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Rochester Institute of Technology

“Effective Approaches to Minimize the Problem of Pharmaceuticals and Other Personal Care Products in the Environment”

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November 2007

Thesis

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Abstract:

Studies have shown that pharmaceuticals and other personal care products (PPCPs) are present in the environment, especially in water, due to different human activities. Some of these compounds are toxic to our eco-system. Although there is no evidence of adverse human health effect from the presence of PPCPs in the environment to date, some adverse effects on aquatic life cycle already have been found. Therefore, protecting our environment as well as human health from adverse effect(s) of PPCPs is a growing concern.

The objective of this thesis work was to collect information about the principal approaches available to pharmaceutical industries for reducing the introduction of PPCPs to the environment and to identify and address any divergence or disagreement about the effectiveness of these approaches to address this issue. Through the use of literature review, case studies, and in-depth interviews where necessary, consistent information has been consolidated and discrepancies have been resolved to the extent possible and this reference document has been created for the purpose of fostering the awareness about this issue and about the possible ways to minimize the problem from pharmaceutical industry perspective.

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Introduction:

Presence of pharmaceuticals and other personal care products in the environment is one of the most serious concerns today. There are different classes of chemicals recognized as continuing or emerging sources of contaminant that are continuously released to environment, mainly through different human activities. These classes include a wide variety of compounds used in industry and in home, for example, surfactants, disinfectants, solvents, etc. and those that constitute prescription and nonprescription drugs like antibiotics, antacids, antimicrobials, etc. Besides these, sex and steroidal hormones are also being recognized as emerging contaminants of environment. All these compounds have high usage rates and also have potential health effects and some undesirable effects on non-target organisms, including endocrine disruption and development of antibiotic resistance or toxicity (Lee, Zaugg, Cahill, and Furlong, 2000, 58).

The common sources of PPCPs in the environment are pharmaceutical wastewater, human excreta and disposal of unused prescription and non-prescription drugs. It is believed that concentrations of different chemicals in wastewater from pharmaceutical industries are negligible, in respect of producing any adverse effect on living creatures. But, still the concentrations of some of these chemicals are of a great concern as many of these chemical compounds have cumulative properties and after a couple of years, when these chemical compounds reach their MEC¹ (Minimum Effective

¹ MEC is the minimum amount of any chemical compound, in body's circulatory system, required to produce any effect of that chemical within the body.

Concentration) in the environment, they produce adverse effects to living creatures to some extents.

Proper disposal of unused prescription² and non-prescription drugs is also important because most of the pharmaceuticals and personal care products get accumulated after disposal in the environment due to their resistant nature to biological degradation process and sometimes their adverse effects on non-target receptors³ can not be identified, even unpredictable, due to their low concentration applications. As for example, reproductive hormones like estrogen which is used for birth control in human also interfere with reproduction and development stages in reptiles. This estrogen hormone also results in widespread sexual disruption in male fishes. Similarly, some antidepressant pharmaceuticals like serotonin reuptake inhibitors inhibit growth rate in frogs and fishes. Sometimes, exposure to these accumulated PPCPs result in the development of drug resistant pathogenic organism⁴ in the environment. As for example, over use of antibiotics today, results in higher concentration of antibiotics residue in wastewater this in turn results in the creation of antibiotic resistant bacteria. Since, all these drug residues are present in very low concentration; it is difficult to identify their immediate adverse effect and combined effects of multiple PPCPs, the persistence and bioaccumulation of these compounds, and long term multi-generational effects⁵ are also difficult to predict. (Viadero. 2000,1)

² Prescription is a physicians order for the preparation and administration of a drug or device for a patient.

³ Receptor - a structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance.

⁴ Disease producing microorganism

⁵ Information on the long-term health effects of low-level, long-term exposures of drug substances is particularly limited.

However, different approaches like product stewardship, end-of-pipe treatment technologies etc. are being currently used to prevent the introduction of PPCPs into the environment.

Background (Preliminary) Literature Review:

“Human exposure to environmental concentrations of pharmaceuticals⁶ is believed to be primarily through ingestion of drinking water and, for compounds that bio-accumulate, through ingestion of meat or fish” (Hagan 2000, 66).

