Dust or hazardous vapor generating processes	Contaminated water
Volatile organic compounds	Chemical storage tanks, drums	Solvents
Off-spec or out-dated products	Manufacturing operations	Miscellaneous products
Spills	Manufacturing and lab operations	Miscellaneous chemicals
Waste water	Equipment cleaning, extraction residues	Contaminated water
Spent solvents	Solvent extraction or wash practices	Contaminated solvents
Used production materials	Manufacturing operations	Miters, tubing, diatomaceous earth
Used chemical reagents	R & D operations	Miscellaneous chemicals
Natural gas combustion products	Steam boilers	Carbon compounds, oxides of nitrogen and sulfur

discharge. Lane [25] described an alternative treatment and disposal of spent beer by spray irrigation. The spent beer frequently contains high amounts of nitrogen, phosphate, and other plant growth factors. However, it is also likely to contain salts, like sodium chloride and sodium sulfate, as a result of the extraction process. The presence of such salts depending on their concentration can cancel out the value of the spent beer as a fertilizer. Spray irrigation is mainly used for the purpose of disposal of the spent beer, rather than just for its value as a fertilizer. This disposal technique has a number of limitations: (a) large land areas are needed in the order of 125 acres (505,875 m^2) for 100,000 gal (378,500 L) of spent beer sprayed per day and (b) the land should be reasonably flat so that runoff from the spraying does not result in erosion or "puddling" in low spots [29]. The "puddling" will result in odors that will most likely render the entire operation a public nuisance.

2.5 Environmental Regulations on Pharmaceutical Wastewater Discharges

Wastes generated from pharmaceutical manufacturing could exert various impacts on the environment, such as the following:

1. Color and odor problems due to the spent solvent, their raw materials, and spent chemicals
2. The growth of bacteria in the biosolids from fermentation and natural extraction processes
3. Oxygen depletion due to the relatively high oxygen demand load
4. Toxic materials such as heavy metal, cyanide, and toxic organic compounds
5. Air pollution due to volatilization of volatile organic solvents

The total pollution load of wastewaters generated by the pharmaceutical manufacturing industry in the USA was reported by the USEPA [13] as shown in Table 2.5.

2.5.1 Regulations for Direct Discharge

To ease the impact of waste discharge to the environment, the Clean Water Act requires a permit for any discharge into the nation's waterways. Direct discharge into surface water must have a National Pollutant Discharge Elimination System (NPDES) permit and/or a State Pollutant Discharge Elimination System (SPDES) permit. The NPDES permit or the SPDES permit is granted on a case-by-case basis.

The USEPA [11, 12, 15] regulation applies to facilities organized into five subcategories for this pharmaceutical industry (40 CFR Part 439): (a) subcategory A (fermentation products), (b) subcategory B (extraction products), (c) subcategory C (chemical synthesis products), (d) subcategory D (mixing/compounding and formulation), and (e) subcategory E (research).

The USEPA has regulated what is known as the Best Practicable Control Technology Currently Available (BPT). The direct discharge limitations are presented in Table 2.6.

The regulation for cyanide is the same in the Best Available Control Technology Economically Achievable (BAT) and the New Source Performance Standards (NSPS). The regulations have been delineated mainly for the four subcategories: fermentation, biological extraction, chemical synthesis, and formulation. The USEPA tends to deregulate the effluent discharge from R & D, because only an

Table 2.5 Characteristics of major pharmaceutical wastewater streams [13]

Process	Waste flow MGD	BOD_5 mg/L	COD mg/L	TSS mg/L	pH	Priority pollutant
Fermentation	0.622	1668	3452	1023	4–8	Cu, Zn
Natural extraction	0.197	42	132	93	6–8	Pb, Zn. solvents
Chemical synthesis	0.477	2.385	4.243	414	1–11	Variety
Formulation	0.296	339	846	308	6–8	

Note: *MGD* million gallon per day (1 MGD = 3.784 m^3/day)

Table 2.6 Organic priority pollutants from pharmaceutical manufacturing

Organic compounds	Concentration (μg/L)	
	Average	Range
1. PAH (polynuclear aromatic hydrocarbons)		
Acemaphtherie	12	0–100
Naphthalene	2.8	0–14
Anthracene	1.8	0–7
Fluorine	3.5	0–41
Phenanthrene	1.8	0–7
2. Nitrogen compounds		
1,2-Diphenylhydrazine	2	0–17
N-Nitrosodiphenylamine	12	0–1400
3. Aromatic compounds		
Benzene	220	0–2100
Chlorobenzene	67	0–600
2.4-Dinitrotoluene	12	0–49
Ethylbenzene	16	0–86
Toluene	2400	0–17,000
4. Halogenatcd hydrocarbons		
Carbon tetrachloride	460	0–6000
1,2-Dichloroethane	8.7	0–74
1,1,1-Trichloroethane	10	0–130
1,1,2-Trichloroethane	95	0–1300
1,1,2,2-Tetrachloroethane	2	0–10
Chloroform	300	0–1600
1,1-dichloroethylene	8.9	0–95
Methylene chloride	2600	0–20,000
Methyl chloride	300	0–1500
Methyl bromide	3	0–15
Tetrachloroethylene	3.5	0–36
Trichloroethylene	8	0–62
5. Ethers		
Bis(2-chloroethyl) ether	19	0–170
6. Phenolic compounds		
2-Chlorophenol	2.4	0–22
2.4-Dichlorophenol	1	0–5
4-Nitrophenol	400	0–3500
Pentachlorophenol	4.4	0–62
7. Phthalates		
Bis (2-ethylhexyl)	37	0–170
Butyl benzyl phthalate	33	0–360
Di-n-butyl phthalate	10	0–90
Diethyl phthalate	8	0–31

insignificant amount of wastes is discharged and the wastes have similarity in quality to those from the other four sections.

Note that many of the priority pollutants which may be found from pharmaceutical discharges are excluded from direct discharge regulation because either they are present at low level or they are infrequent for occurrence, or their presence amount is too small to be effectively reduced by the current technology.

2.5.1.1 Best Practicable Control Technology Currently Available (BPT)

The USEPA is revising the BPT effluent limitation guidelines for chemical oxygen demand (COD) for subcategories A, B, C, and D. Appendix 1 presents these final limitations, which are based on the application of advanced biological treatment. The existing BPT effluent limitation guidelines for pH, BOD_5, and TSS are being maintained for all subcategories. The existing BPT effluent limitation guidelines for cyanide are being refined; the compliance monitoring requirements for these limitations have been clarified. Limitations on cyanide for B and D subcategories are being withdrawn.

2.5.1.2 Best Available Control Technology Economically Achievable (BAT)

The EPA is revising the BAT effluent limitation guidelines for subcategories A and C. For subcategories A and C, the EPA is adding BAT effluent limitations for ammonia as nitrogen (N), COD, and 30 priority and nonconventional organic pollutants. For subcategories B and D, the EPA is setting a BAT effluent limitation for COD that is equivalent to the BPT limitation. No additional BAT effluent limitations are being set for subcategories B and D. However, EPA is withdrawing the current BAT effluent limitations for cyanide for subcategories B and D. Appendixes 2 and 3 present these final effluent limitation guidelines, which are based on the following: end-of-pipe advanced biological treatment with nitrification for subcategories A and C and end-of-pipe advanced biological treatment for subcategories B and D.

2.5.1.3 New Source Performance Standards (NSPS)

The USEPA is setting NSPS for priority and nonconventional pollutants for subcategories A and C. The NSPS for subcategories A and C include ammonia (as N) and 30 priority and nonconventional organic pollutants, based on advanced biological treatment with nitrification.

The USEPA is also revising the NSPS controlling discharges of BOD_5, COD, and TSS for subcategories A, B, C, and D based on advanced biological treatment. The USEPA is withdrawing cyanide standards for subcategories B and D. Final NSPS for subcategories A and C are presented in Appendix 4. Final NSPS for subcategories B and D are presented in Appendix 5.

2.5.2 Regulations for Indirect Discharge

As mentioned earlier, an alternative way to discharge wastewaters from pharmaceutical plants is discharging their wastewaters to the publicly owned treatment works (POTW) for further treatment. However, the wastes and wash water from pharmaceutical plants, especially from chemical synthesis manufacturing, are not always compatible with biological waste treatment plants. The waste and wash water may be too concentrated or too toxic (such as heavy metal and cyanides) that will harm the POTW biological treatment systems. Moreover, high-acid waste can seriously destroy the material used to seal the sewer joints and can retard biological treatment; flammable solvents may cause fire or explosion and then cause damage and interruption of sewer systems.

To assist control authorities and approval authorities for industrial discharge to POTWs, the USEPA has developed the National Categorical Pretreatment Standards for point sources. These categorical pretreatment standards are designed to prevent the discharge of pollutants which pass through, interfere with, or are otherwise incompatible with the operation of POTWs. Specifically, the Pretreatment Standards for Existing and New Sources (PSES and PSNS) were established for the indirect dischargers to prevent the pollutants which are incompatible with or not susceptible to treatment in a POTW [15]. The priority pollutants considered for pretreatment standards are listed in Table 2.7.

The PSES and PSNS regulate an indirect discharge limitation for cyanide.

The waste to be discharged to the POTW must meet the influent requirements, and the factory must pay attention to the municipal sewer system. Pretreatment is usually required before discharging to the POTW.

2.5.2.1 Pretreatment Standards for Existing Sources (PSES)

The USEPA is revising PSES for priority and nonconventional pollutants for subcategories A, B, C, and D. For subcategories A and C, the USEPA is setting PSES for ammonia (as N) and 23 priority and nonconventional organic pollutants based on steam stripping. For subcategories B and D, the USEPA is setting PSES for five priority and nonconventional organic pollutants based on steam stripping. Revised PSES for subcategories A, B, C, and D are presented in Appendixes 6 and 7.

Table 2.7 Statistical data for the three types of wastewater discharges

Type of discharge	Number of plants	Wastewater flow MGD	
Direct discharger	52	24.9	11%
Indirect discharger	285	39.9	62%
Zero discharger	127	0	27%
Total plant	464	64.8	100%

Note: *MGD* million gallon per day (1 MGD = 3.784 m^3/day)

2.5.2.2 Pretreatment Standards for New Sources (PSNS)

The USEPA is revising PSNS for priority and nonconventional pollutants for subcategories A, B, C, and D equal to PSES. Revised PSNS for subcategories A, B, C, and D are presented in Appendixes 8 and 9.

2.5.3 Historical View on Regulations

To protect the environment, the USEPA has regulated the BPT, which is basically identical to those shown in Table 2.6. As mentioned earlier, the wastewaters from fermentation and chemical synthesis of products may have COD ranging between 10,000 and 20,000 mg/L. According to the BPT, which is defined as a COD removal of 74%, the fermentation and chemical plants may be able to discharge their treated wastewater with COD concentration from 2600 to 5200 mg/L to meet 1976 BPT [26]. In November 1982, the USEPA proposed the BAT and the NSPS to control the discharge of nonconventional pollutant, COD, as well as other pollutants from pharmaceutical manufacturing facilities [9, 10, 15]. However, the industry commented that the proposed regulations could not be met based on the USEPA-proposed technology. In 1983 and modified in 1998, the USEPA promulgated final Pharmaceutical Manufacturing Point Source Effluent Limitation Guidelines, Pretreatment Standards, and NSPS [11, 12, 15].

The Agency decided to return to the 1976 BPT subcategorization discharge. The 1982-proposed COD regulations are no longer valid. Therefore, the BPT limitations listed in Table 2.6 are basically the 1976 version and finalized in 1983. However, the USEPA reserved a final decision on appropriate BAT limitations and NSPS for COD which is postponed until additional information could be obtained on applicable COD removal technologies and their achievable concentrations.

On December 16, 1986, the USEPA promulgated the BCT limitations for the existing pharmaceutical manufacturing facilities. The existing pharmaceutical manufacturers that are subcategorized A–D productions are covered by this regulation, which set equal to the BPT limitations in 1983. All these guidelines have been reissued in 1998 [15].

It should be pointed out that the US pharmaceutical industry is largely an international industry in which many companies have manufacturing facilities and sales and distribution operations in countries other than the USA. In addition to US federal statutes and regulations, there are international laws, regulations, treaties, conventions, and initiatives which are drivers of the environmental programs of pharmaceutical companies. The Basel Convention, the ISO 14000 standards, the environmental requirements of NAFTA, and the evolving European Union Directives and Regulations are a few examples of important international environmental standards and programs which affect this industry [14].

2.5.4 Regulations for Managing Pharmaceutical Wastes

Managing Pharmaceutical Waste A 10-Step Blueprint for Healthcare Facilities In the United States [108] was published by the USEPA in 2008, and therefore, does not cover the most recent federal and state regulations for hazardous waste pharmaceuticals. On February 22, 2019, the USEPA published *Management Standards for Hazardous Waste Pharmaceuticals and Amendment to the P075 Listing for Nicotine* (referred to as the "Final Rule") [109]. The Final Rule became effective in the US federally managed states and territories on August 21, 2019. All states in the USA are expected to adopt the Final Rule by the deadline of July 1, 2022. One aspect of this rule, prohibiting the disposal of hazardous waste pharmaceuticals into sewers, took effect in all states and territories on August 21, 2019, under the Hazardous and Solid Waste Amendments (HSWA) regulations.

In 2021, the USEPA work was initiated to update the 10-Step Blueprint to reflect the 2019 regulatory changes. It is anticipated that this work will be completed by March 2022 and the new document will be available on the Healthcare Environmental Resource Center (HERC). Although the 2008 document is not current with regard to federal regulation of hazardous waste pharmaceuticals, it does contain valuable non-regulatory waste management information that remains valid today.

A "10-Step Blueprint for Managing Pharmaceutical Waste of Healthcare Facilities In the United States" [108, 109] is introduced in this section. The steps in this blueprint do not necessarily have to be taken consecutively. Some steps will occur in parallel, and other steps will probably be referenced throughout the development of your pharmaceutical waste management program. The following is a summary of the ten steps and how each can be used to develop and implement your pharmaceutical waste management program:

1. Step l begins with some action items that you can begin immediately.
2. Step 2 is an overview of how the federal Resource Conservation and Recovery Act (RCRA) regulations apply to pharmaceutical waste management.
3. Step 3 begins where the regulations leave off providing guidance on how to manage non-regulated hazardous pharmaceutical waste.
4. Step 4 walks you through the steps necessary to perform a drug inventory review. This step can be very tedious and time consuming.
5. Step 5 alerts you to waste minimization opportunities. It will be helpful to become familiar with the waste minimization opportunities before assessing your current practices based on the guidance provided in Step 6. Review these opportunities again upon completion of the department reviews.
6. Step 6 discusses performing department reviews and determining your generator status.
7. Step 7, taking on the communication/labeling challenge, is one of the most critical aspects of implementing a pharmaceutical waste management program and possibly the most challenging. How you decide to communicate pharmaceutical disposition information to the people handling the waste will depend

and be dependent upon which of the management options presented in Step 8 you select.
8. Step 8, considering the management options, introduces you to five implementation models that have worked for other hospitals. You may choose one model or a hybrid.
9. Step 9, getting ready for implementation, assists you with vendor selection, satellite and storage accumulation, and pilot program development.
10. Step 10, launching the program, is the culmination of the first nine steps, plus the actual rollout to the entire facility.

After the program is launched, the next steps will be (a) providing additional pharmaceutical waste management assistance to hospitals; (b) clarifying, reconsidering, and expanding RCRA hazardous waste regulations, (c) eliminating drain disposal; (d) making the hazardous waste determination, a communications challenge; (e) broadening national knowledge base of pharmaceutical waste generation; (f) managing waste minimization; and (g) managing routinely wasted drugs.

2.6 Waste Management

2.6.1 Strategy of Waste Management

The main objectives of pharmaceutical waste management are to reduce waste generation through improved manufacturing process and enhanced solvent recovery; to remove suspended matter, odor, BOD matter, and hazardous and toxic materials; and to prevent air pollution.

This section discusses three main tasks of waste management in pharmaceutical industry:

1. In-plant control
2. In-plant treatment
3. End-of-pipe treatment

The load on the end-of-pipe treatment process depends on how well the in-plant control is practiced. The in-plant control usually analogs to waste minimization. However, waste minimization is defined by the USEPA as source reduction and recycling, which covers a somewhat different practice from the traditional in-plant control, including the interplanetary efforts to minimize wastes such as waste exchange. In general, in-plant control is a means of waste management, and an interplanetary waste exchange program in waste minimization cannot be practiced without a well-oriented in-plant management. The waste exchange will be presented in the section of in-plant control.

Since wastewater treatment and pollutant removal costs are highly influenced by the pollutants and volume of water to be treated, the costs for treating a segregated stream are considerably less than that would be in treating combined wastewater.

Also, chemicals other than those being treated are less likely to interfere with the treatment technology if treatment occurs before mixing [11, 13]. The importance of waste separation has been recognized, which is reflected by the fact that in-plant treatment deals with a segregated particular pollutant. The in-plant control is mainly a source control to reduce generation of waste, while the end-of-pipe treatment mainly deals with overall waste in the plant. From the view point of treatment, inplant treatment can be visualized as end-of-pipe treatment or a pretreatment for a particular production process, while from another point of view, it is an in-plant process to reduce waste before being discharged to an overall waste stream.

2.6.2 In-Plant Control

In-plant control includes water conservation, raw material substitution, chemical substitution, material recovery, extensive recycling of wastewater, and modification and improvement of processes, so that the amount of wastewater can be reduced and pollution can be minimized. The following are some examples of in-plant controls that have been demonstrated effectively in reducing pollution loads.

2.6.2.1 Material Substitution

Material substitution is a replacement of one or more of the raw materials used in production to reduce the toxicity or volume of wastes generated.

Material substitution has been demonstrated to be successful in pharmaceutical tablet coating operations to reduce hazardous waste generation. Wayman and Miller [30] reported a successful material substitution in tablet coating which reduced the usage of methylene chloride from 60 to 8 ton/year by converting the conventional film coating to aqueous film coating. The other example, a water-based solvent and new spray equipment for a tablet coating developed in a manufacturing plant, eliminated expensive (US $180,000) air pollution control equipment, resulting in a savings of US $15,000 per year in solvent makeup cost [31]. Other material substitutions that may be suitable for pharmaceutical manufacturing include the use of aqueous-based cleaning solutions instead of solvent-based solutions and the replacement of chlorinated solvents with non-chlorinated solvents [13]. Moreover, using nontoxic or less toxic biocides to substitute the heavy-metal-containing biocides in the fermentation processes can avoid the correlated heavy-metal contamination.

For the pharmaceutical industry, however, product reformulation seems to be very difficult, because the reformulation must have the same therapeutic effect, stability, and purity profile as the original formulation. Moreover, it takes a considerable amount of time for the US Food and Drug Administration (USFDA) to approve of the reformulated drug. Another problem that a reformulation may encounter is the possibility of customer rejection of the product due to changes of the product's aesthetic qualities such as taste, color, dosage, or form. Because of the difficulties in

reformulation, waste minimization should be introduced at the research and development phase [16].

Another sort of material substitution is to substitute the toxic materials used in the waste recovery and cycling processes, such as using nontoxic chemicals to substitute for zinc and lead containing agents in a precipitation process.

2.6.2.2 Process Modification

Modification or modernization of the existing processes is another opportunity to reduce waste generation.

The modification can be accomplished through, for example, controlling a suitable feed rate, a proper agitating and mixing, optimizing operating temperatures, and automation control. In most cases, the product/process yield determines the product/waste ratio. Inadequate feeding rate, mixing, or temperature control in pharmaceutical manufacturing can cause a high byproduct yield. Reactor efficiency can be improved, and byproduct formation can be reduced by controlling reaction parameters.

Increased automation can reduce operation errors. For example, introducing automation in material handling and transfer processes can reduce spillage.

Another process modification option is to redesign chemical transfer system to reduce physical material losses [13]. For example, replacing gas pressurization with a pumped transfer eliminates the tank pressurizing step and its associated material losses [32].

Other design considerations for waste minimization include modifying tank and vessel dimensions to improve drainage, installing internal recycle systems for cooling wasters and solvents, selecting new or improved catalysts, switching from batch to continuous processes for solvent recovery, and optimizing process parameters to increase operating efficiency. Manufacturing processes have demonstrated that excessive solvent emissions from the purging of autoclaves used for the manufacture of synthetic steroids can be considerably reduced by installing rotameters with integral needle valves to control nitrogen flow into the reactor; nitrogen flow and resulting solvent vapor pickup can be reduced by a factor of six compared with the baseline situation where nitrogen flow is not controlled and operated in an on-off fashion without throttling [16].

The major obstacles of process modification to the waste minimization are new processes must be tested and validated to ensure that the resulting product is acceptable; a considerable amount of time may be needed for the US FDA approval, if applicable, before instituting any change; extension process changes can be expensive; and downtime will occur when production is stopped for new equipment installation.

The routine cleanup in the pharmaceutical plant can be carried out most effectively by vacuum cleaning. Wash water may be a water pollutant. Special attention should be given to prevent such material from entering the sewer system. Lane [25] has shown that a central wash area with portable equipment can be usable. The

portable (even large) equipment can be moved to a central wash-up area, providing better prevention of dumping of hazardous pollutants to the sewer system.

2.6.2.3 Recycling Wastewater and Recovering Materials

Recovering and recycling include directly reusing waste material, recovering used materials for a separate use, and removing impurities from waste to obtain relatively pure substances. The goal is to recover materials for reuse in the process or for reuse in a different application. The restricted quality control requirements of the pharmaceutical industry often restrict reuse opportunities. After a high degree of purification, materials recovered from manufacturing processes may be reused. Recycling can be performed either on-site or off-site. On-site can be either integral to an operation or in a separate operating area. The value of a waste depends on the type, market, purity, quantity and frequency of generation, and distance between the generator and the recycling operation.

One of the important recycling programs in the pharmaceutical industry is the recycling of solvent. Solvents are used for reaction media, extraction media, equipment cleaning, and coating media. Processes for solvent recovery from concentrated waste streams include distillation, nebulization, evaporation, liquid-liquid extraction, filtration, decantation, centrifugation, flotation, and sedimentation. The commonly used and recycled solvents are acetone, cyclohexane, methylene chloride, ethyl acetate, butyl acetate, methanol, ethanol, isopropanol, butanol, pyridine, methyl ethyl ketone, methyl isobutyl ketone, and tetrahydrofuran [33]. Solvent waste recyclability can be improved through special arrangement of recycling procedure: for example, minimizing solid concentration in solvent wastes, segregating chlorinated solvent wastes from non-chlorinated solvent wastes, segregating aliphatic from aromatic solvent wastes, segregating chlorofluorocarbons from methylene chloride, and segregating water wastes from flammables.

2.6.2.4 Water Conservation and Reuse

It is more cost-effective to treat the waste with smaller volume but higher concentration than a waste with greater volume but lower concentration. Recycling and reusing renovated wastewater is recommended. It has been estimated that about 1–100 tons (0.9072–90.72 metric tons) of water are used per ton of product. By modifying processing procedures or auxiliary equipment, water usage and wastewater generation may be significantly reduced [21]. Examples are the use of surface rather than barometric condensers, reuse of noncontact water, concentration of reaction mixtures to limit waste volume, and combining several processes.

King [34] has described an oil-dehydration evaporator/pyrolysis system for energy recovery from pharmaceutical wastewater. Gas produced in the pyrolysis unit is burned to provide steam required by the evaporator for oil dehydration.

2.6.2.5 Segregation and Concentration of Wastes

Concentrating waste may reduce treatment cost. Concentration of wastewater may also minimize the impact of intermittent hydraulic surges, specifically in fermentation operations. Segregation of waste streams, which allows concentrating the individual waste for individual treatment, often allows more efficient removal of particular pollutants. Segregation of wastes also allows using an individual treatment method for the individual waste, such as using various evaporation or dewatering methods to treat the separated waste streams for the fermentation wastes in an in-plant treatment program. For example, cyanide destruction, metal removal, and steam stripping to remove ammonia and organic solvents are utilized in the pharmaceutical industry for in-plant treatment. They need to be separated individually. Individual process units are now commonly designed with allowance for waste stream segregation.

For a similar reason, separation and treatment for storm runoff and sewer system may eliminate the discharge of contaminated runoff and reduce treatment cost, because the storm water from certain manufacturing areas can contain high levels of toxic pollutants, while the storm runoff from some other areas and the sewer may not. For the factories practicing in-plant treatment and direct discharge, the domestic wastewater should be separated from polluted storm runoff. The latter should be discharged directly to POTW or treated in-plant separately, while the non-polluted storm runoff can be separated from polluted streams and discharged directly to a river.

Sewers and pumps must be designed for peak flows to avoid flooding the mill or bypassing the treatment plant. Also a good pipe and storage system are needed for collecting the spills and the wastewater from various stages and storing wastewater and biosolids.

2.6.2.6 Good Operating Practices

Good operating practices, which can help reduce waste generation, material losses, and production cost, include closer supervision, production scheduling, material tracking, inventory control, spill prevention, material handling and storage procedures, documentation for process procedure, maintenance programs, employee training, and management incentives. As these practices all apply to the general waste minimization in all industries.

2.6.2.7 Reduction of Air and Dust Problems

Air pollution control in the pharmaceutical industry is mainly practiced by in-plant control. Air and dust control technologies are fully described in *Air Pollution Control Engineering* [35] and *Advanced Air and Noise Pollution Control* [36].

There are three main sources of air pollution: fermentation process gas, dust, and volatile solvents.

Most of the fermentations carried out in the pharmaceutical industry are aerobic [25]. Air must be supplied to the fermentation organism. Compressed air is injected, or sparged, into the lower end of the fermentor, which is simply a large, vertical, circular tank. Supplying fresh air to the fermentation vessel on a constant basis makes it necessary to vent or discharge an equal volume of what is termed "used" air from the top of the fermentation vessel. The used air, or vent gas, has scrubbed a number of materials, including carbon dioxide and many other more complex organic materials from the fermentation as it moves up through the fermenting mass. The organic materials generate odor. These odors vary with the material being fermented and vary somewhat between different fermentors of the same material. This "used" air, or vent gas, from the fermentor is the principal air pollutant. Wet scrubbing of the vent gases may be practiced, though it may not be particularly successful in many cases.

On large fermentors, the volume of gases is so great that the water needed to do a scrubbing job (if water is used alone to do the job) is so large that, consequently, generates even larger dimensions of polluted water to eliminate or even partially reduce air pollution. Activated carbon can be used to adsorb the odor of the vent gas. This method, however, may be practical only for large fermentors, because the method requires a larger amount of carbon to accomplish a satisfactory end point.

Incinerating vent gas is a satisfactory solution. However, sometimes fuel is needed to raise the vent gas temperature from fermentation temperature (generally well below 40 °C) to an incineration level. At this point, this method may be uneconomical. A possible more economical method may be piping the vent gas from the fermentor to a boiler house and using it for combustion air in the boiler. This method was used in large-scale operations such as in the fermentation plant at Abbott Laboratories in North Chicago, IL, and at Eli Lilly and Company in Lafayette, IN, both in the USA.

Air emission of volatile organic solvent can be a big air pollution problem, which may be reduced by employing scrubbers or condensers to reclaim the solvent vapors. Some factories may generate acid and solvent vapors such as methanol and butyl acetate, which are sent to a house vacuum system for disposal. The waste mycelium, or filter cake, which results from the initial separation of solids from the fermented beer, is a frequent source of odor. The living cell biomass is quite perishable. If housekeeping standards are not maintained at a high level, this part of the evaporation is also likely to contribute to the odor problem. Thus, good housekeeping throughout the entire plant will do much to improve an odor situation.

Dust is a secondary pollution source. Dust inside a plant may cause "cross contamination," i.e., contamination of one drug by another. Penicillin is one of the materials that are capable of causing extremely toxic reactions even when present in trace quantities [25]. For example, aspirin tablet can cause a reaction of very serious proportions (might result in death) in the presence of minute amount of penicillin. Thus, penicillin dust should be absolutely isolated from the areas where other pharmaceuticals are manufactured. Besides the isolation of penicillin production in a

separate area, the intake air to the areas producing other pharmaceuticals should be carefully filtered, because the intake air may contain the air out of the penicillin manufacturing area.

There are many methods used to remove dusts. A scrubber or RotoClone can be used for removing many pollutants. However, the use of water with a scrubber or RotoClone may result in water pollution problems. In such a case, a dry filter system may be recommended. McNeil Laboratories used an extremely large Pangborn baghouse-type dust collector to exhaust all the air from most manufacturing operations. It was 33 ft (10 m) long by 17 ft (5.2 m) wide by 20 ft (6 m) high. The inlet duct was 44 in. (112 cm) in diameter. This single unit had a capacity of 36,000 scfm (1019 m^3/min). On this point, the pharmaceutical manufacturing areas in McNeil Laboratories were supplied with 100% outside air [25], thus preventing secondary pollutant from dust.

2.6.2.8 Waste Exchanges

Waste exchange is an alternative to recycling. It involves the transfer of waste to another company for use "as is" or for reuse after treatment. Waste exchanges are private or government-subsidized organizations that help identify the supply and demand of various wastes. Waste exchanges have been established in some areas of the USA to put waste generators in contact with potential users of the waste. The USEPA [16] listed 48 state programs which offer technical and/or financial assistance for waste minimization and treatment in the USA and 24 exchange operating offices in the USA and Canada.

There are three types of waste exchanges: information exchanges, material exchanges, and waste brokers. Metals and solvents are the most frequently recycled materials via waste exchange, because of their high recovery value. Other wastes commonly recycled through waste exchanges include acids, alkali salts and other inorganic chemicals, organic chemicals, metal sludge, and solid residue from fermentation and natural product extraction processes. The biosolids from the treatment plant can also be beneficially reused off-site, which will be detailed in the section of end-of-pipe treatment.

2.6.3 In-Plant Treatment

In-plant treatment in the pharmaceutical industry is mainly for treating priority pollutants, such as solvents, metals, and cyanide, before combining the factory overall waste stream. Although all three pollutants may be removed by the end-of-pipe treatment, they can be removed more effectively by the in-plant treatment when they are concentrated in the segregated stream. Therefore, the in-plant treatment can also be regarded as a pretreatment to biological waste treatment.

2.6.3.1 Cyanide Destruction Technologies

Chemical oxidation and high pressure and temperature hydrolysis are two treatment processes which are effective in treating cyanide-bearing waste streams in the pharmaceutical industry.

Chemical oxidation is a reaction in which one or more electrons are transferred from the chemical being oxidized, here the cyanide waste, to the chemical initiating the transfer, the oxidizing agent [37–39].

2.6.3.1.1 Chlorination

Cyanide can be destructed by oxidation either with chlorine gas under alkaline conditions or with sodium hypochlorite. The oxidation of cyanide by chlorine under alkaline condition can be described by the following two-step reactions:

$$Cl_2 + NaCN + 2NaOH = NaOCN + 2NaCl + H_2O \tag{2.1}$$

$$3Cl_2 + 6NaOH + 2NaOCN = 2NaHCO_3 + N_2 + 6NaCl + 2H_2O \tag{2.2}$$

Cyanide is oxidized to cyanate at a pH of about 9.5–10.0. Usually 30 min are required to complete the reaction, which markedly reduces the volatility and toxicity (thousand fold reduction) of the waste. Figure 2.3 sketches a chlorination process for a cyanide destruction system.

Since cyanate may revert to cyanide under some conditions, additional chlorine is provided to oxidize cyanate to carbon dioxide and bicarbonate. The complete oxidation of cyanate requires several hours at pH about 9.5–10.0 but only 1 h at a pH between 8.0 and 8.5. Also, excess chlorine must be provided to break down cyanogen chloride, a highly toxic intermediate compound formed during the

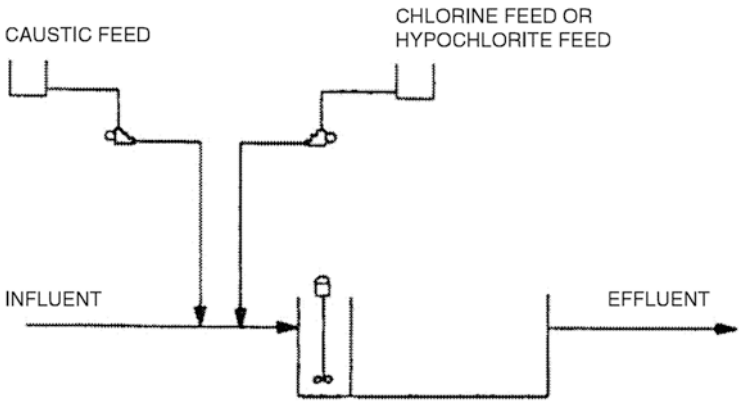

Fig. 2.3 Chlorination process for a cyanide destruction system [13]

oxidation of cyanate. Although stoichiometric oxidation of a part of cyanide to cyanate requires only 2.73 parts of chlorine and complete oxidation of a part of cyanide to carbon dioxide and nitrogen gas requires 6.82 parts of chlorine, nearly 3–4 parts of chlorine are needed for oxidizing 1 part cyanide to cyanate, and 8 parts of chlorine are needed for oxidizing 1 part of cyanide to gases in practice.

Iron interferes seriously with the alkaline chlorination of cyanide wastes. However, it has been reported that ferrocyanides are treatable by alkaline chlorination at a temperature of 71 °C and at a pH of about 12.0.

Ammonia also interferes with the chlorine oxidation process by the formation of chloramines, resulting in an increase of chlorine demand.

Cyanide levels around 0.040 mg/L are achievable by in-plant chlorination processes in electroplating industry, if reaction interferences are not present [13]. It was reported that in inorganic chemical industries, the free cyanide level after chemical oxidation treatment is generally below 0.1 mg/L.

Chlorination process is a relatively low-cost system and does not require complicated equipment and has received widespread application in the chemical industry. It also fits well into the flow scheme of a wastewater treatment facility.

There are limitations and disadvantages for the chlorination process. For example, toxic, volatile intermediate-reaction products can be formed. Thus, it is essential to control properly the pH to ensure that all reactions are carried to their end point. Also, for waste streams containing other oxidizable matter, chlorine may be consumed in oxidizing these materials, and this may interfere with the treatment of the cyanide. A potential hazardous situation may exist in storage and handling when gaseous chlorine is used.

2.6.3.1.2 Ozonation

Ozonation is an alternative oxidation treatment for cyanide destruction [13]. In fact, ozone oxidizes many cyanide complexes (e.g., iron and nickel complexes) that are not broken down by chlorine.

The oxidation of cyanide by ozone to cyanate occurs in about 15 min at a pH of 9.0–10.0, but the reaction is almost instantaneous in the presence of traces of copper or manganese as catalysts. The pH of the cyanide waste is often raised to 12.0 to obtain complete oxidation.

Oxidation of cyanate to the final end products, nitrogen and bicarbonate, is a much slower and more difficult process unless catalysts are present. Since ozonation will not readily affect further oxidation of cyanate, it is often coupled with such independent processes as dialysis or biological oxidation.

The disadvantages of ozonation include the following:

1. Higher capital and operating costs than chlorination.
2. Toxicity problems similar to chlorination.
3. Ozone demand is increased when other oxidizable matter is present in the waste stream.
4. The cyanide is not effectively oxidized beyond the cyanate level in most cases.

2.6.3.1.3 Alkaline Hydrolysis

Alkaline hydrolysis is a process based on the application of heat and pressure [13]. In this process, a caustic solution is added to the cyanide-bearing wastewaters to raise the pH to between 9.0 and 12.0. Then, the wastewater is transferred to a continuous flow reactor at temperatures in the range of 165–185 °C and pressures of 90–ll0 psi (625–763 kPa). The breakdown of cyanide in the reactor is generally accomplished within a residence time of about 1.5 h.