When pharmaceuticals and personal care products⁷ (PPCP) are present in very low concentrations in surface or groundwater, which is a source of drinking water, the most serious concern associated with their presence is not necessarily immediate acute effects on human health, but rather with the effects that can accumulate over a long

⁶ Pharmaceuticals are substances that are aimed to cure, prevent, or recognize diseases and relieve pains through their application in the organism.

⁷ PPCP includes cosmetics, fragrances, skin care products, nutritional supplements, and over-the-counter medications.

period of time to produce truly distinguishable changes (Daughton & Ternes, 1999). Sometimes, it becomes difficult to identify any of these changes in certain non-target populations as they take a long period of time to occur. Current comprehensive environmental risk assessments and epidemiologic studies⁸ lack consideration of this type of long-term effects (Drewes, Heberer and Reddersen, 2002, 269).

Sometimes, water characteristics get changed according to its use by humans. We use a variety of chemicals everyday for different purpose like for industrial purpose or for domestic purpose. After use, a portion of these chemicals find their way to either industrial wastewaters or domestic sewage. We are able to remove some of these chemicals through different treatment methods. After treatment, this wastewater is discharged to a receiving stream or water body. At any point of downstream flow of water, user receives the water and chemicals from all upstream users and this process goes to continue throughout the downstream of water flow. In this way, some chemicals are destroyed by means of some physical, chemical or biological treatment methods and those which remain unaffected, ultimately reaching a final receiver, e.g. oceans where they are precipitated due to evaporation of water and are accumulated (Hagan. 2000, 64).

In some closed watersheds⁹, e.g., the Great Salt Lake, the final receptor is a lake and/or wetland. Planned reuse of treated wastewater is important in water-short

⁸ Epidemiologic Studies - Studies designed to examine associations—commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of epidemiologic studies are case-control studies, cohort studies, and cross-sectional studies.

⁹ A watershed (also called a drainage basin or a catchment area) is defined as an area of land that intercepts and drains precipitation through a particular river system or group of river systems. In other words it is a

areas of the US and many other countries where water resources are limited relative to need. Planned reuse can be divided into two categories:

(1) use that does not involve human consumption of the water such as irrigation of golf courses and landscaping; and

(2) uses that result in human exposure, including drinking water supply.

Planned reuse is currently always indirect rather than direct (i.e., using treated sewage effluent as drinking water supply influent). Indirect reuse includes recharging an aquifer used for a ground water supply with treated effluent and discharging treated effluent to a water supply reservoir (Hagan 2000, 64).

Advanced sewage treatment methods like activated carbon adsorption and membrane filtration in conjunction with planned water reuse is always much more rigorous than that used for discharges to surface waters (Hagan 2000, 64).

The contaminants enter the environment by means of different transport pathways such as, on one hand, through direct disposal in sewage systems and landfills, and on the other hand, as runoff or infiltration from fields following application of wastewater treatment sludge or animal manure (Lee, Zaugg, Cahill, and Furlong, 2000, 58). The main route by which pharmaceuticals enter the environment is via water discharges, as most of the pharmaceuticals found in the environment have been proved water-soluble.

region of interconnected rivers and streams which functions as a unified system for water transport. Watersheds may be of various forms: a closed watershed empties into an inland body of water, whereas an open watershed drains to the ocean.

Among the different routes into the environment, the therapeutic use¹⁰ of pharmaceuticals and the subsequent excretion of the active ingredients or their metabolites in urine and feces, quantitatively constitutes the most important one.

When applying pharmaceuticals to humans, many of these compounds are excreted with only slight transformations or even unchanged and often conjugated to polar molecules (e.g. as glucuronides). Due to an incomplete elimination of a number of pharmaceuticals used in human medical care in sewage treatment plants several classes of drugs are found in sewage effluent. Among these classes are antirheumatics (e.g. Diclofenac), analgesics (e.g. Propyphenazone) as well as the above mentioned blood lipid regulators (e.g. Clofibrilic acid). High concentrations of sewage contaminants may be expected in the receiving surface waters with regard to the high contribution of sewage treatment work's effluents, especially in areas with a high population density (Scheytt, Leidig, Marsmann and Heberer 2000, 253). The chemicals which are excreted by human beings, first enter into sewage treatment systems and then enter into surface water and groundwater when the treated wastes are discharged (Hagan. 2000, 64).

Although it has been cited in some literature that neither manufacturing of pharmaceuticals nor disposal of sewage sludge on land constitute a major source of pharmaceuticals in the environment, still manufacturing, wastewater and waste from

¹⁰ Therapeutic use means use for the purpose of preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons; or influencing, inhibiting or modifying a physiological process in persons; or testing the susceptibility of persons to a disease or ailment.

pharmaceutical industries are considered to be important sources. The pathways of contamination from disposal of sewage sludge would be to surface water by runoff that contacted the sludge or to ground water by precipitation that percolates through the sludge into an underlying aquifer (Hagan 2000, 64). Sewage Treatment plant effluent has been recognized a source of certain natural chemicals like human estrogen, caffeine etc., in the aquatic environment.

In order to determine the right approach to address this issue, it is first necessary to identify what types of pharmaceuticals are normally found in the environment. But, unfortunately, still there is no single analytical method to detect all pharmaceuticals. Very sophisticated analytical research methods with very low detection limits and highest accuracy are necessary to detect most of the pharmaceuticals in the environment at very low concentrations. Such testing can only be done by using special analytical equipment which is only available in certain analytical research laboratories, or certain commercial laboratories that also specialize in methods research (Pontius. 2002, 9).

Information about the treatment methods of pharmaceutical compounds is not very common in the public literature. However, granular activated carbon, powdered activated carbon, nano-filtration and reverse osmosis are the most common methods used to remove synthetic organic pharmaceuticals compounds from water. Flocculation¹¹ with ferric chloride and slow-sand filtration had proven ineffective as treatment processes to remove low levels of pharmaceuticals found in drinking-water where a combination of

¹¹ Flocculation - The agglomeration of finely divided suspended solids into larger, usually gelatinous, particles.

ozonation and filtration with or without granular activated charcoal has been proven as a very important treatment (Pontius, 2002, 8).

Again, in order to eliminate pharmaceuticals completely from wastewater and sewage sludge, it is assumed that an advanced treatment technology, like reverse osmosis, may be very effective. Research is going on to determine the most effective wastewater treatment method.

USEPA has not set a national primary drinking water regulation (NPDWR) for PPCPs. USEPA believes there is not sufficient information to warrant regulation of PPCPs at this time. (USEPA 2002b) Other countries are considering how pharmaceuticals might be regulated. (Lange and Dietrich 2002)

Under the National Environmental Policy Act of 1969, the U.S. Food and Drug Administration (FDA) requires Environmental Assessments on the impact of individual pharmaceuticals on the environment. (Daughton and Ternes 1999) USEPA does not require routine monitoring for PPCPs at this time. USEPA has not included contaminants on the Drinking Water Contaminant Candidate List (DWCCCL) solely on the possibility of their endocrine disruption potential. But, USEPA may add certain representative PPCPs to the DWCCCL and Unregulated Contaminants Monitoring Rule (UCMR) in the future. (USEPA 2002b) (Pontius, 2002, 8)

Although, there is no drinking water regulation or routine monitoring requirement for PPCPs has been set by USEPA till-to-date because of the unavailability of enough information needed to justify regulating PPCPs in drinking water but, now-a-days federal regulators and scientists are becoming more and more concerned about the issues of emerging contaminants i.e. PPCPs and continue to include and evaluate PPCPs in contaminant selection process and carrying out research efforts to determine whether regulation is necessary or not (Grumbles. 2006). USEPA might reconsider drinking water regulations for all of these contaminants in near future.