It has been reported [13] that an average effluent level of 5.25 mg/L is achievable for cyanide destruction. Alkaline hydrolysis is an economic process and has much less storage and handling problems than chlorination. It is more likely suitable for wastewaters with high concentrations of cyanide.

2.6.3.2 Metal Removal

Although the USEPA does not promulgate effluent guideline limitations for metals in the pharmaceutical industry, it is useful to improve metal removal to release the impact of heavy metals on the environment. In fact, some factories are practicing removal of heavy metals in the waste stream [13]. The methods usually used for metal removal are precipitation through adjustment to the optimum pH, sulfide precipitation, and chemical reduction.

2.6.3.2.1 Alkaline Precipitation

The solubility of metal hydroxides, in most cases, is a function of pH. Therefore, adjustment to the optimal pH for precipitation of the metal hydroxide will result in an effective removal of the metal. The alkaline precipitation for metal removal system is schematically shown in Fig. 2.4. It should be noted that the solid contact clarifier shown in Fig. 2.4 can be either a settling or a dissolved air flotation (DAF) clarifier [40].

The solid metal hydroxides are coagulated (using coagulating agents) in clarifier and deposited as sludge.

Lime is the commonly used chemical. In wastewaters containing substantial sulfate compounds, insoluble calcium sulfate precipitates will form when using lime. In such instances, sodium hydroxide may be used.

The alkaline precipitation method is a well-demonstrated wastewater treatment technology. It is easy to operate and has lower cost than other methods. Its limitations and disadvantages are that (a) alkaline precipitation is subject to interference when mixed wastes are treated and (b) relatively high quantities of residue can be generated.

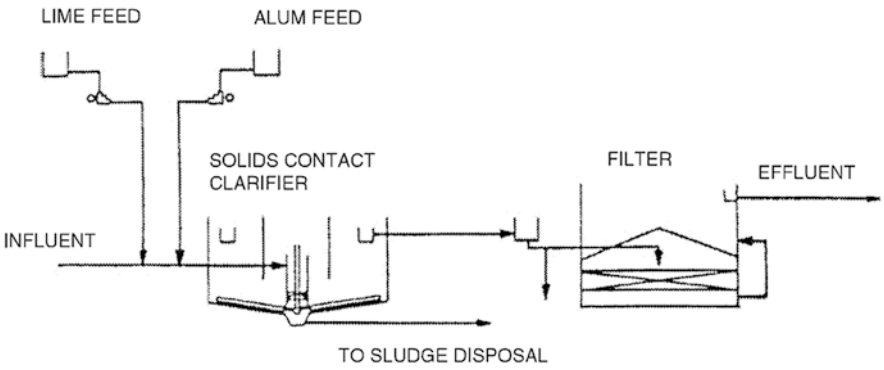

Fig. 2.4 Alkaline precipitation for a metal removal system [13]

2.6.3.2.2 Sulfide Precipitation

For many heavy metals (such as copper, nickel, and zinc), their sulfides have much lower $_{Ksp}$ than their hydroxides (see Table 2.8). Hence, the sulfide precipitation method is applicable to the removal of all heavy metals by precipitating them as metal sulfides. In the process, sulfide is supplied by the addition of a slightly soluble metal sulfide that has solubility somewhat greater than that of the sulfide of the metal to be removed. Normally ferrous sulfide is used [40].

Heavy metal sulfide sludges are less subject to leaching than hydroxide sludges. However, sulfide precipitation produces sludge in greater volumes than does alkaline precipitation. Separation of heavy metal sulfides by dissolved air flotation is also a viable alternative [41].

2.6.3.2.3 Chemical Reduction

Some heavy metals (e.g., chromium which is a common metal contaminant in pharmaceutical wastewater) have higher solubility in their higher valency (e.g., hexavalent chromium) than those in their lower valency (e.g., trivalent chromium). The general procedure is first to reduce the valency of chromium from +6 to +3 adnd then second to precipitate the product, chromium sulfate, at a suitable pH range by either alkaline precipitation or sulfide precipitation, forming insoluble chromium precipitates (either chromium hydroxide or chromium sulfide depending on the process method used). Sulfur dioxide, sodium bisulfite, sodium metabisulfite, and ferrous sulfate are strong reducing agents in aqueous solution and are used for chromium reduction. The chromium precipitates can be removed by filtration, sedimentation clarification, or dissolved air flotation clarification [41, 42].

Some heavy metals are bonded in organic compounds, making their removal more complicated. A typical example is from Merck, one of the largest

Table 2.8 Annual mass loadings from direct and indirect pharmaceutical wastewater discharges

Pollutants	Mass loadings for direct dischargers (1000 lb/year				Mass loadings for indirect dischargers (1000 lb/year)+			
	Subcategories A, B, and C		Subcategory D		Subcategories A, B, and C		Subcategory D	
	Raw waste water	Final effluent	Raw waste water	Final effluent	Raw waste water	Discharge to POTW	Raw-waste water	Discharge to POTW
Conventional pollutants								
BOD_5	83,000	5900	4100	300	169,000	169,000	5600	5600
TSS	45,000	4600	1200	290	64,500	64,500	3000	3000
Priority pollutants								
Volatile organics	2000	77	240	6	2400	2000	18	18
Semivolatile organics	120	2	17	0.2	390	330	16	16
Pesticides	–	–	–	–	0.02	0.02	–	–
Metals	60	22	1.2	0.7	51	45	2	2
Cyanide	22	7	0.3	0.2	4.3	4.1	0.3	0.3
Nonconventional pollutants								
COD	192,000	44,000	7500	800	411,000	411,000	24,000	24,000
Volatile organics	5100	–	1000	–	7700	–	2200	–
Semivolatile organics	59	–	10	–	87	–	25	–
Pesticides/ Herbicides	63	–	II	–	92	–	26	–
Industry characteristics								
Number of facilities	30		21		130		155	
Wastewater flow, MGD	21.38		3.54		31.1		8.8	

– Negligible

pharmaceutical companies. The company used an organomercury compound (thimerosal, RSHgEt) as a slow killing biocide in the fermentation process [43].

They developed an at-source treatment technology to remove and recover mercury from the spent fermentation wastewater. The removal and reclamation of mercury from wastewater is accomplished by the following four steps:

1. Using aluminum (at pH = 11.5) to reduce the sulfur-hydrogen of thimerosal to release mercury at cationic state in water with the reaction:

$$\mathrm{Al} \rightarrow \mathrm{A1}^{3+} + 3\mathrm{e}^{-} \tag{2.3}$$

and one of the following reactions:

$$2\mathrm{e}^{-} + \mathrm{RSHgEt} + 2\mathrm{H_2O} \rightarrow \mathrm{RH} + \mathrm{HSHgEt} + 2\mathrm{OH}^{-} \tag{2.4}$$

$$2\mathrm{e}^{-} + \mathrm{RSHgEt} + \mathrm{H_2O} \rightarrow \mathrm{RH} + \mathrm{HOHHgEt} + \mathrm{S}^{2-} \tag{2.5}$$

$$4\mathrm{e}^{-} + \mathrm{RSHgEt} + 2\mathrm{H_2O} \rightarrow \mathrm{RH} + \left[\mathrm{HHgEt}\right] + \mathrm{S}^{2-} + 2\mathrm{OH}^{-} \tag{2.6}$$

(Note: Since most of the biocides are associated with cell mass, caustic hydrolysis is used to release organomercury compound from cell paste before treatment.)

2. Using sodium borohydride to reduce mercury ions to the element state:

$$4\mathrm{Hg}^{2+} + \mathrm{NaBH_4} + 8\mathrm{OH}^{-} \rightarrow 4\mathrm{Hg} + \mathrm{NaBO_2} + 6\mathrm{H_2O} \tag{2.7}$$

This process is at the ambient temperature and at pH = 10; the pH should be maintained at 10 for about 10 min to complete the reaction. It should be noted that at low pH borohydride is unstable. For example, at pH = 7, the following reaction will occur:

$$\mathrm{BH_4^{-}} + \mathrm{H_2O} \rightarrow \mathrm{B}\left(\mathrm{OH}\right)_3 + \mathrm{OH}^{-} + 4\mathrm{H_2} \tag{2.8}$$

3. Applying ultrafiltration: the treated water is stirred for 1 h and the colloid mercury is separated by ultrafiltration; 99.7% removal can be reached (the Hg concentration in the effluent will be 110 ppb from an initial Hg concentration of 56 ppm).
4. Using granular activated carbon adsorption, the mercury concentration can be reduced from the 110 to 10 ppb. The overall mercury removal can be reduced by as much as 99.99% with the GAC filtration/polishing process (from an initial Hg concentration of 56 ppm to l0 ppb in the effluent). Mercury can be reclaimed from the filter cake of the ultrafiltration process.

2.6.3.3 Solvent Recovery and Removal

Solvents are used extensively in pharmaceutical manufacturing. Because solvents are expensive, most factories try to recover and purify them for reuse whenever possible. Solvent recovery and recycling is one of the in-plant source control operations and is also an in-plant treatment process. Typical techniques used for solvent recovery are decantation, evaporation, distillation, extraction [13], and nebulization [44]. Stripping has also been proved to be an effective method to recover solvents from pharmaceutical manufacturing processes.

2.6.3.3.1 Steam Stripping

Steam stripping transfers the volatile constituents of a wastewater to a vapor phase when steam is passed through preheated wastewater. The basic theory of steam stripping is associated with the partitioning of the organic compound in the vapor phase and in the wastewater phase. The partitioning coefficient (K_i), also called the vapor-liquid equilibrium constant, of compound i is expressed as follows:

$$K_i = V_i / W_i \tag{2.9}$$

where K_i is the partitioning coefficient, also called the vapor-liquid equilibrium constant, V_i is the mole fraction of organic compound i in the vapor phase, and W_i is the mole fraction of organic compound i in the wastewater phase. K_i can be calculated, for low pressures, from

$$K_i = r_i\left(P_i / P\right) \tag{2.10}$$

where r_i is the activity coefficient of organic compound i in the wastewater at a certain temperature, P_i is the vapor pressure of the pure substance at the operating temperature, and P is the total pressure.

Equations (2.9) and (2.10) show that the extent of separation is a function of the physical properties of the volatile compounds and the temperature and pressure in the stripper. The separation is also governed by the arrangement and type of equipment.

The process is performed in a steam stripper which has various types, such as packed tower, tray column, and steam flash tank. Flash tanks, which provide essentially one stage of liquid-vapor contact, are used to strip extremely volatile compounds. For the more difficult separations, columns filled with packing materials, which provide large surface areas for liquid-vapor contact, can be used.

Figure 2.5 shows the processes and flow directions in a typical column stripper. The solvent-containing wastewater is preheated, allowing the components of the wastewater to separate by partial vaporization, then is introduced at the top or near the middle of the column, and flows by gravity through the stripper. Steam is injected through a sparger and rises countercurrent to the flow of the water. When contacted with steam, the volatile organic compounds in a wastewater are driven into the vapor phase.

Solvent-containing wastewater and condensed overhead vapors from the stripper are allowed to accumulate in a gravity-phase separation tank. Because the condensate mixes with fed wastewater accumulated in the tank, the solvent concentration increases to the point at which it is saturated with solvent, when a two-phase mixture is formed. The difference between the specific gravities of water and solvents creates two immiscible liquid layers. One layer contains the immiscible solvents; the other layer is an aqueous solution which is saturated with solvents.

The solvent layer is pumped to storage. The solvent can be recovered by decanting the immiscible liquid layers or by recycling the condensed vapors directly to the

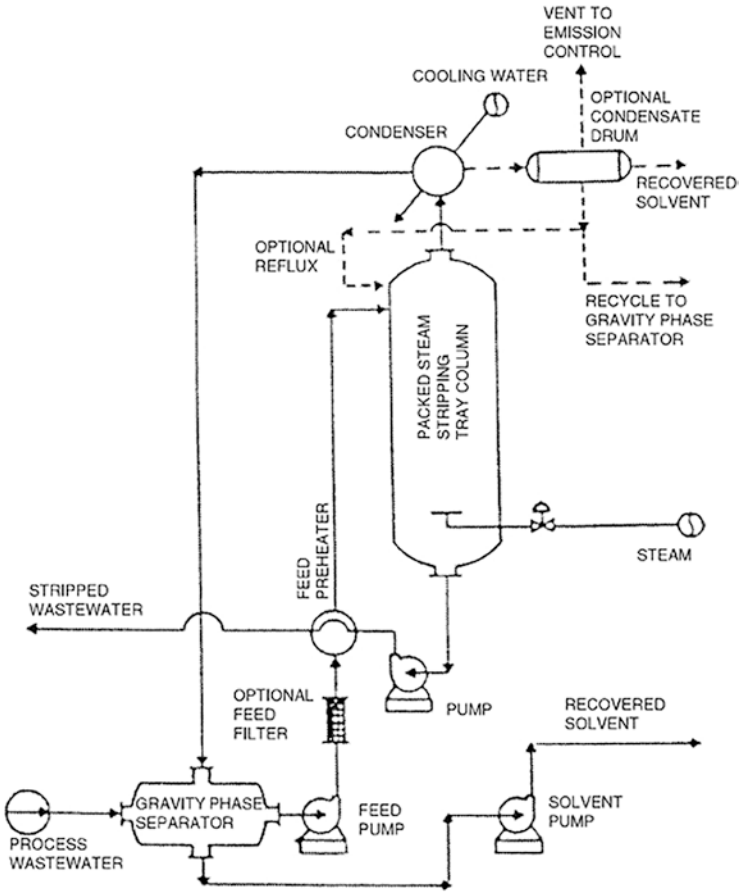

Fig. 2.5 Equipment for stream stripping solvents from wastewater [13]

gravity-phase separation tank, while the aqueous phase from the gravity-phase separation tank is pumped through a preheater where the temperature is raised by heat exchange with the stripper effluent. After preheating, the solvent-saturated water is introduced with the feed wastewater at the top or near the middle of the column and flows by gravity through the stripper.

The hot effluent, which is discharged at the bottom of the stripper, is used as a heating medium in the feed preheater. The temperatures of the feed, overhead, and bottom are controlled at about boiling point. For example, the temperatures for a methylene chloride removal in packed column steam stripper are at about 85–100 °C, with the highest for the bottom temperature and the lowest for the feed temperature (Table 2.9). The table indicates a poorer removal occurred under an upset condition when the overhead temperature is too low (<85 °C). The pressure is usually under atmospheric pressure.

Table 2.9 Summary of BPT Regulation [11, 12]

Parameter	Maximum 30-day average	Daily maximum
BOD_5 (mg/L)	Reduction 90% from raw waste	
COD (mg/L)	Reduction 74% from raw waste	
pH (unit)	6.0–9.0	
TSS (mg/L)	1.7 times BOD concentration limitation	–
Cyanide (mg/L)		
Alternative A[a]	9.4	33.5
Alternative B[b]	9.4 (0.35) R	33.5 (0.18) R

[a] Alternative A: Measure at diluent from cyanide destruction unit. Applies only when all cyanide-bearing wastes are diverted to a cyanide destruction unit and subsequently arc discharged to a biological treatment system

[b] Alternative B: Measure at final effluent discharge point. R: equals the dilution ratio of the cyanide contaminated waste streams to the total process wastewater discharge flow

This practice is particularly advantageous in cases where the wastewater to be stripped contains low concentration of the recovering solvents. The most economical operation of a wastewater steam stripper occurs when the feed is saturated with the solvent to be recovered. The composition of the recovered solvent and economic factors determines whether the solvent is reused within the plant, disposed of, used as incinerator fuel, sold to solvent reclamation facility, or sold for other users. Solvents recovered by steam stripping are normally not used directly in pharmaceutical synthesis because of the US FDA purity requirements.

If the feed contains high concentrations of suspended solids, a filter may be installed prior to the preheater to prevent fouling in the preheater and the column.

Steam stripping usually is a pretreatment method. It can effectively remove solvent from wastewater. Steam stripping has been successfully used to remove methylene chloride, toluene, chloroform, and benzene.

Many factories have reported that steam stripping enables the plants to meet a POTW requirement that the concentration of explosive vapors in the plant sewer pipes not exceed 40% of the lower explosion limit (LEL). Moreover, it has been reported [13] that greater than 99% removal and an effluent with less than 10 mg/L concentration have been achieved for a toluene wastewater. The stripped wastewater is combined with other wastewater processes in another pretreatment system for further end-of-pipe treatment, or further combined with sanitary wastewater and then discharged to the POTW.

2.6.3.3.2 Air Stripping

Air stripping is also used to recover volatile organic compounds, such as benzene, chloroform, 1,1,-I-trichloroethane, 1,2-dichloroethane, ethylbenzene, methyl chloride tetrachloroethylene, trichloroethylene, and toluene in pharmaceutical plants. The air stripping process is similar to steam stripping. The basic theory of air

stripping is associated with the partitioning of the organic compound between air and wastewater.

2.6.3.3.3 Advanced Physocochemical Treatment Processes

Carbon adsorption can also be used to remove organic solvents from a segregated waste stream, especially in small quantities. Carbon adsorption method is widely used in tertiary treatment.

The feasibility and extent of recovery and purification are governed largely by the quantities involved and by the complexity of the solvent mixtures to be separated. If recovery is not economically practicable, the used solvents may have to be disposed of by means of incineration, landfilling, or contract disposal. It is expected that some solvents can still be present in the wastewater even after an effort for recovery. Further removal of solvents can be accomplished in the end-of-pipe treatment in the combined overall waste stream.

Advanced physicochemical treatment processes available for treating the pharmaceutical wastewater include coagulation and clarification, dissolved air flotation (DAF), flotation-filtration (DAFF; filtration can be either sand filtration or GAC filtration), granular activated carbon (GAC) adsorption, powdered activated carbon (PAC) adsorption, wet air oxidation (WAO), supercritical water oxidation (SCWO), Fenton oxidation, UV photocatalytic oxidation, ultrasound oxidation, air stripping, distillation, electrochemical oxidation, ozonation, membrane filtration (MF, UF, RO, ED, MBR), or other advanced oxidation processes (AOP), combined oxidation-reduction process, etc. Evaluation of these processes is presented in Sects. 2.7.7.1 and 2.7.7.2. Of these advanced treatment processes, DAF, DAFF, GAC, air stripping, distillation, and membrane processes are suitable for recycling and reusing of chemical compounds and/or water. In view of the pollution load reduction and chemical cost saving, it is necessary to recover chemical compounds or raw materials as much as possible. In view of the scarcity of water resources, it is necessary to understand and develop methodologies for the treatment of pharmaceutical wastewater as part of water management. While most of the advanced treatment processes are technically feasible for treating the pharmaceutical wastewater, their economical feasibility needs to be carefully evaluated before any implementation.

2.6.4 End-of-Pipe Treatment Technologies

End-of-pipe treatment is mainly designed to treat a number of pollutants in a plant's overall waste stream before it is discharged directly to a body of surface water, although it is sometimes used for pretreating the waste stream when a wastewater is designed for indirect discharge, i.e., discharging to the POTW for further treatment. The pretreatment for pharmaceutical waste is mainly for reducing the toxicity of the wastewater in order not to be harmful for the biological treatment system.

Pretreatment is mainly accomplished by the so-called in-plant treatment as stated previously. This section discusses the end-of-pipe treatment for direct discharge.

Generally, a secondary treatment facility is needed for an end-of-pipe treatment for pharmaceutical wastes [13]. The treatment schemes involve primary treatment (screening, equalization, neutralization) followed by either a secondary biological treatment or a secondary physicochemical treatment. Additional tertiary treatments may also be needed.

2.6.4.1 Primary Treatment

The common primary treatment methods in the pharmaceutical industry are (a) coarse solid removal by screening; (b) primary sedimentation, applying gravity separation to remove grit and settleable solids and using a skimmer to remove floating oil and grease; (c) primary chemical flocculation/clarification; and (d) dissolved air flotation.

2.6.4.1.1 Equalization and Neutralization

Flows are usually required to be equalized, especially if the waste from the production plant is not equally distributed (either in flow rate or in waste characteristics) around the clock. In this case, an equalization tank is needed to minimize or control fluctuations in wastewater characteristics to provide optimum conditions for the subsequent treatment processes. The main benefits of equalization are as follows:

1. Providing continuous feed to biological systems over periods when the manufacturing plant is not operating
2. Providing adequate dampening of organic: fluctuations to prevent shock loading to biological systems
3. Preventing high concentrations of toxic materials from entering the biological systems
4. Minimizing chemical requirements necessary for neutralization

Also, neutralization and nutrients addition can be accomplished in the equalization step. A pH between 6.5 and 8.5 should be maintained in a biological system to ensure optimum biological activities. Neutralization is important for chemical synthesis plants as shown in Table 2.2.

Neutralization is performed by adding basic or acidic substances depending on the pH of the waste stream. An economical option is by adding a proportional combination of acid and basic wastewater streams.

The raw materials used in fermentation and biological product extraction manufacturing are mainly from natural plants and animals. Nutrients (such as nitrogen and phosphorous) may not be needed. However, for some other wastes, nutrient addition may be necessary prior to biological waste treatment. Mixing is usually

provided to ensure adequate equalization and to prevent settleable solids from depositing in the basin [45].

2.6.4.1.2 Screening and Clarification

All waste flows should be passed through screens to remove large suspended matter and through clarification (sedimentation or flotation) tanks to remove suspended solids. Rectangular gravity clarifiers are usually used for primary sedimentation, although circular gravity tanks or dissolved air flotation tanks are equally efficient.

Chemical coagulation and flocculation can also be combined with primary treatment to increase TSS removals. Primary treatment is an important pretreatment for the subsequent secondary biological waste treatment, which may remove 20–50% of 5-day BOD.

2.6.4.1.3 Primary Flotation Clarification and Secondary Flotation Clarification

When conventional sedimentation cannot effectively remove suspended solids or oil and grease, primary flotation may be used instead of primary sedimentation before secondary biological waste treatment [46, 47].

In dissolved air flotation (DAF), wastewater is pressurized to 50–90 psi (347–624 kPa) in the presence of sufficient air to approach saturation [40, 45, 48, 49]. When the pressure in the air-liquid mixture is released to atmospheric pressure in the flotation unit, micro air bubbles are released from solution. The suspended solids or oil globules are floated by these micro air bubbles, rising to the surface where they are skimmed off.

DAF can also be used as a secondary clarifier.

2.6.4.2 Secondary Biological Treatment

2.6.4.2.1 Activated Sludge

Activated sludge is the most widely used secondary biological process for treating pharmaceutical wastewater [50–56]. It is mainly used for medium and large wastewater flows.

A typical activated sludge treatment system consists of an aeration tank for aerobic biological treatment, a secondary clarifier for solid separation, and an activated sludge return system for sludge recycle [57]. The aeration tanks are loaded with the equalized, neutralized, and pretreated wastewater. In the aerobic biological degradation, the soluble biodegradable wastes are transferred to insoluble microbial biomass.

The secondary sedimentation clarifiers settle the biosolids from the biologically treated wastewater, resulting in a clear effluent which meets the standards (mainly

the BOD and TSS) for direct discharge. The major part of the settled biosolids is further treated before disposal or reuse. A part of the settled biomass is returned to the aeration tank as the return activated sludge.

The return activated sludge is fed to the aeration tank to ensure a sufficient amount of microbial population for the degradation of the organic waste is present. The biomass is measured by the mixed liquor volatile suspended solids (MLVSS).

Complete mixing and adequate aeration are essential in the aeration tanks. Sufficient oxygen should be furnished to maintain dissolved oxygen throughout the aeration volume.

There are various types of modes for operating the activated sludge system, such as conventional, extended aeration, step aeration, contact stabilization, and completely mixed. Figure 2.6 shows the flow diagrams of a few selected activated sludge

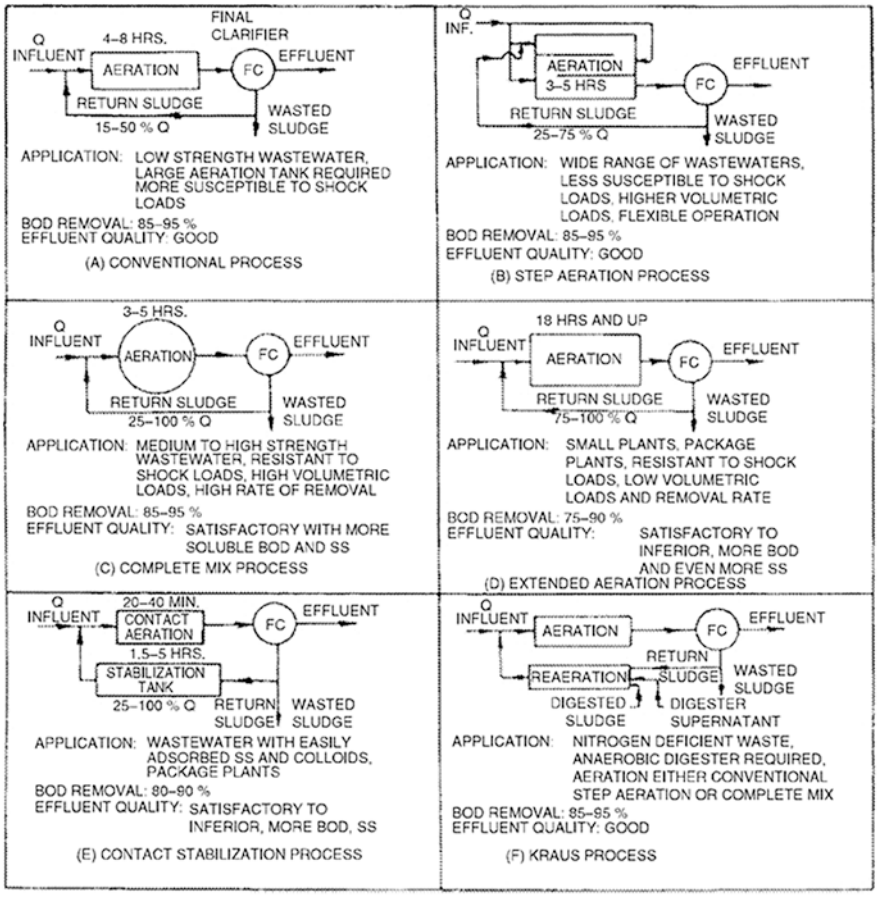

Fig. 2.6 Flow diagrams and applications of major activated sludge processes

processes. The treatment mode is selected according to the characterization of the wastes and the goal of treatment [58–60].

Once maximum and normal raw waste loads and flows have been determined, the design criteria for the biological treatment plant can be established. In addition to the removal of 5-day BOD and suspended solids, some toxic organic matters are slightly reduced during the process. Activated sludge treatment systems can be designed for the purpose of nitrogen removal by operating the system to accomplish nitrification and denitrification [61, 62].

Some activated sludge treatment systems experience severe filamentous microorganisms buildup accompanied with very poor settling. A pilot-scale experiment was conducted to improve sludge settling for a nitrifying activated sludge system, treating 1.2 MGD (4.54 MLD), equivalent to 10,000–15,000 kg 5-day BOD per day, of pharmaceutical wastewater from both synthetic and fermentation processes. The concentration of filamentous organisms and the mixed liquor sludge volume index (SVI) can be reduced by changing the aeration pattern from three aeration basins in parallel flow to three completely mixed compartments in series. Such process change results in reducing the filamentous population and improving settling characteristics.

Alternatively, a secondary flotation clarifier can be adopted to replace a secondary sedimentation clarifier to solve the problems of sludge bulking and rising [40, 57, 63].

According to Mayabhate et al. [64], an oxidation ditch activated sludge system was capable of providing acceptable treatment for pharmaceutical wastes.

Datta Gupta et al. [28] described a complete treatment system for antibiotic production wastewater including lime neutralization, clarification, activated sludge treatment, postaeration, and chlorination. The effluent was disposed of by irrigation, while the biosolids were dried and utilized as fertilizer.

Schumann [65] described a treatment system for high-strength pharmaceutical wastewater, which included neutralization and aerobic activated sludge treatment with aerobic sludge stabilization [29].

2.6.4.2.2 Aerated Lagoon

Aerated lagoons are usually rectangular in shape, with a length-to-width ratio of 2:1. The depth of lagoons is usually about 8–12 ft (2.44–3.66 m). The lagoon bottom and sides are lined and have a freeboard of at least 3 ft About 1–2 months of retention time are required for treatment by an aerated lagoon. The detention time and waste loading determine the required lagoon volume, which in turn determines the surface area of the lagoon [66].

Complete mixing and adequate aeration are essential. Sufficient oxygen should be furnished to maintain dissolved oxygen throughout the entire 8–12-ft depth (Fig. 2.7). Aerators should be spaced to provide uniform blending for dispersion of dissolved oxygen and suspension of microbial mass. The oxygen provided for aerated lagoons is commonly provided by mechanical aeration, diffused aeration, or

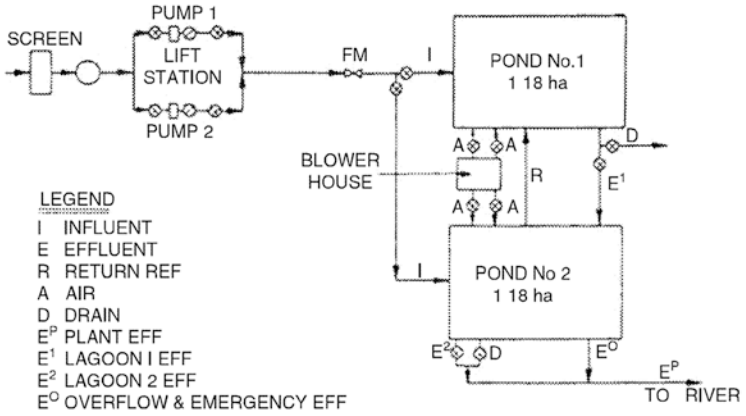

Fig. 2.7 Aerated lagoon system

induced surface aeration. The mechanical aeration units can be either floating or platform-mounted.

The aerated lagoon is the second widely used biological treatment method for treating pharmaceutical wastewater. It is mainly used for relatively small plants and can achieve 85–95% reduction of 5-day BOD.

2.6.4.2.3 Trickling Filter

Trickling filters are fixed film reactors using a biological process for wastewater treatment [67]. It is widely used in pharmaceutical waste treatment for plants medium to large in size. The filter medium consists of a bed of coarse material such as broken stones, plastic rings, corrugated plastic sheets, or plastic tubes over which wastewater is distributed. The plastic media are predominant for high-rate filters such as for strong industrial wastewaters with high loading rates. Nitrification-denitrification can be accomplished by using low loading rates and multistage trickling filtration.

Wastewater is applied to trickling filters by a rotary distributing system. The wastewater then trickles downward through the media, on which a zoogleal slime layer is formed (Fig. 2.8). Dissolved organic material in the wastewater is transported into the slime layer where biological oxidation takes place. The effluent liquid is then collected by an underdrain system. Organic removal occurs by adsorption and assimilation of the soluble and suspended waste materials by microorganisms attached to the media. Oxygen for the process is supplied from air circulating through the interstices between the filter media, which increases dissolved oxygen in wastewater.

The quantity of biological slime produced is controlled by available food. Growth will increase as the organic load increases until a maximum effective thickness is reached. This maximum growth is controlled by physical factors including hydraulic dosage rate, type of media, type of organic matter, amount of essential nutrients

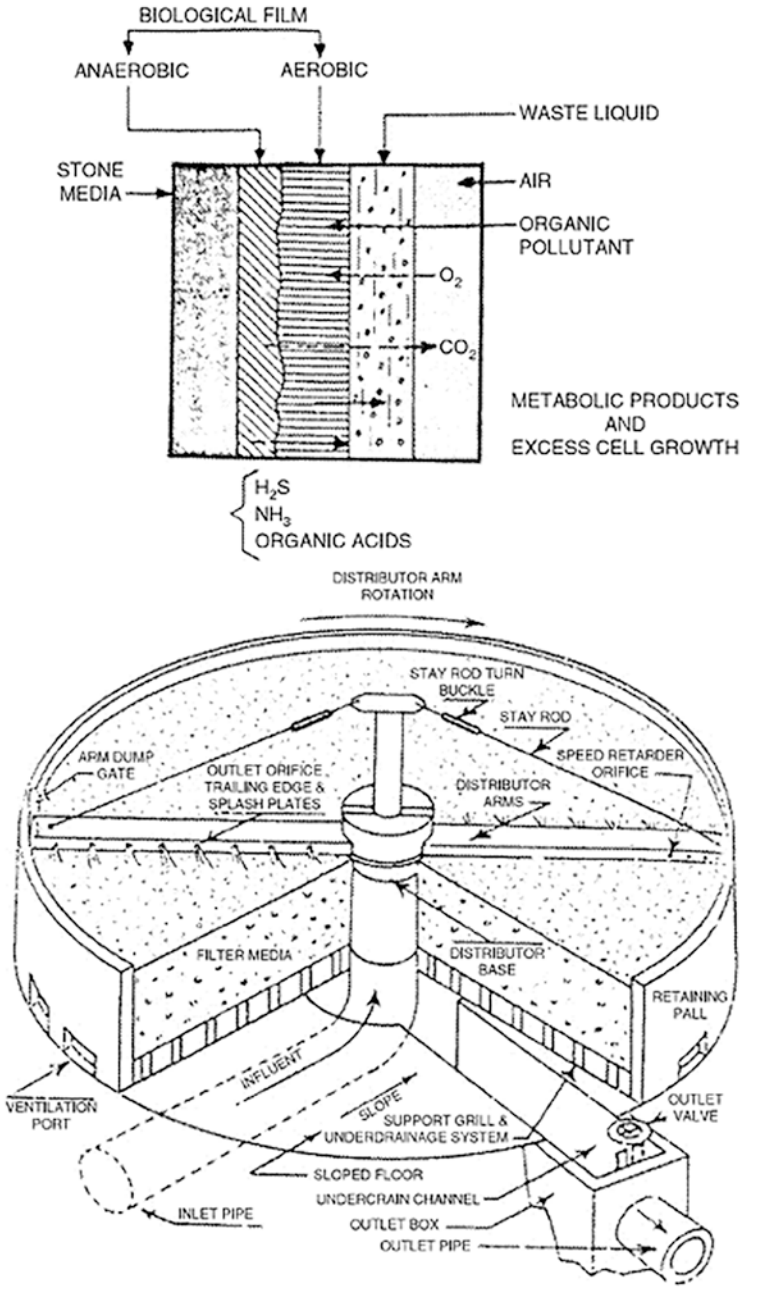

Fig. 2.8 Trickling filter

present, temperature, and the nature of the particular biological growth. During trickling filter operations, biological slime is sloughed off, either periodically or continuously. The sloughed biomass is removed in the subsequent clarification process. Recirculation of trickling filter effluent is practiced in high-rate trickling filters which improve the filter efficiency.

The overall performance of trickling filters is related to the hydraulic and organic loading. The performance can be correlated to either hydraulic loading or organic loading when the BOD concentration in wastewater and the depth of the filter remain constant [67–69]. Other factors that affect the performance of trickling filter plants include the specific surface area of media, flow distribution and dosing frequencies, wastewater temperature, recirculation rate, underdrain and ventilation system, filter staging, and secondary clarification [67, 70, 71].

It is important to note that either sedimentation clarifiers or dissolved air flotation clarifiers can be used as the secondary clarification units for separating the biomass from the effluent of trickling filters [63].