Today, many companies are using a cradle-to-cradle stewardship¹² concept to address this issue. According to this concept, companies are taking many actions like altered drug design and packaging system for drugs, modified drug delivery pattern, improved drug dispensing methods, more effective methods of drug disposal, etc. in order to reduce the risk from introduction of pharmaceuticals into the environment. Manufacturing facilities are making every effort to assure that product is not lost to the waste stream. Manufacturing releases would be localized and likely a minor contributor to the environment. Some of these ideas for minimizing the release of PPCPs to the environment have already been put forth (Daughton and Ternes 1999). As per Daughton, “For true cradle-to-cradle stewardship of PPCPs, a holistic integration of all aspects of the production-consumption cycle is required – one that takes into consideration the needs and costs of the complete cycle from drug discovery/design to distribution, end use, and disposal/recycling.”

¹² Cradle-to-cradle stewardship means extended product responsibilities.

In one study regarding the avenues towards “Green Pharmacy” by Christian G. Daughton, he recommended some methods for disposal of PPCPs by the end user i.e. disposal of drugs to domestic sewage systems is probably the least desirable way to dispose of any drug while the two better alternatives might include pharmacy take back program as a part of cradle-to-cradle stewardship and disposal in household trash destined for engineered landfills (still not desirable) to address the issue of PPCPs in environment.

Methodology:

I.Literature Review:

For the purpose of this thesis work, a literature review has been conducted to collect information from the U.S. and Western Europe. That means literature published in these geographical areas have been reviewed as it is believed by the researcher that most advanced technologies are being practiced in the U.S. and Western Europe.

Literature published in English, from 1985 through the present have only been considered for review as it is assumed by the researcher that the technologies used before 1985, are mostly outdated now, particularly in these geographical area and bear no relevance with purpose of this thesis work.

Articles from professional journals, books by acknowledged experts, papers published on the WebPages of academic institutions and professional organizations and official documents posted on WebPages of governmental agencies and corporations have been considered as an appropriate sources for review while writings from, supported by, or posted on the WebPages of: advertising or marketing groups, advocacy organizations, or organizations with vested interests in one outcome or another have been considered inappropriate sources of information for this thesis work.

The literature review has been conducted thus to find out information to answer the following questions:

- What are the approaches available to address the issue of PPCPs?
- How effective are these approaches are to address this issue?
- What are their limitations?
- Is there any disagreement or discrepancy about the effectiveness of these approaches to address this issue?
- Which one is the best approach (most effective) from all aspects?
- Is there any possibility of improving the effectiveness of these approaches?

- What new approaches, companies are planning to take in future to address the issue of PPCPs?

For the purpose of this thesis work, only manufacturing process stage in pharmaceutical industries has been considered as the potential source of contaminant to pharmaceutical wastewater and other stages of pharmaceuticals and other personal care products manufacturing like packaging etc. have been excluded from the list of potential sources of contaminant to wastewater.

II. Case Studies

Information has been collected, through case studies, about the view of pharmaceutical industries regarding the issue of pharmaceuticals and other personal care products in environment. Case study approach has been considered as an appropriate methodology for this work to answer ‘What’, ‘Why’, ‘How’ – types of questions, over which little or no control could be exerted, as there was no scope of any hand-on laboratory work during the course of this thesis work.

For the purpose of case study, Websites of 10 leading pharmaceutical companies have been visited to find out specific information about their current approaches towards this issue and their future plan (if any) towards this issue. These 10 pharmaceutical companies have been selected for case study purpose based upon the availability of information, in their respective websites, required for this thesis work. Case studies have been performed by reviewing their electronic copies of annual report (s), EHS

performances, corporate responsibilities, and newsroom as it is believed that companies, in general, put their most recent environmental health and safety information in all or any one of these mentioned areas. Specifically, the following information has been looked for during case studies:

- What current approaches are being taking?
- How these approaches are being applied?
- Why any company has chosen any particular approach?
- What will be their next plan to address this issue?

III. In-Depth Interviews

For the purpose of this paper, in-depth interview processes with pharmaceutical company personnel have been conducted to verify the reliability of the information collected through literature survey and case study and to collect additional information about their specific approaches. Both EHS personnel as well as production personnel of pharmaceutical companies have been interviewed as it has been believed that these personnel keep the most updated EHS information of the respective companies and about their future EHS goal (s). Specifically, the following information has been looked for during this interview stage:

- What are the most recent approaches from company's perspective to address this issue?
- Why they have chosen these particular approaches?
- Why they are not using any other approaches?
- What they are thinking to do in near future regarding this issue?