2.6.4.2.4 Anaerobic Treatment

Anaerobic treatment involves the breakdown of organic wastes to gas (mainly methane and carbon dioxide) in the absence of oxygen. This process involves two steps: the breakdown of organics by facultative and anaerobic organisms to organic acids and the subsequent breakdown of these acids to methane and carbon dioxide [51, 72].

Since the anaerobic process has less cell synthesis than that in the aerobic system, the nutrient requirements are correspondingly less. The conversion of organic acids to methane gas yields little energy. The rate of growth is slow, and the yield of organisms by synthesis is low. Therefore, the kinetic rate of removal and the sludge yield are considerably less than those in the activated sludge process or the trickling filter process. Figure 2.9 illustrates several anaerobic processes that have been used in the treatment of pharmaceutical wastewater [73–76].

The conventional anaerobic treatment process provides a continuous or intermittent feeding without solid separation. The detention time is usually 10–30 days and the minimum time is 3–5 days.

An anaerobic-contact process provides for separation and recirculation of seed organisms, therefore allowing process operation at detention periods of 6–12 h. A 90% removal of COD was reported for wastewater at a loading of 2.5 kg COD/m^3/day [77].

In an anaerobic filter, the growth of the anaerobic microorganisms occurs on the surface of packed media. The filter is operated either in the upflow or downflow mode, and part of the effluent is recirculated. The packed filter media also provide for the separation of solids and the gas generated in the anaerobic process. Jennet and Dennis [78] treated pharmaceutical wastewater and achieved a 97% removal of COD at a loading of 3.5 kg COD/m^3/day at 37 °C. Sachs et al. [79] used an anaerobic filter to treat biological or chemically synthesized pharmaceutical wastewater.

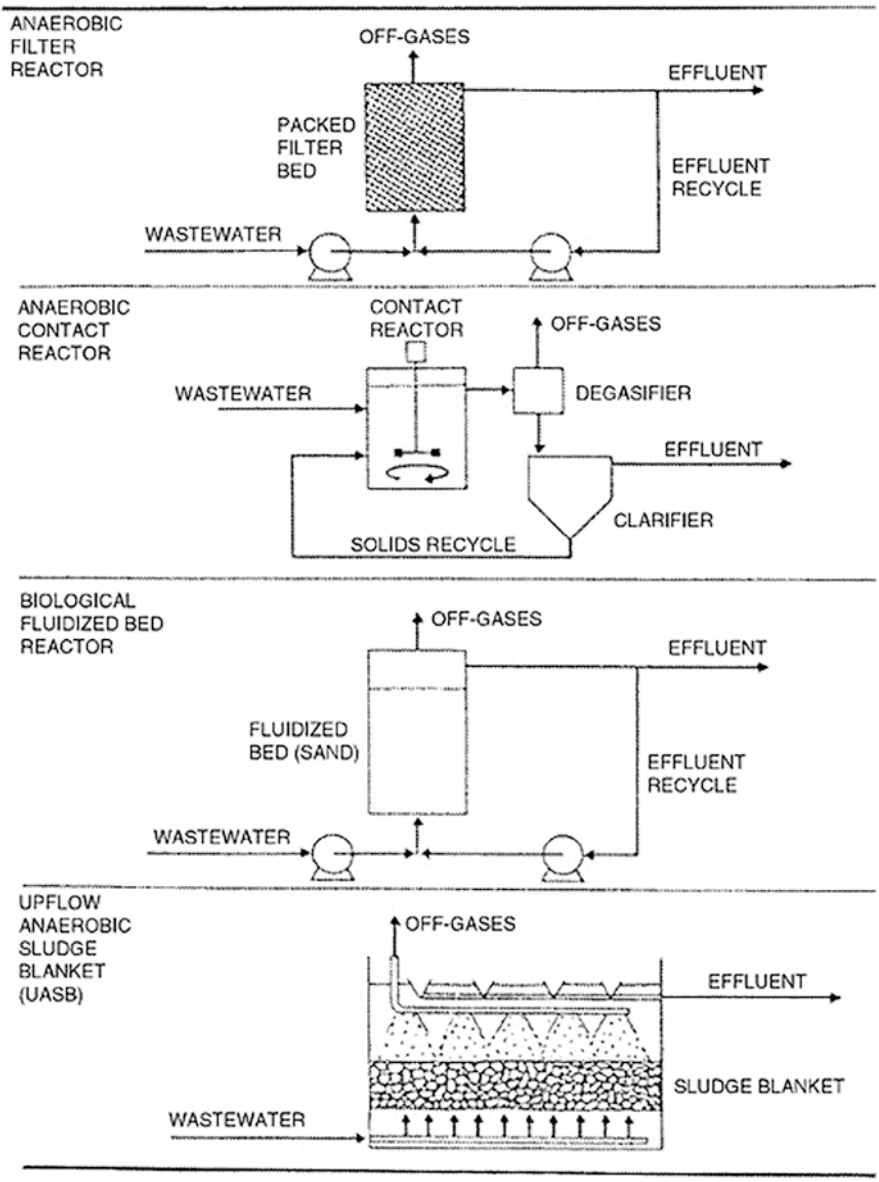

Fig. 2.9 Anaerobic wastewater treatment processes

With a loading of 0.56 kg COD/m^3/day at 35 °C and 36 h hydraulic retention time, they achieved 80% COD removal.

In a fluidized bed reactor, the wastewater is pumped upward through a sand bed. Part of the effluent is recycled. Stronach et al. [80] utilized anaerobic fluidized beds to treat two types of wastes. The first waste, a propanol-containing waste, was

nutrient limited and caused inhibition of methanogenesis, whereas the second waste, a methylformamidecontaining waste, appeared to contain a non-biodegradable and toxic fraction, which did not inhibit methanogenesis but caused a reduction in COD removal and erratic volatile acid production. The feed flow had a COD concentration of 2500 mg/L, which was applied at an organic loading rate of 4.5 kg COD/m^3/day and with a hydraulic retention time of 0.53 day. Final COD removal was 54 and 45% for the first and second wastes, respectively.

In an upflow anaerobic sludge blanket process reactor, wastewater is directed to the bottom of the reactor where it is distributed uniformly. Methane and carbon dioxide rise upward and are captured in a gas dome. The flow passes into the settling portion of the reactor where solid-liquid separation takes place.

An anaerobic degradation of pharmaceutical antibiotic fermentation wastewater was studied at a pilot scale [81] and then was applied to a full-scale treatment plant. The waste contained a high proportion of suspended solids representing about 40% of the COD as well as residual amounts of antibiotics, extraction solvents, grain flours, sugars, protein, and nutrients. Four treatment configurations were piloted: a downflow anaerobic filter, a downflow/upflow anaerobic filter, an upflow anaerobic sludge blanket, and a low- rate anaerobic reactor. The high-rate systems were ultimately incapable of assimilating the feed pollutants, resulting in excessive loss of biomass and, therefore, low soluble COD removals. The low-rate system adequately hydrolyzed the feed pollutants and yielded 70% COD and 80–90% TSS removals. The presence of antibiotic residuals did not affect the system.

Shafai and Oleszkiewicz [82] investigated the anaerobic ammonification of wastewater from an estrogen-extracting pharmaceutical plant. Both flow-through and batch anaerobic reactors were used to treat a waste with high loading of total dissolved solids (TDS), TKN nitrogen, and total organic carbon (TOC). It was found TDS concentrations over 17 g/L in the flow-through reactors and in excess of 10 g/L in the batch reactors to be inhibitory to both ammonification and methanogenesis.

Anaerobic treatment has also been used as an additional treatment to supplement the main treatment system. One example is at the Abbott Laboratories in North Chicago, Illinois. The healthcare product manufacturer operates a large fermentation and chemical synthesis plant. The total wastewater flow from the factory is 0.92 MGD (3.48 MLD); the COD, BOD, and TSS loads are 25,000, 11,500, and 3500 lb/day, respectively (11,340, 5216, and 1588 kg/day, respectively). About 70–85% of the waste is from the fermentation process. The wastewater flow was treated in an extended aeration activated sludge plant. To accommodate the growth and expanding load from the fermentation process, a low-rate anaerobic reactor was added as a pretreatment step for the high-strength fermentation wastewater prior to aerobic treatment. The anaerobic reactor was also used for the digestion of the raw waste solids from fermentation and for the wasted sludge from the aerobic system. The flow diagram of the treatment plant is shown in Fig. 2.10. The low-rate anaerobic reactor performance operating at a temperature of 28.5–32.5 °C and with a hydraulic retention time of 9.5–10.0 days was as follows: 79% removal of COD, 86% removal of 5-day BOD, and 83% removal of TSS.

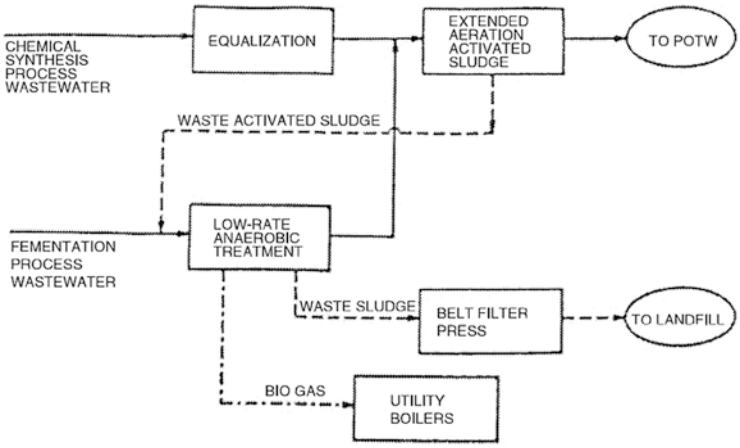

Fig. 2.10 Aerobic-anaerobic treatment of chemical synthesis and fermentation wastewater effluents

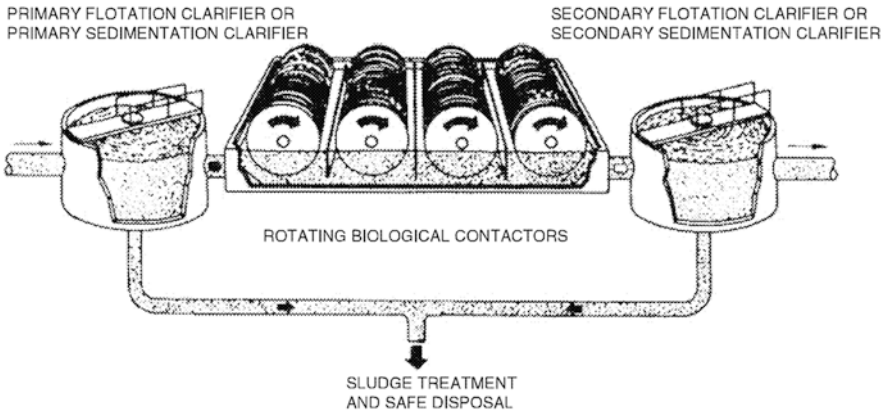

Fig. 2.11 Schematic diagram of rotating biological contactors

2.6.4.2.5 Advanced Biological Treatment Methods

Other biological treatment methods utilized in pharmaceutical wastewater are waste stabilization ponds [66], rotating biological contactors (RBC) [83–85] (see Fig. 2.11), polishing ponds, sequencing batch reactors (SBR) [86], membrane bioreactor (MBR), and sequencing batch biofilters [87]. For detailed description of these processes, the readers are referred to the books *Biological Treatment Processes* [51], *Advanced Biological Processes* [72], *Membrane and Desalination Technologies* [123], *and Environmental Flotation Engineering* [124]. Additional biological treatment processes are introduced in other chapters of this book [175–176].

2.6.4.3 Tertiary Treatment

Tertiary treatment using physicochemical processes is usually applied for further improving the quality of the secondary effluent following biological treatment. Examples of these additional treatment methods are the polishing pond, coagulation/flocculation/clarification, secondary neutralization, chlorination, ion exchange, and filtration (multimedia, sand, and granular activated carbon) [40, 88].

2.6.4.3.1 Filtration and Carbon Adsorption

Filtration is widely used for polishing wastewater. The most common filter type is a multimedia of activated carbon and sand. The filter needs a periodical backwash and is used mainly for removal of relatively coarse particles. Granular activated carbon is more versatile in dealing with various kinds of small suspended solid particles, colloidal, and dissolved pollutants [164, 169].

Carbon adsorption uses activated carbon which has a great specific surface area (surface area per unit volume) to effectively adsorb pollutants [40, 88]. Granular activated carbon is an effective and economical adsorbent because besides its higher specific surface area, it has a high hardness, which lends itself to reactivation and repeated use.

The granular activated carbon adsorption process is usually preceded by preliminary filtration or clarification to remove insoluble particles. Once the carbon is depleted, it can be reactivated by heating to a temperature between 1600 and 1800 °F (871–982 °C) to volatilize and oxidize the adsorbed contaminates. Oxygen in the furnace is normally controlled at less than 1% to avoid loss of carbon by combustion [13].

The application of carbon adsorption in pharmaceutical industry is limited. Most of the priority pollutants (heavy metals, volatile organics, and cyanide) are generally reduced more effectively and with less cost by other technologies. This method is particularly applicable in situations where pollutants in low concentrations not amenable to treatment by other technologies must be removed from waste streams. Holler and Schinner [89] arrived at the same conclusion and stated that for economic reasons carbon adsorption should be mainly used as a tertiary treatment for final polishing of secondary effluents. Bauer et al. [90] used activated carbon filtration in an activated sludge system to remove toxic compounds. More details on the removal of organics and toxic material from pharmaceutical wastewater effluents can be found in [91–99].

Besides the usage of granular activated carbon as a filtration media, powdered activated carbon (PAC) has been used as an additive in an activated sludge system [26]. One of the experiments showed that the MLSS concentration increased from 5850 to 8830 mg/L as the PAC dosage to the influent was increased from 208 to 1520 mg/L. The 0.7 mg/mg PAC dosage resulted in 50% additional removal of COD.

2.6.4.3.2 Coagulation, Flocculation, and Clarification

Coagulation is a process used for the removal of colloidal and fine suspended particles [100, 101]. Kharlamova et al. [102] used alum, lime, and bentonite clay as coagulants to treat pharmaceutical waste effluents. The treated effluents had lighter coloring and increased transparency. The reduction in BOD and COD, however, was limited. On the other hand, the researchers were successful in destroying synthetic surfactants used in the production of antibiotics using hydrogen peroxide as an oxidant and iron and aluminum ions as catalysts. However, flocculation and coagulation may not be effective or cost-efficient for pharmaceutical wastewater treatment, although it is able to reduce COD concentrations [64].

PAC can also be applied to a coagulation/flocculation/clarification system for removal of toxic substances [63]. Clarification can be either a sedimentation clarification or a flotation clarification.

2.6.4.3.3 Chlorination

Chlorination as a means of disinfection is needed before the discharge of effluent after biological treatment. For example, post-aeration and chlorination are used in addition to activated sludge treatment for wastewater treatment at a penicillin production facility [28].

Table 2.10 shows a summary of end-of-pipe treatment methods used for wastewater treatment in the pharmaceutical industry. It is estimated [13] that the activated sludge process is the most widely used biological treatment method, at about 60% of the biological treatment plants. Physicochemical treatment methods have been used in only 20% of the plants, out of which thermal oxidation is the most widely used.

2.6.4.4 Residue Treatment and Waste Disposal

A large proportion of the material input to the manufacturing process ends up as process waste. Fermentation and biological extraction, as well as the formulation processes, are typical examples. Besides excess sludges generated during production processes, sludge can also be generated in the processes of pretreatment, primary treatment, secondary treatment, and tertiary treatment.

Fat and oil may also occur during biological extraction manufacturing procedures, which are skimmed-off in flotation or settling tanks. The sludges generated in the pretreatment stages usually contain contaminants such as traces of solvents and heavy metals. Organic contaminants in the sludge are either (a) traces of solvents used in the fermentation, chemical synthesis, and biological extraction manufacturing steps or (b) reactants or byproducts of the chemical synthesis steps. Biological sludges, also known as biosolids, need to be thickened, dewatered, conditioned, and stabilized before disposal. Disposal methods of sludge include incineration, landfill,

Table 2.10 Pretreatment pollutants standards [13]

Pollutant	No. of occurrences in wastewaters	Max. wastewater concentration level (μg/L)
Cyanide	5	590
Acrolein	2	100
Acrylonitrile	1	100
Benzene	6	580
Carbon tetrachloride	1	300
Chlorobenzene	2	11
1,2-dichloroethane	2	290
1,1,1-trichloroethane	4	360.000
1,1-dichloroethane	3	27
Chloroform	6	1350
1,1-dichloroethylene	2	10
1,2-trans-dichloroethylene	1	550
Ethylbenzene	3	21
Methylene chloride	9	890.000
Bromoform	1	12
Tetrachloroelhylene	1	2
Toluene	6	1050
Trichloroethylene	1	7

and reuse. In the latter two cases, sludge stabilization and disinfection will be needed [29, 65].

Recovered solvents may be used as fuel for incineration or other kinds of beneficial uses. Fats and oil may be incinerated or landfilled along with sludge or may also be transferred to other industry such as soap manufacturing to be used as raw materials. Such a beneficial usage of residue is one of the waste exchange programs that should be encouraged.

Sludge may be spread on land for agricultural purposes [103] or sold as an animal feed supplement. However, the wasted biological sludges are generally contaminated with varying degrees of potentially toxic materials, which may exclude the above two types of beneficial usage.

Wickramanyake [104, 105] discussed the treatment of sludge generated at a DNA processing facility. The sludge consisted mainly of biological solids (i.e., biosolids), such as cells and cell debris. The solid levels in the sludge samples can vary depending on the process used to concentrate solid materials. The solid content and physical properties of biosolids significantly affect decontamination processes including incineration, thermal (dry heat and steam) treatment, gamma and electron radiation, microwave radiation, and chemical decontamination [29]. Each of these microbial inactivation techniques can be effective in the treatment of the DNA biosolids. Since verification of the extent of decontamination is difficult with biosolids, high safety factors should be incorporated into the design of treatment units, and good maintenance and operating procedures should be employed.