- Are they doing so actually to protect our environment, or just due to some regulatory concern to look the company doing better?

IV. Analysis

Information about the past and present approaches of pharmaceutical companies towards the issues of PPCPs that collected through literature review, have been verified with that collected through case studies and finally, validated against the information collected through interview stage and the final conclusion has been drawn based on these validated information.

Findings

I. Literature Review

Generally, five types of manufacturing processes are common in pharmaceutical industries. These are research, fermentation¹³, biological or natural extraction¹⁴, chemical

¹³ Fermentation - The process of growing microorganisms to produce chemicals or pharmaceutical compounds. Microorganisms are usually grown under controlled condition in large tanks called fermentors.

¹⁴ Extraction - the process of obtaining something from a mixture or compound by chemical or physical or mechanical means.

synthesis and finally, mixing-compounding-formulating. Many pharmaceutical industries use any one of these five manufacturing processes while the others use a combination of two or more manufacturing processes in their regular practice. (The research type of manufacturing process has not been considered as a potential source of contaminant to wastewater for this thesis work as the volume of wastewater that produces everyday from a research process is negligible as compared to that of the other four types of manufacturing processes and therefore, has not been discussed further in this paper.)

Examples of different classes of pharmaceutical products, manufactured by using the above four processes, are given in the following table:

Table 1

Type of Process	Example of Pharmaceutical Products
Fermentation	Antibiotics – Chlortetracycline, Penicillin G, Penicillin V, Streptomycin; Therapeutic Nutrients; Vitamins - Ascorbic acid (C), Riboflavin (B2); Steroids etc.
Biological or natural extraction	Enzymes and Digestive Aids; Central Depressants – Codeine, Morphine Sulfate; Hematological Agents – Heparin; Insulin etc.
Chemical Synthesis	Antibiotics – Clindamycin; Cardiovascular Agents – Methyldopa; Central Stimulants – Amitriptyline, Caffeine; Central Depressants – Acetaminophen, Aspirin; Hormones - Cortisone acetate, Dexamethasone acetate, Hydrocortisone, Testosterone; Vitamins – Niacinamide etc.
Mixing, compounding or formulating	Mouthwash – Listerine; Powders; Tablets and Capsules; Ointments – Caladryl, Vicks Vaporrub etc.

From a portfolio survey by EPA, it can be said that the number of pharmaceutical industry using the fermentation method is increasing since 1990 (USEPA Technical Development Document. 1998, 3-40). As per the survey report, this number has been increased by 100% since before 1990, while the use biological or natural extraction method has decreased by 15% and the other two methods have remained point as before. These manufacturing processes are being used in pharmaceutical industries, either in batch operation or in continuous operation or in a combination of both. Therefore, wastewater characteristics from different manufacturing facilities are not unique and vary according to the manufacturing process type.

Fermentation process is very important in antibiotics and steroid manufacturing units. Fermentation is carried out as a large-scale batch operation. Therefore, before charging a new batch, water wash and sterilization of the fermenter vessel is a compulsory step to prevent cross contamination and phase infection. This wastewater from the fermenter vessel, spill cleanup water, wastewater that is generated from product recovery stage and that from liquid scrubber (often is used to clean fermentation waste-off gas before discharging it to air), along with spent broth and infested batch (if any), constitute the waste stream of a fermentation unit.

Biological or natural extraction is one of the most important process in pharmaceutical manufacturing because by this method, most of the natural active ingredients of medicinal and other personal care products are extracted from natural resources like plant, fungus etc. These active ingredients fall into different categories like

alkaloids, glycosides, tannins, resins, volatile oils etc. Different portion of plants are being used for these extraction processes, e.g., Senna leaves are used to extract sennoside alkaloid which is used as an active ingredient in laxative and purgative preparations; similarly, digitalis leaves are used to extract dioxin and digitoxin glycosides which are active ingredients in many cardiac medicinal preparations like those are used in cardiac arrhythmia¹⁵ etc; similarly, clove oil is used as dental analgesic, antiseptic preparation etc. . Many of the natural volatile oils, extracted by this method, are used as flavoring agents in different cosmetics preparations like, soaps, body spray, cream etc. Therefore, biological or natural extraction processes are very much essential in pharmaceutical and other personal care products manufacturing.