Incineration may not be legally practiced in some areas, such as New York City. The New York City Department of Environmental Protection has developed comprehensive plans to handle sludge problems [106]. The plan includes heat drying, composting, chemical stabilizing of dewatered biosolids, landfilling (mainly for toxic-containing biosolids), and, more importantly, beneficial usage. The beneficial applications include the spreading of biosolids on or just below the surface of land to benefit soil and plants and as a substitute for soils imported by the city for daily cover at active landfills or as capping material for closed landfills.

2.7 Case Study

This section uses a factory producing antibiotics by fermentation as an example of waste generation and end-of-pipe treatment in the fermentation pharmaceutical industry.

2.7.1 Factory Profiles

Ansa, a plant at Izmit, Turkey, produces antibiotic pharmaceutical products by fermentation. It has the capacity to produce 120 metric ton/year of tetracycline and oxytetracycline derivatives and 1.5–2.0 metric ton/year of gentamicin sulfate. The following description covers the period when the production rate of the factory was 50–60% of full capacity. The production was carried out year round, 7 days a week and 24 h a day with three shifts. The maximum daily production capacity was 400 kg/day for tetracycline and oxytetracycline and 20 kg per 3 days (intermittent production) for gentamicin [107].

2.7.2 Raw Materials and Production Process

The production used different raw materials from agricultural sources and used various chemicals (Table 2.11).

Figure 2.12 shows the production mode. A bacterial-based mycelium was first produced in the microbiology laboratory.

The fermentation involved two phases: solubilization of antibiotics by acidification and filtration. The whole process was carried out on a batch basis.

The processes following the filtration of fermentation product were slightly different between tetracycline and oxytetracycline production and gentamicin production. For tetracycline and oxytetracycline production, the fermentor filtrates were treated by extraction, pH adjustment, filtration, precipitation, centrifugation, complex formation and crystallization, and purification, before yielding the final

Table 2. 11 Solubility Products (K_{sp}) for Insoluble Metal Salts [13]

Compound	K_{sp}	Metal Ion Conc. (μg/L)
CuS	6×10^{-36}	1×10^{-10}
NiS	2×10^{-25}	8×10^{-6}
ZnS	1.6×10^{-25}	2×10^{-5}
$Cu(OH)_2$	3.5×10^{-19}	25
$Ni(OH)_2$	1.5×10^{-15}	400
$Zn(OH)_2$	1.8×10^{-14}	1×10^{-3}

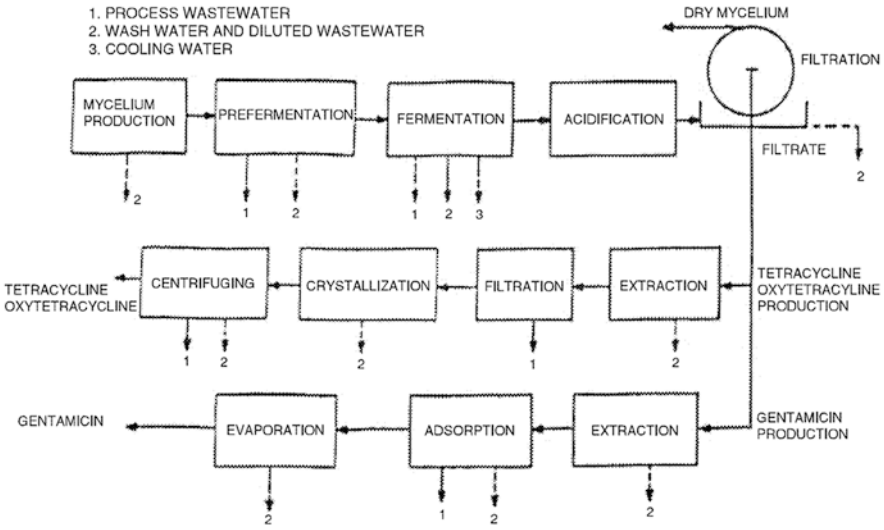

Fig. 2.12 Antibiotic production process system [107]

product. For gentamicin production, the filtrates were treated by extraction, chromatographic resin adsorption, evaporation, filtration, crystallization, or spray drying to yield the final product.

2.7.3 Waste Generation and Characteristics

The production generated 33 sources of wastewater discharges. They can be grouped into seven main processes:

1. Wastewaters from fermentation processes (strong)
2. Wastewaters from extraction and purification processes (strong)
3. Wastewaters from recovery process (strong)
4. Floor and equipment washings (dilute)

5. Laboratory wastes, miscellaneous wastes (varied)
6. Sanitary wastes
7. Waste cooling water (uncontaminated)

These waste streams can be further grouped into three groups: the strong process wastes, the diluted wastes, and the cooling water. The strong process wastes were from fermentation process, extraction and purification processes, and recovery process. The diluted wastes were from the floor and equipment washings, laboratory wastes, and miscellaneous wastes (varied). The cooling water was confined, without contacting with processing water, which, in fact, was uncontaminated and generated no waste.

The flow rates for the three main streams were as follows:

1. Strong process wastes: $Q = 120\ m^3/day$
2. Diluted wastes: $Q = 160\ m^3/day$
3. Cooling water: $Q = 1000\ m^3/day$

Table 2.12 lists the flow and concentrations of some major traditional wastes for the above first two major types of wastewater. The process wastes were very strong in organic content, having a 5-day BOD of 13,500 mg/L, a COD of 34,000 mg/L, and a BOD/COD ratio of 1:2. The total loads were 1680 kg/day of 5-day BOD and 4180 kg/day of COD. The diluted wastes had 400 mg/L of 5-day BOD and 600 mg/L of COD.

In fact, full segregation of the strong and dilute waste streams was not possible due to the complexity of existing piping system. The process wastes and dilute wastes were actually diluted with the wasted cooling water down to a 5-day BOD of 8400 and 50 mg/L, respectively, and the flow rates at 200 and 800 m^3/day,

Table 2.12 Methylene chloride removal in packed column steam stripper [13]

Sample number	Feed temp. (°C)	Overhead temp. (°C)	Bottoms temp. (°C)	Feed rate (gpm)	Steam rate (L/h)	Methylene chloride (mg/L)	
						Influent	Effluent
1	87	97	104	9.6	160	NA[a]	0.926
2	86	98	102	8.9	160	NA	5.10
3	86	94	101	9.0	150	NA	4.94
4	86	89	102	9.0	150	NA	3.00
5	85	89	102	9.0	150	NA	1.99
6	85	86	102	9.0	150	NA	5.70
7	85	84	102	9.0	155	NA	22.80[b]
8	84	84	101	9.0	155	NA	38.05[b]
Composite of Influent samples						260	NA
Average of all effluent datum points							10.31
Average of effluent datum points obtained under normal operating conditions							3.61

[a] NA means not analyzed. 1 gpm = 3.785 LPM = 3.785 L/min

[b] Efffluent concentrations under upset conditions, overhead temperature < 85°

respectively, as shown in Table 2.12. Combining the waste streams yielded a total flow of 1000 m^3/day and 5-day BOD of 1720 mg/L.

The strong process waste didn't maintain a uniform composition, which was drastically affected when tetracycline and oxytetracycline were alternately produced together with gentamicin. Moreover, the strong waste had strong sulfate level and frequent changes in the products and wastewater properties. An adequate dilution of process waste could avoid the toxicity and BOD shock load when otherwise treating a smaller flow and stronger waste, where a high concentration of sulfate and more variable discharge were encountered. These factors all affected the treatability properties of the wastes.

2.7.4 End-of-Pipe Treatment Case Histories and Green Environmental Technologies

2.7.4.1 Case Histories of Current Technologies

Table 2.13 presents a summary of all end-of-pipe treatment processes [11, 12]. However, aerobic treatment scheme was selected for end-of-pipe waste treatment as an engineering project. Anaerobic treatment was not chosen because (a) a total of 360,000 m^3/day of air, with oxygen content, was regularly discharged from the plant, favoring an aerobic process as an economic treatment system, and (b) the inhibition problems were possibly due to high sulfate levels, frequent changes in products, and fluctuation in wastewater characteristics.

An activated sludge treatment system shown in Fig. 2.13 was selected and designed for the pharmaceutical plant [107]. Tables 2.14 and 2.15 introduce the raw material consumption and the wastewater characteristics, respectively, of the antibiotic production plant [107]. It basically involved a separate equalization of waste streams, pH adjustment, aeration, activated sludge system, secondary clarification, and biosolid treatment.

The strong and diluted wastes (flow rates of 200 and 800 m^3/day and with 5-day BOD at 8400 and 50 mg/L, respectively) were equalized in separate tanks, because they had quite different waste discharge rates and continuous variation in waste characters around the clock. The two equalized waste streams were then combined for the next treatment step: pH adjustment. The combined waste had a 5-day BOD of 1720 mg/L and a flow rate of 1000 m^3/day.

The waste stream was then sent to a single-stage activated sludge unit. The aeration tank had four aeration compartments in series and was designed for a hydraulic detention time of 24 h.

The two alternating process wastes (i.e., tetracycline and oxytetracycline were alternately produced together with gentamicin) showed substantially different properties affecting the mode of treatment. The yield value was much lower for oxytetracycline waste. Oxytetracycline had also a very high maximum substrate utilization rate (k), but it took a significantly large range of substrate concentration to reach this

Table 2.13 Summary of end-of-pipe treatment processes [11, 12]

End-of-pipe technology	Number of plants
Equalization	62
Neutralization	80
Primary treatment	61
Coarse settleable solids removal	41
Primary sedimentation	37
Primary chemical flocculation/clarification	12
Dissolved air dotation	3
Biological treatment	76
Activated sludge	52
Pure oxygen	1
Powdered activated carbon	2
Trickling filter	9
Aerated lagoon	23
Waste stabilization pond	9
Rotating biological contactor	1
Other biological treatment	2
Physical/chemical treatment	17
Thermal oxidation	3
Evaporation	6
Additional treatment	40
Polishing ponds	10
Filtration	17
Multimedia	7
Activated carbon	4
Sand	5
Other polishing	17
Secondary chemical flocculation/clarification	5
Secondary neutralization	5
Chlorination	11

level as attested by a high half saturation constant (Ks). The tetracycline waste appeared to be biodegradable at a much slower rate (k = 0.5/day), but it had an inherent instability as far as substrate removal rates to be employed in the treatment, since its half saturation constant was comparatively too low. The operation showed that, under the hydraulic detention time of 1 day, the activated sludge system could yield an effluent 5-day BOD of 120 mg/L with a substrate removal rate of 0.31/day and an MLVSS concentration of 4200 mg/L. The designed treatment plant was capable to achieve 90% removal for 5-day BOD and 80% removal for COD.

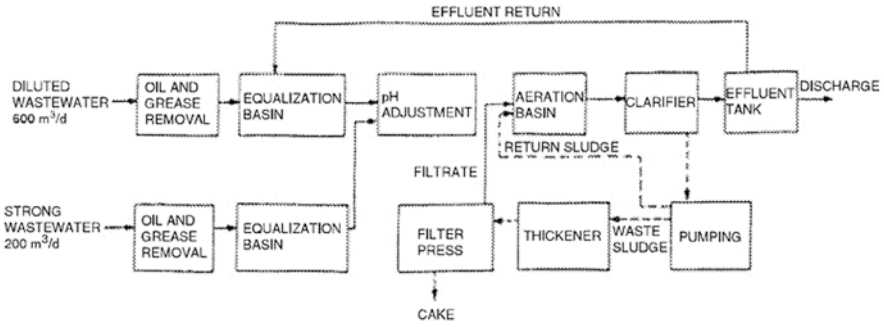

Fig. 2.13 Wastewater treatment system: a case study [107]

Table 2.14 Raw materials consumption for antibiotic production—case study [107]

Raw materials	Usage (tone per year)
Carbohydrate sources: Starch, dextrin, sugars, vegetable oils	1500
Protein sources: Soy meal, soy flour, com. Steep liquor gluten	300–100
Minerals: ammonium sulfate, ferrous sulfate, manganese sulfate, cobalt chloride, calcium chloride, sodium ferrocyanide, sodium hydrogen sulfide. Phosphates	25
Ammonia. 23%	100–200
Acids, Bases: NaOH, HCl, H_2SO_4, oxalic acid	600–700
Quarternary ammonium salts	100–125
Antifoams	30
Solvents (all regenerated): acetone, methanol, oxitol. n-butanol	500
Urea	150–200

Note: 1 ton/year = 907.2 kg/year

2.7.4.2 Green Environmental Technologies Developed by the Lenox Institute of Water Technology (LIWT)

The Lenox Institute of Water Technology (LIWT) has developed many modern dissolved air flotation (DAF) clarifiers, dissolved air flotation-filtration (DAFF) package plants, and DAF-DAFF package plants. The filtration portion can be either sand filtration or GAC filtration. Through Krofta Engineering Corporation (KEC) and its partners, over 3000 DAF, DAFF, and combined DAF-DAFF water and wastewater treatment plants have been installed around the world. The LIWT has also developed several multistage hybrid green environmental technologies which are both technically feasible and economically feasible for treating the pharmaceutical and other industrial wastewater depending on the characteristics of original industrial effluent: (a) DAF-DAFF-UV photocatalytic oxidation (one of AOP) for pretreatment, (b) DAF-aerobic biological-DAFF-UV photocatalytic oxidation for treating low-concentration wastewater, (c) DAF-anaerobic-aerobic biological-DAFF-UV photocatalytic oxidation for treating medium- to high-concentration wastewater, and (d) DAF-anaerobic-aerobic biological-DAFF-UF-UV photocatalytic oxidation

Table 2.15 Characteristics of wastewater streams—case study [107]

Parameters	Process wastes	Other diluted wastes
Flow, m^3/day	120	160
pH	6.5–8.5	7.0–8.0
Alkalinity, mg/L	2000	–
BOD_5. mg/L	13,500	400
COD, mg/L	34,000	600
SS, mg/L	1500	300
TKN-N, mg/L	1500	40
Total P, mg/L	70	10
Sulfates, mg/L	3000	
Temperature, °C	Ambient	Ambient

for treating extremely high-concentration wastewater. The researchers and PhD students are invited to study the LIWT systems further. Adopting a hybrid green environmental technology consisting of both biological system (aerobic alone or anaerobic-aerobic depending on the organic concentration of the wastewater) and UV-photocatalytic oxidation will be a feasible solution to treating the pharmaceutical wastewater or similar.

2.7.5 Pharmaceutical Waste Minimization Case Study of Hennepin County Medical Center

2.7.5.1 Company Overview [108]

Hennepin County Medical Center (HCMC), a public teaching hospital in Minneapolis, Minnesota, is a nationally recognized level one trauma center and the third largest hospital in the Twin Cities. HCMC has over 356,000 patient visits annually.

2.7.5.2 Waste Reduction Project [108]

In 2006, HCMC returned over 900 different outdated pharmaceuticals, most in multiple quantities, through the reverse distribution process. The total cost to purchase was $146,411. Of this amount, only 202 items were credited for a total of $75,657. Therefore, a waste reduction project was conducted at HCMC that focused on reducing pharmaceutical waste from the reverse distribution process at the inpatient pharmacy. Waste reduction resulted in over $80,000 in cost savings and 378 lbs of pharmaceutical waste.

2.7.5.2.1 Crash Boxes

Crash boxes, similar to crash carts, were found to be a significant source of waste. These boxes contain emergency medicine needed to revive someone in the event of a cardiac event. Waste occurs when boxes contain drugs that are not used by their expiration date. When this occurred in the past, the pharmacy exchanged the box and updated all the drugs so they are good for about 1 year. Outdated and nearly outdated drugs were sent for reverse distribution.

In investigating the crash boxes, it was determined that many of the drugs found in the boxes are regularly used in other locations in the hospital. It was recommended the pharmacy bring back the crash boxes 3 months prior to expiration and move the drugs to locations where they are used more frequently, potentially using them prior to expiration.

Other recommendations for the crash box drugs included the following:

(a) Replacing the specialty epinephrine intracardiac syringe that was rarely used. It expired and was returned 98% of the time. The use of a more commonly used epinephrine syringe and an 18-gauge, 3-inch needle banded to the epinephrine box was recommended.

(b) Changing the dosage of glutose gel from the 45 g dosage type, much of which was wasted. In most cases, a 30 g dose of glucose is used. A recommendation was made to lower the dosage carried from 45 g to 15 g for the drug to be used in more applications.

(c) Lowering the size of the nitroglycerin bottle from 100 count to 25 count and switching to a generic form from a brand name.

2.7.5.2.2 Other Reverse Distribution Drugs

Review of reverse distribution manifests helped identify the most common and costly drugs returned. HCMC also found they were returning 4% of their inventory, which is 2% above the average as determined by the American Society of Health-System Pharmacists. The top ten of these were (a) crash box epinephrine, (b) epinephrine, (c) glucagon, (d) glutose gel, (e) Nitrostat, (f) hydralazine, (g) lidocaine, (h) amiodarone, (i) adenosine, and (j) naloxone.

It was recommended that HCMC review par usage reports for the top ten returns and adjust inventory quantities accordingly. Doing so would save at least $80,000 and eliminate 210 pounds of pharmaceutical waste.

2.7.5.3 Results

HCMC implemented all the recommendations. It is estimated they are saving $80,000 annually and have eliminated 378 pounds of drug waste.

2.7.6 Pharmaceutical Waste Minimization Case Study of Falls Memorial Hospital

2.7.6.1 Company Overview [108]

Falls Memorial Hospital (FMH), a 25-bed facility, is a charitable, not-for-profit Critical Access Hospital located in International Falls, Minnesota. It has planned to reduce its drug inventory and pharmaceutical waste.

2.7.6.2 Inventory Reduction Project [108]

Prior to undergoing the inventory reduction project, FMH was checking for outdated drugs every other month, stock was not rotated regularly, and par usage reports were not available. In 2006, a staff pharmacist noticed many drugs on site were outdated and the facility was stocking too many extra medications. Because par usage reports had not been used previously, FMH, at that point, did not know how many drugs were required for the facility. Due to these factors, the facility began to look at ways to reduce inventory, save money, and decrease pharmaceutical waste.

2.7.6.2.1 Chemotherapy Drugs [108, 109]

Looking closely into quantities ordered and costs, FMH realized that chemotherapy drugs were the largest expense for the facility. They were being ordered monthly, and in December 2007, the facility spent over $90,000. Because of the long holding time for some of the chemotherapeutics, they were outdating on the shelf. FMH also realized, through facility-wide research, that some chemotherapy drugs were extremely expensive and came in multiple strengths. FMH changed their ordering for chemotherapeutic drugs from once per month to once a week.

2.7.6.2.2 Routine Stock on Floors

FMH utilizes AcuDose, an automated dispensing machine, to supply most of their stock of drugs. AcuDose machines were stationed in the emergency room, medical/surgical area, operating room, and intensive care unit. As part of the inventory reduction project, the pharmacist noted that the AcuDose machine in the intensive care unit was rarely used because most of the pharmaceuticals were special order for the patients and resulted in numerous expired drugs and the inventory not being rotated frequently enough. Therefore, the pharmacist recommended placing the medications only where they are needed and rotating the stock on a more regular basis.

2.7.6.2.3 Therapeutic Substitution

In order to reduce the amount of drugs at the hospital, the pharmacist recommended using therapeutic substitution lists. For example, there are five medications in a class of drugs called proton pump inhibitors, or PPI. Instead of having all five medications on the formulary, FMH chose to carry just two of them. This would ensure that the hospital was not carrying multiple medications in the same category and make it easier to rotate stock. If a patient comes into the hospital on a PPI not on the formulary, they will be automatically switched to an equivalent dose of a PPI that is on the formulary.

Multiple dosage types were also noted. The number of dosage forms has been reduced to those used most often and multiples of those to achieve the strengths for esoteric doses. The pharmacy now also searches out and purchases only from those vendors that have the least packaging.

2.7.6.3 Pollution Prevention Impacts

Due to FMH's inventory reduction project, the facility is ordering and stocking fewer drugs, reducing packaging waste and shipping costs. This project reduced FMH's monthly overhead from $210,000 in January 2006 to $87,000 in October 2007 and dramatically reduced the amount of waste from expiring medications and excess stock.

2.7.7 Recent Investigations of Pharmaceutical Wastewater Treatment Technologies

A detailed review of available technologies for wastewater treatment and water reuse in pharmaceutical industry has been conducted by Gadipelly et al. [110]. In their review, the various sources of wastewaters in the pharmaceutical industry are identified, and the best available technologies (BAT) for removing pollutants from them are critically evaluated. Effluents arising from different sectors of active pharmaceutical ingredients (API), bulk drugs, and related pharmaceutics, which use large quantities of water, are analyzed, and strategies are proposed to recover valuable compounds, and finally the treatment of very dilute but detrimental wastewaters is discussed [110]. It appears that no single technology can completely remove pharmaceuticals and other pollutants from pharmaceutical wastewaters. The use of conventional biological treatment methods along with innovative membrane reactors and advanced posttreatment methods resulting in a combined hybrid wastewater treatment system appears to be the best [110–136]. Appendix I and Appendix II document many researchers' investigations reviewed by Gadipelly et al. [110]. The authors of this publication list the original research sources of many useful

investigations for reference by the readers. The environmental technologies used for treating various pharmaceutical wastes and their process terminologies have been introduced in the previous sections of this book chapter, and they can also be found from the literature [1–136] for further research.

2.7.7.1 Chemical Synthesis-Based Pharmaceutical Wastewater Treatment Technologies

The chemical synthesis-based pharmaceutical wastewater treatment technologies, which have been investigated with various degrees of success, are as follows:

1. Sulfate anion radical oxidation (Fe and Co sulfate salts used with hydrogen peroxide and ozone) [132]
2. Dissolved air precipitation with solvent sublation simulated water: mineral oil layer with organic solvents (toluene, methylene chloride, benzene, chlorobenzene, hexane, butyl acetate) [133]
3. Electrocoagulation (EC) followed by heterogeneous photocatalysis (TiO_2; iron electrodes were used as cathode and anode) [130]
4. Upflow anaerobic sludge blanket (UASB) + micro-aerobic hydrolysis acidification reactor (NHAR) + two-stage aerobic process, cyclic activated sludge system (CASS), and biological contact oxidation tank (BCOT) [143]
5. Two-phase anaerobic digestion (TPAD) system and a subsequential membrane bioreactor (MBR). TPAD system comprised of a continuous stirred tank reactor (CSTR) and an upflow anaerobic sludge blanket-anaerobic filter (UASBAF), working as the acidogenic and methanogenic phases [131]
6. Adsorption: granular activated carbon (a series of columns of GAC were used) [164]
7. Electrochemical treatment (boron doped diamond BDD anode for corrosion stability) [168]
8. Continuous heterogeneous catalytic wet peroxide oxidation (CWPO) process using a Fe2O3/SBA-15 nanocomposite catalyst [134]
9. Acidogenic reactor (USAB sludge from an alcohol industry was used with high glucose as initial feed and then varying pharmaceutical wastewater) [135]
10. Hybrid upflow anaerobic sludge blanket reactor [149]
11. Conventional treatment: activated sludge reactor using sequencing batch reactor (SBR) [142]
12. Hybrid upflow anaerobic sludge blanket reactor (ASBR) [153]
13. Catalytic wet air oxidation [136]
14. Membrane bioreactor (MBR) [143]
15. Photo/Fenton followed by lime or sodium hydroxide precipitation/coagulation [160]

2.7.7.2 Fermentation Process-Based Pharmaceutical Wastewater Treatment Technology

The fermentation process-based pharmaceutical wastewater treatment technologies, which have been investigated with various degrees of success, are as follows:

1. Photocatalysis (TiO_2) + H_2O_2; a single baffled reactor for the process [159].
2. Biodegradation using bacterial strains (*Pseudomonas aeruginosa* and *Pseudomonas pseudomallei*) [165].
3. Photocatalysis (Fenton + photo-Fenton + ozonation) [155].
4. Ozonation (pretreatment) + biological activated sludge reactor combination in series [157].
5. Fenton-biological process: first Fenton coagulation and then biological treatment by activated sludge [161].
6. Chemical oxidation ozonation and ozonation coupled with treatment with hydrogen peroxide [156].
7. Membrane bioreactor technology (hollow fiber membrane) [144].
8. Upflow anaerobic stage reactor (UASR) [148, 153].
9. Upflow anaerobic stage reactor (UASR) [152].
10. Ozonation (pretreatment) + biological activated sludge treatment by synthetic biomass with 30% COD [158].
11. Activated sludge reactor in batch and continuous flow [146].
12. Anaerobic biological treatment using activated sludge reactor [151].
13. Hybrid treatment technology (aerobic biological pretreatment + ozonation + MBR), the biological treatment for reducing the ozone demands. Ozonation reduces almost all of the organic compounds [145, 157].
14. Anaerobic granulation batch/column reactor [150].
15. Catalytic wet air oxidation coupled with anaerobic biological oxidation [154].
16. Aerobic biological treatment with variable temperature study [51].
17. Biological treatment by activated sludge: in seven stages, a pilot plant study [55].
18. Suspended growth photo-bioreactor: non-sulfur photosynthetic bacterium isolated from the soil and fluorescent light reactor [137].
19. Membrane bioreactor (GE ZeeWeed membrane bioreactor technology) [138].
20. Semiconductor photocatalysis Ti/TiO_2: RuO_2-IrO_2 as anode, graphite as cathode, and chloride as electrolyte [163].
21. Penraporation through water-selective membranes [139].
22. Sequencing batch reactor (SBR): an activated sludge reactor [140].
23. Solar photo-Fenton and biological treatment [162].
24. Anaerobic multichamber bed reactor (AMCBR) + AMCBR with continuous stirred tank reactor (CSTR) [166].
25. ANAMMOX (anaerobic ammonium oxidation) process with sequential biocatalyst (ANAM-MOX granules) addition (SBA-ANAMMOX process) [167].
26. Fenton oxidation (pretreatment) by oxidation and coagulation stage followed by aerobic biological degradation in sequencing batch reactor [147].

27. Catalytic wet air oxidation (CWAO) mixtures of waste streams used in autoclave to form polyoxometalates (POMs) as a cocatalyst system [141].

2.8 Summary and Conclusions

1. Toxic or hazardous pharmaceutical pollutants are typically produced in batch pharmaceutical manufacturing processes leading to the presence of a wide variety of undesirable pharmaceuticals in wastewaters, air, and soil. Common use of pharmaceutical compounds by human consumption and farming operations is also an input source of undesirable pharmaceuticals in the environment. It is concluded that the presence of pharmaceutical compounds in drinking water, livestock, and human body comes from both of the above two sources: (a) production processes of the pharmaceutical industry and (b) common use of pharmaceutical compounds resulting in their presence in urban and farm wastewaters.
2. The pharmaceutical wastewaters generated in different processes in the manufacture of pharmaceuticals and drugs contain a wide variety of chemical compounds. Some pharmaceutical pollutants are biodegradable; some are not biodegradable or toxic to microorganisms. Conventional cost-effective biological waste treatment technologies (i.e., gray environmental technologies), such as activated sludge, trickling filters, lagoons, sequencing batch reactor, membrane bioreactor, composting, sanitary landfill, etc., alone cannot properly treat the liquid and solid wastes. An integrated approach must be taken to manage all wastes within a pharmaceutical manufacturing plant. A "10-Step Blueprint for Managing Pharmaceutical Waste of Healthcare Facilities In the United States" has been developed by the US Environmental Protection Agency (USEPA), and this blueprint must be examined and followed in order to reduce the hazardous pharmaceuticals; in turn, a sustainable green biotechnology, bioreactor landfill, can be used to treat the nonhazardous pharmaceutical solid waste, generate methane gas as biofuel, and protect groundwater.
3. Pharmaceutical industry manufactures drugs, vaccines, antibiotics, products with therapeutic value, etc. using chemical reactors, biological systems or organisms, and many different raw materials. Pharmaceutical products are produced by chemical synthesis, fermentation, extraction from naturally occurring plant or animal substances, or by refining a technical grade product. The USEPA regulation applies to pharmaceutical industrial facilities which are organized into five subcategories: (a) subcategory A (fermentation products), (b) subcategory B (extraction products), (c) subcategory C (chemical synthesis products), (d) subcategory D (mixing, compounding, and formulation), and (e) subcategory E (research organizations).
4. Fermentation process of pharmaceutical plants produces most antibiotics and steroids using three basic steps: inoculum and seed preparation, fermentation, and product recovery. Fermentation is conventionally a large-scale batch process. The fermentation step begins with a wash water and steam sterilization of

the fermenter vessel. Sterilized nutrient raw materials in water are then charged to the fermenter. The process wastewater from fermentation plants is characterized by high BOD, COD, and TSS concentrations, relatively large flows, and a pH range of approximately 4.0–8.0.

5. Biological and natural extraction operations of pharmaceutical plants use many materials as pharmaceuticals are derived from such natural sources as the roots and leaves of plants, animal glands, and parasitic fungi. These products have numerous and diverse pharmaceutical applications, ranging from tranquilizers and allergy-relief medications to insulin, morphine, plasma, and its derivatives. The extraction process consists of a series of operating steps beginning with the processing of a large quantity of natural or biological material containing the desired active ingredient. Residual wastes from an extraction plant essentially will be equal to the weight of raw material. Solid wastes are the greatest source of the pollutant load; however, solvents used in the processing steps can cause both air and water pollution. The principal sources of wastewater from biological/natural extraction operations are (a) spent raw materials, (b) floor and equipment wash water, (c) chemical wastes (e.g., spent solvents), and (d) cleanup of spills. Wastewater from extraction plants is generally characterized by low BOD, COD, and TSS concentrations, small flows, and pH values of approximately 6.0–8.0.
6. Chemical synthesis operations of pharmaceutical plants manufacture most of the active ingredients marketed and sold as drugs using organic and inorganic chemical reactions. The conventional batch reaction vessel is the major piece of equipment used on the process line. The reaction vessel is one of the most standardized equipment designs in the industry. Chemical synthesis effluent generally has a high BOD and COD waste load. The pollutants in chemical synthesis wastewater vary with respect to toxicity and biodegradability. Chemical synthesis wastewater may be incompatible with biological treatment systems because it is too concentrated or too toxic for the biomass in the treatment system. Thus, it may be necessary to equalize and/or chemically pretreat some chemical synthesis wastewater prior to biological treatment. Primary sources of wastewater from chemical synthesis operations are (a) process wastes such as spent solvents, filtrates, and concentrates; (b) floor and equipment wash water, (c) pump seal water, (d) wet scrubber wastewater, and (e) spills. Wastewater from chemical synthesis plants can be characterized as having high BOD, COD, and TSS concentrations, large flows, and extremely variable pH values, ranging from 1.0 to 11.0.
7. Mixing, compounding, or formulating operations of pharmaceutical plants produce pharmaceutically active ingredients batch processes in bulk form and convert them to dosage form such as tablets, capsules, liquids, and ointments, for consumer use. In addition, active ingredients can also be incorporated into patches and time release capsules. Wastewater sources from mixing, compounding, or formulating operations are (a) floor and equipment wash water, (b) wet scrubbers, and (c) spills. The use of water to clean out mixing tanks can periodically flush dilute wastewaters of unusual composition into the plant

sewer system. In general, this wastewater is readily treatable by biological treatment systems. The wastewater from mixing, compounding, or formulating plants normally has low BOD5, COD, and TSS concentrations, relatively small flows, and pH values of 6.0–8.0.

8. The USEPA pharmaceutical industry effluent limitations (pretreatment or end-of-the pipe treatment) are provided in this publication for the US readers. The readers in other countries must contact their own country for the effluent limitation details. Knowing both the government effluent limitations and the wastewater characteristics will help select an integrated waste management plan and a feasible wastewater treatment system.
9. Advanced treatment processes available for treating the pharmaceutical wastewater include coagulation and clarification, dissolved air flotation (DAF), flotation-filtration (DAFF; filtration can be either sand filtration or GAC filtration), granular activated carbon (GAC) adsorption, powdered activated carbon (PAC) adsorption, wet air oxidation (WAO), supercritical water oxidation (SCWO), Fenton oxidation, UV photocatalytic oxidation, ultrasound oxidation, air stripping, distillation, electrochemical oxidation, ozonation, membrane filtration (MF, UF, RO, ED, MBR), or other advanced oxidation processes (AOP), combined oxidation-reduction process, etc. Of these advanced treatment processes, DAF, DAFF, GAC, air stripping, distillation, and membrane processes are suitable for recycling and reusing chemical compounds, and/or water. In view of the pollution load reduction and chemical cost saving, it is necessary to recover chemical compounds or raw materials as much as possible. In view of the scarcity of water resources, it is necessary to understand and develop methodologies for treatment of pharmaceutical wastewater as part of water management. While most of the advanced treatment processes are technically feasible for treating the pharmaceutical wastewater, their economical feasibility needs to be carefully evaluated before any implementation.
10. The Lenox Institute of Water Technology (LIWT), a nonprofit educational institute, has developed several multistage hybrid green environmental technologies which are both technically feasible and economically feasible for treating the pharmaceutical and other industrial wastewater depending on the characteristics of original industrial effluent: (a) DAF-DAFF-UV photocatalytic oxidation (one of AOP) for pretreatment, (b) DAF-aerobic biological-DAFF-UV photocatalytic oxidation for treating low-concentration wastewater, (c) DAF-anaerobic-aerobic biological-DAFF-UV photocatalytic oxidation for treating medium- to high-concentration wastewater, and (d) DAF-anaerobic-aerobic biological-DAFF-UF-UV photocatalytic oxidation for treating extremely high-concentration wastewater. The researchers are invited to study the LIWT systems further. Adopting a hybrid green environmental technology consisting of both biological system (aerobic alone or anaerobic-aerobic depending on the organic concentration of the wastewater) and UV photocatalytic oxidation will be a feasible solution to treating the pharmaceutical wastewater or similar.

Glossary of Biotechnology and Pharmaceutical Industry

Agricultural Biotechnology (a) It focuses on developing genetically modified plants to increase crop yields or introduce characteristics to those plants that provide them with an advantage growing in regions that place some kind of stress factor on the plant, namely, weather and pests; (b) development of pest-resistant crops and improvement of plant and animal breeding are typical examples; (c) green biotechnology refers to specific agricultural biotechnology that creates new plant varieties of agricultural interest, biopesticides, biofertilizers, etc. This area of agricultural biotechnology is based on transgenics (genetic modification), i.e., an extra gene or genes inserted into their DNA. The additional gene may come from the same species or a different species.

Biological and Natural Extraction (Pharmaceutical) Many materials used as pharmaceuticals are derived from such natural sources as the roots and leaves of plants, animal glands, and parasitic fungi. These products have numerous and diverse pharmaceutical applications, ranging from tranquilizers and allergy-relief medications to insulin and morphine. Also included in this group is blood fractionation, which involves the production of plasma and its derivatives. The extraction process consists of a series of operating steps beginning with the processing of a large quantity of natural or biological material containing the desired active ingredient. After almost every step, the volume of material being handled is reduced significantly. Neither continuous processing methods nor conventional batch methods are suitable for extraction processing. Residual wastes from an extraction plant essentially will be equal to the weight of raw material, since the active ingredients extracted are generally present in the raw materials at very low levels. Solid wastes are the greatest source of the pollutant load; however, solvents used in the processing steps can cause both air and water pollution. Detergents and disinfectants used in equipment cleaning operations are normally found in the wastewater. Priority pollutants, including methylene chloride, toluene, chloroform, 1,2-dichloroethane, and phenol, were identified as being used in the manufacturing of extractive pharmaceuticals. The principal sources of wastewater from biological/natural extraction operations are (a) spent raw materials (e.g., waste plasma fractions, spent media broth, plant residues), (b) floor and equipment wash water, (c) chemical wastes (e.g., spent solvents), and (d) cleanup of spills. Wastewater from extraction plants is generally characterized by low BOD, COD, and TSS concentrations, small flows, and pH values of approximately 6.0–8.0.

Biotechnology It is an engineering science field involving the use of biological systems found in organisms or the use of the living organisms themselves to make scientific advances and adapt those knowledge to various application branches, such as (a) medical biotechnology (including pharmaceutical biotechnology), (b) agricultural biotechnology, (c) industrial biotechnology (including industrial fermentation biotechnology), (d) environmental biotechnology, (e) computational biotechnology, and (f), military biotechnology:

Blue Biotechnology It is a specific environmental biotechnology which is based on the use of marine resources to create products, energy, or pollution control.

Chemical Synthesis (Pharmaceutical) Most of the active ingredients marketed and sold as drugs are manufactured by chemical synthesis. Chemical synthesis is the process of manufacturing pharmaceuticals using organic and inorganic chemical reactions. The conventional batch reaction vessel is the major piece of equipment used on the process line. The reaction vessel is one of the most standardized equipment designs in the industry. By using heating or refrigeration devices, the chemicals may be boiled or chilled in them, according to process needs. By adding reflux condensation equipment, the vessel may perform complete reflux operations (i.e., recycling of condensed vapors). The vessels can also become evaporators if vacuum is applied. The reactors may also be used to perform solvent extraction operations, and, by operating the agitator at a slow speed, the vessels can serve as crystallizers. Synthetic pharmaceutical manufacture consists of using one or more of these reactor vessels to perform, in a step-by-step fashion, the various operations necessary to make the product. Chemical synthesis effluent generally has a high BOD and COD waste load. The pollutants in chemical synthesis wastewater vary with respect to toxicity and biodegradability. The production steps may generate acids, bases, cyanides, metals, and other pollutants, while the waste process solutions and vessel wash water may contain residual organic solvents. Occasionally, chemical synthesis wastewater is incompatible with biological treatment systems because it is too concentrated or too toxic for the biomass in the treatment system. Thus, it may be necessary to equalize and/or chemically pretreat some chemical synthesis wastewater prior to biological treatment. Primary sources of wastewater from chemical synthesis operations are (a) process wastes such as spent solvents, filtrates, and concentrates, (b) floor and equipment wash water, (c) pump seal water, (d) wet scrubber wastewater, and 5) spills. Wastewater from chemical synthesis plants can be characterized as having high BOD, COD, and TSS concentrations, large flows, and extremely variable pH values, ranging from 1.0 to 11.0.

Computational Biotechnology (a) It can be defined as "conceptualizing biotechnology" to address biotechnology problems using computational techniques and makes the rapid organization as well as analysis of biotechnological data possible; (b) it can also be termed gold biotechnology or bioinformatics.

Dark Biotechnology It means the military biotechnology that is associated with bioterrorism or biological weapons and bio-warfare using microorganisms and toxins to cause diseases and death in humans, domestic animals, and crops.

Environmental Biotechnology (a) It is an interdisciplinary branch of biotechnology using biological systems and/or organisms for conservation of environment, resources, and energy and for protection of humans, animals, and plants on Earth and beyond; it can be of green biotechnology, gray biotechnology, blue biotechnology, gold biotechnology, or white biotechnology; (b) modern green environmental biotechnology has a symbol of "green cross" that involves the construction of resource recovery facilities (RRF), bioreactor landfills, in-vessel or in-bin composting reactors, bioremediation sites, wildlife sanctuary areas,

environmental protection parks, global warming control facilities, salmon ladders, etc. using the best available technologies (BAT) for reclamation of water, air, land, nutrients, methane gas, animals, plants, etc. and production of biofuels, bio-plastics, waste-converted animal foods, etc., in turn achieving environmental conservation, resource sustainability, biodiversity, climate control, ozone layer protection, etc. (c) Gray biotechnology refers to an old traditional environmental biotechnology applications to maintain biodiversity and the partial removal of certain pollutants or contaminants using microorganisms and plants to isolate and dispose of many kinds of substances such as heavy metals and hydrocarbons, but without sustainability of natural resources. Typical examples are the old biological secondary wastewater treatment plants (WWTP) and old sanitary landfills. Modern environmental biotechnology is considered to be a green biotechnology. (d) Blue biotechnology is based on the use of marine resources to create products, energy, or pollution control.

Fermentation (Pharmaceutical) Most antibiotics and steroids are produced by the fermentation process, which involves three basic steps: inoculum and seed preparation, fermentation, and product recovery. Fermentation is conventionally a large-scale batch process. The fermentation step begins with a wash water and steam sterilization of the fermenter vessel. Sterilized nutrient raw materials in water are then charged to the fermenter. Microorganisms grown from seed to aid in the fermentation process are transferred to the fermenter from the seed tank and fermentation begins. During fermentation, air is sparged into the batch, and temperature is carefully controlled. After a period that may last from 12 h to 1 week, the fermenter batch whole broth is ready for filtration. Filtration removes mycelia (i.e., remains of the microorganisms), leaving the filtered aqueous broth containing product and residual nutrients that are ready to enter the product recovery phase. There are three common methods of product recovery: solvent extraction, direct precipitation, and ion exchange or adsorption. Fermentation broth contributes pollutants to wastewater from the food materials contained in the broth, such as sugars, starches, protein, nitrogen, phosphate, and other nutrients. Fermentation wastes are very amenable to biological treatment. The spent broth can be satisfactorily handled by biological treatment systems in a concentrated form. Equalizing the broth prior to treatment helps avoid system upsets that may occur if the biota receive too high feed concentrations at one time. The process wastewater from fermentation plants is characterized by high BOD, COD, and TSS concentrations, relatively large flows, and a pH range of approximately 4.0–8.0.

Gold Biotechnology It is equivalent to bioinformatics, or computational biotechnology, that addresses biotechnology problems using computational techniques and makes the rapid organization as well as analysis of biotechnological data possible.

Gray Biotechnology It refers to an old traditional environmental biotechnology applications to maintain biodiversity and the partial removal of certain pollut-

ants or contaminants using microorganisms and plants to isolate and dispose of many kinds of substances such as heavy metals and hydrocarbons, but without sustainability of natural resources. Typical examples are the old biological secondary wastewater treatment plants (WWTP) and old sanitary landfills. Modern environmental biotechnology is considered to be a green biotechnology.

Green Biotechnology (a) It is modern environmental biotechnology that achieves environmental conservation and resource sustainability, or a specific agricultural biotechnology that creates new plant varieties of agricultural interest, biopesticides, biofertilizers, etc. (b) Modern green environmental biotechnology has a symbol of "green cross" that involves the construction of resource recovery facilities (RRF), bioreactor landfills, in-vessel or in-bin composting reactors, bioremediation sites, wildlife sanctuary areas, environmental protection parks, global warming control facilities, salmon ladders, etc. using the best available technologies (BAT) for reclamation of water, air, land, nutrients, methane gas, animals, plants, etc., in turn achieving environmental conservation, resource sustainability, biodiversity, climate control, ozone layer protection, etc.; (c) the area of green agricultural biotechnology is based on transgenics (genetic modification), i.e., an extra gene or genes inserted into their DNA. The additional gene may come from the same species or a different species.

Industrial Biotechnology (including industrial fermentation biotechnology) (a) It is the utilization of cells, such as microorganisms, or components of cells like enzymes, to generate products in sectors that are industrially useful, such as food and feed, chemicals, detergents, paper and pulp, textiles, biofuels, and biogas, or to create genetically modified organisms (GMOs) that enhance the diversity of applications and the economic viability of industrial biotechnology; (b) development of biocatalysts (such as enzymes, to synthesize chemicals), improvement of fermentation process, and production of new plastics/textiles, biofuels, etc. are typical examples; (c) a specific industrial biotechnology related to production of wine, cheese, and beer by fermentation is also termed yellow biotechnology; (d) designing more energy-efficient, less polluting, and low resource-consuming processes and products that can beat traditional ones is also termed white biotechnology.

Medical biotechnology (including pharmaceutical biotechnology) (a) It has a symbol of "red cross" and involves the use of living cells and other cell materials to find cures for preventing diseases and bettering the health of humans; (b) development of vaccines and antibiotics is a typical example; (c) a specific pharmaceutical biotechnology related to medicine and veterinary products (vaccines, antibiotics, molecular diagnostics techniques, genetic engineering techniques, etc.) is also termed red biotechnology.

Military Biotechnology It is also termed dark biotechnology because it is associated with bioterrorism or biological weapons and bio-warfare using microorganisms and toxins to cause diseases and death in humans, domestic animals, and crops.

Mixing, Compounding, or Formulating (Pharmaceutical) Pharmaceutically active ingredients are generally produced by batch processes in bulk form and must be converted to dosage form for consumer use. Common dosage forms for the consumer market are tablets, capsules, liquids, and ointments. In addition, active ingredients can also be incorporated into patches and time release capsules. Wastewater sources from mixing, compounding, or formulating operations are (a) floor and equipment wash water, (b) wet scrubbers, and (c) spills. The use of water to clean out mixing tanks can periodically flush dilute wastewaters of unusual composition into the plant sewer system. In general, this wastewater is readily treatable by biological treatment systems. The wastewater from mixing, compounding, or formulating plants normally has low BOD5, COD, and TSS concentrations, relatively small flows, and pH values of 6.0–8.0.

Pharmaceutical Biotechnology It is a part of medical biotechnology (or a part of red biotechnology) related to manufacturing of drugs, vaccines, antibiotics, etc. using biological systems or organisms.

Pharmaceutical Industry Pharmaceutical industry manufactures drugs, vaccines, antibiotics, products with therapeutic value, etc. using chemical reactors, biological systems or organisms, and many different raw materials Pharmaceutical products are produced by chemical synthesis, fermentation, extraction from naturally occurring plant or animal substances, or refining a technical grade product. The USEPA regulation applies to pharmaceutical industrial facilities are organized into five subcategories: (a) subcategory A (fermentation products), (b) subcategory B (extraction products), (c) subcategory C (chemical synthesis products), (d) subcategory D (mixing, compounding, and formulation), and (e) subcategory E (research organizations).

Red Biotechnology It is a specific medical (including pharmaceutical) biotechnology related to medicine and veterinary products (vaccines, antibiotics, molecular diagnostics techniques, genetic engineering techniques, etc.).

White Biotechnology It is a specific industrial biotechnology involving white biotechnology designing more energy-efficient, less polluting, and low resource-consuming processes and products that can beat traditional ones.

Yellow Biotechnology It is a specific industrial biotechnology related to production of wine, cheese, and beer by fermentation.

Appendix 1: BPT effluent limitations for subcategory A (fermentation operations), subcategory B (biological and natural extraction operations), subcategory C (chemical synthesis operations), and subcategory D (mixing, compounding, or formulating operations)

Subcategory	Pollutant or pollutant property	BPT effluent limitation for end-of-pipe monitoring points	
		Maximum for any one day (mg/L)	Monthly average (mg/L)
A: Fermentation operations	COD	1675	856
B: Biological and natural extraction operations	COD	228	86
C: Chemical synthesis operations	COD	1675	856
D: Mixing, compounding, or formulating operations	COD	228	86

Appendix 2: BAT effluent limitations for subcategory A (fermentation operations) and subcategory C (chemical synthesis operations)

Pollutant or pollutant property	BAT effluent limitations for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	0.5	0.2
Acetonitrile	25.0	10.2
Ammonia as N	84.1	29.4
n-Amyl acetate	1.3	0.5
Amyl alcohol	10.0	4.1
Benzene	0.05	0.02
n-Butyl acetate	1.3	0.5
Chemical oxygen demand (COD)	1675	856
Chlorobenzene	0.15	0.06
Chloroform	0.02	0.01
o-Dichlorobenzene	0.15	0.06
1,2-Dichloroethane	0.4	0.1
Diethylamine	250.0	102.0
Dimethyl sulfoxide	91.5	37.5

Pollutant or pollutant property	BAT effluent limitations for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Ethanol	10.0	4.1
Ethyl acetate	1.3	0.5
n-Heptane	0.05	0.02
n-Hexane	0.03	0.02
Isobutyraldehyde	1.2	0.5
Isopropanol	3.9	1.6
Isopropyl acetate	1.3	0.5
Isopropyl ether	8.4	2.6
Methanol	10.0	4.1
Methyl cellosolve	100.0	40.6
Methylene chloride	0.9	0.3
Methyl formate	1.3	0.5
MIBK	0.5	0.2
Phenol	0.05	0.02
Tetrahydrofuran	8.4	2.6
Toluene	0.06	0.02
Triethylamine	250.0	102.0
Xylenes	0.03	0.01

Appendix 3: BAT effluent limitations for subcategory B (biological and natural extraction operations) and subcategory D (mixing, compounding, or formulating operations)

Pollutant or pollutant property	BAT effluent limitations for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Chemical oxygen demand (COD)	228	86

Appendix 4: NSPS for subcategory A (fermentation operations) and subcategory C (chemical synthesis operations)

Pollutant or pollutant property	NSPS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	0.5	0.2
Acetonitrile	25.0	10.2

Pollutant or pollutant property	NSPS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Ammonia as N	84.1	29.4
n-Amyl acetate	1.3	0.5
Amyl alcohol	10.0	4.1
Benzene	0.05	0.02
n-Butyl acetate	1.3	0.5
Chlorobenzene	0.15	0.06
Chloroform	0.02	0.01
o-Dichlorobenzene	0.15	0.06
1,2-Dichloroethane	0.4	0.1
Diethylamine	250.0	102.0
Dimethyl sulfoxide	91.5	37.5
Ethanol	10.0	4.1
Ethyl acetate	1.3	0.5
n-Heptane	0.05	0.02
n-Hexane	0.03	0.02
Isobutyraldehyde	1.2	0.5
Isopropanol	3.9	1.6
Isopropyl acetate	1.3	0.5
Isopropyl ether	8.4	2.6
Methanol	10.0	4.1
Methyl cellosolve	100.0	40.6
Methylene chloride	0.9	0.3
Methyl formate	1.3	0.5
MIBK	0.5	0.2
Phenol	0.05	0.02
Tetrahydrofuran	8.4	2.6
Toluene	0.06	0.02
Triethylamine	250.0	102.0
Xylenes	0.03	0.01
BOD_5	267	111
COD	1675	856
TSS	472	166

Appendix 5: NSPS for subcategory B (biological and natural extraction operations) and subcategory D (mixing, compounding, or formulating operations)

Pollutant or pollutant property	NSPS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
BOD_5	35	18
COD	228	86
TSS	58	31

Appendix 6: PSES for subcategory A (fermentation operations) and subcategory C (chemical synthesis operations)

Pollutant or pollutant property	PSES for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	20.7	8.2
Ammonia as N	84.1	29.4
n-Amyl acetate	20.7	8.2
Benzene	3.0	0.6
n-Butyl acetate	20.7	8.2
Chlorobenzene	3.0	0.7
Chloroform	0.1	0.03
o-Dichlorobenzene	20.7	8.2
1,2-Dichloroethane	20.7	8.2
Diethylamine	255.0	100.0
Ethyl acetate	20.7	8.2
n-Heptane	3.0	0.7
n-Hexane	3.0	0.7
Isobutyraldehyde	20.7	8.2
Isopropyl acetate	20.7	8.2
Isopropyl ether	20.7	8.2
Methyl cellosolve	275.0	59.7
Methylene chloride	3.0	0.7
Methyl formate	20.7	8.2
MIBK	20.7	8.2
Tetrahydrofuran	9.2	3.4
Toluene	0.3	0.1
Triethylamine	255.0	100.0
Xylenes	3.0	0.7

Appendix 7: PSES for subcategory B (biological and natural extraction operations) and subcategory D (mixing, compounding, or formulating operations)

Pollutant or pollutant property	PSES for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	20.7	8.2
n-Amyl acetate	20.7	8.2
Ethyl acetate	20.7	8.2
Isopropyl acetate	20.7	8.2
Methylene chloride	3.0	0.7

Appendix 8: PSNS for subcategory A (fermentation operations) and subcategory C (chemical synthesis operations)

Pollutant or pollutant property	PSNS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	20.7	8.2
Ammonia as N	84.1	29.4
n-Amyl Acetate	20.7	8.2
Benzene	3.0	0.6
n-Butyl acetate	20.7	8.2
Chlorobenzene	3.0	0.7
Chloroform	0.1	0.03
o-Dichlorobenzene	20.7	8.2
1,2-Dichloroethane	20.7	8.2
Diethylamine	255.0	100.0
Ethyl acetate	20.7	8.2
n-Heptane	3.0	0.7
n-Hexane	3.0	0.7
Isobutyraldehyde	20.7	8.2
Isopropyl acetate	20.7	8.2
Isopropyl ether	20.7	8.2
Methyl cellosolve	275.0	59.7
Methylene chloride	3.0	0.7
Methyl formate	20.7	8.2
MIBK	20.7	8.2
Tetrahydrofuran	9.2	3.4
Toluene	0.3	0.1

Pollutant or pollutant property	PSNS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Triethylamine	255.0	100.0
Xylenes	3.0	0.7

Appendix 9: PSNS for subcategory B (biological and natural extraction operations) and subcategory D (mixing, compounding, or formulating operations)

Pollutant or pollutant psroperty	PSNS for end-of-pipe monitoring points	
	Maximum for any 1 day mg/L	Monthly average mg/L
Acetone	20.7	8.2
n-Amyl Acetate	20.7	8.2
Ethyl acetate	20.7	8.2
Isopropyl acetate	20.7	8.2
Methylene chloride	3.0	0.7

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