In this extractive process, the active ingredient(s) is (are) extracted with a solvent or with a mixture of solvents, depending on the specific type of active ingredient(s) through a series of batch operations. This equipment wash water, spent raw material like plant residue, chemical waste like spent solvent, spill cleanup water etc. are considered the major sources of waste in the effluent of a extraction unit. The waste load in the effluent is normally very high because natural active ingredients are present in a very minute quantity in the plant or animal sources. Solid wastes constitute the major portion of this waste load.

Chemical synthesis is another important method of pharmaceutical manufacturing and is now being widely used in the industry to manufacture medicinal and other

¹⁵ Cardiac Arrhythmia - Irregularity of the heartbeat caused by damage to or defects in the heart tissue and its electrical system. An unusually fast rhythm (more than 100 beats per minute) is called tachycardia. An unusually slow rhythm (fewer than 60 beats per minute) is called bradycardia.

cosmetic products where the biological method is not economically feasible and the required ingredients can be manufactured in a chemical set up, using a number of organic and/or inorganic chemical reactions. This is a batch operating process.

In chemical synthesis, the same equipment is used for different product manufacturing and the wastes characteristics vary accordingly. The equipment wash water, process waste like spent solvents, precipitates, reaction by-products etc., spill cleanup water, wet scrubber water etc. are the major sources of contaminant of the wastewater effluent from a chemical synthesis unit.

Active ingredients are converted into different dosage form like tablet, capsule, liquid preparations etc. by the mixing, compounding or formulating processes. These dosage forms are the final usable forms. The equipment wash water, floor wash water, water from wet scrubber and spill cleanup water are the major sources of wastewater in a mixing, compounding or formulating unit.

Therefore, all types of pharmaceutical manufacturing industry generate wastewater containing a variety of pollutants. Generally, three types of pollutants are presents in pharmaceutical wastewater. These are conventional pollutants, priority pollutants and non-conventional pollutants. The following table represents a general list of these three category pollutants which may be presents in pharmaceutical wastewater:

Table 2

Pollutants	Examples
Conventional Pollutants	BOD ₅ , Oil & Grease, pH, Fecal Coliform, TSS
Non conventional Pollutants	Acetaldehyde, Acetic acid, Acetone, Acetonitrile, Acetophenone, Allyl chloride, 4-Aminobiphenyl, Ammonia, n-Amyl acetate Amyl alcohol, Aniline, Benzaldehyde, Benzotrichloride, Benzyl alcohol, Benzyl chloride, Benzyl bromide, Biphenyl, Bis(chloromethyl)ether, 2-Bromo-Propanoylbromide, 2-Butanone (MEK), n-Butyl acetate, n-Butyl alcohol, tert-Butyl alcohol, sec-Butyl alcohol, n-Butylamine, Carbon disulfide, Catechol, Chloroacetic acid 2-Chloroacetophenone, 3-Chloro-4-Fluoroaniline, Chloromethyl methyl ether, COD, Cresol (Mixed), Cumene, Cyclohexane, Cyclohexanone, Cyclopentanone, Cyclohexylamine, 1,2-Dibromoethane, 1,2-trans-Dichloroethene, Diethylaniline, Diethyl ether, Diethylamine, Diethyl carbonate, Diethyl-ortho formate Dimethylamine, 1,1-Dimethylhydrazine, N,N-Dimethylacetamide N,N-Dimethylformamide, N,N-Dimethylaniline, Dimethylcarbamyl chloride, Dimethyl sulfoxide, 1,4-Dioxane, N-Dipropylamine, Epichlorohydrin, Ethanol, Ethylene oxide, Ethylamine, Ethyl bromide Ethyl cellosolve, Ethyl acetate, Ethylene glycol, Ethyl cyanide, Formaldehyde, Formamide, Formic acid, Furfural, Glycol ethers, n-Heptane, 2-Hexanone, n-Hexane, Hydrazine, Iodoethane, Iodomethane, Isobutyraldehyde, Isopropyl ether, Isopropanol, Isopropyl acetate, Isobutyl alcohol, Methanol, Methyl cellosolve Methyl amine, Methyl formate, 2-Methyl pyridine, 2-Methoxyaniline, Methyl methacrylate, Methyl-t-butyl-ether, Methylal, Methyl isobutyl ketone (MIBK), N-Nitrosomorpholine, n-Octane, n-Pentane, Petroleum naphtha, Poethylene glycol 600, 1,3-Propane sulfone n-Propanol, B-Propiolactone, Propionaldehyde, 1,2-Propyleneimine Propylene oxide, Pyridine, Styrene, Tetrachloroethene, Tetrahydrofuran, Trichlorofluoromethane, 2,4,5-Trichlorophenol, Triethylamine, Vinyl acetate, Xylenes
Priority Pollutants	Acrolein, Acrylonitrile, Benzene, Benzidine, Bromoform, Bromomethane, Chlorobenzene, Chloroethane, Chloroform, Chloromethane, Cyanide, 1,1-Dichloroethane, 1,2-Dichloroethane 1,1-Dichloroethene, 1,2-Dichloropropane, Ethylbenzene, Hexachlorocyclopentadiene, Hexachloroethane, Methylene chloride Nitrobenzene, 2-Nitrophenol, 4-Nitrophenol, o-Dichlorobenzene p-Dichlorobenzene, Phenol, 1,1,2,2-Tetrachloroethane, Tetrachloromethane, Toluene, 1,1,1-Trichloroethane, Trichloroethylene, 1,1,2-Trichloroethane, Vinyl chloride.

(Source: USEPA Technical Development Document. 1998, Table 6-1, 6-12)

Wastewater is characterized in terms of its BOD₅¹⁶, COD¹⁷, TSS content, flow rate and pH. These characteristics of wastewater from different pharmaceutical industries vary according to the specific type of manufacturing process. The following table represents a general comparison of the characteristics of wastewaters from four different types of manufacturing process units, assuming that each unit uses only one type of process.

Table 3

Type of Process	BOD ₅	COD	TSS	Flow Rate	pH
Fermentation	High	High	High	Large	4.0 – 8.0
Biological or Natural Extraction	Low	Low	Low	Small	6.0 – 8.0
Chemical Synthesis	High	High	High	Large	1.0 – 11.0
Mixing, Compounding or Formulating	Low	Low	Low	Small	6.0 – 8.0

(Source: USEPA Technical Development Document. 1998, 3-29:38)

But, in actual practice, each pharmaceutical industry uses a combination of two or more of the above four processes. Therefore, the characteristics of wastewater vary from industry to industry, depending on the types of processes in use.

Pharmaceutical industries discharge these wastewaters to the water of United States either directly or indirectly through publicly owned treatment works (POTWs). It is generally believed that concentrations of different chemicals in wastewater from the pharmaceutical industries are negligible, with respect to the potential of producing any adverse effect on living creatures. However, recent studies have shown that although

¹⁶ BOD₅ - Biochemical Oxygen Demand is a biological laboratory procedure that measures the rate of oxygen use while stabilizing decomposable organic mater under controlled conditions of time (5 days) and temperature (20°C).

¹⁷ COD (Chemical oxygen demand) - the amount of oxygen in mg/l required to oxidize both organic and oxidizable inorganic compounds.

these chemicals are present in a minute quantity, some of them produce adverse effects on aquatic life due to their cumulative effects. To address this issue, besides onsite wastewater treatment technologies, pharmaceutical industries are using product stewardship technology. The following table represents the common trends in treatment technologies used at pharmaceutical industries before 1990 and after 1990 onwards on a percentage basis;

Table 4

Treatment Technology	Percentage of facilities using this type of treatment technology Prior to 1990	Percentage of facilities using this type of treatment technology in 1990 Onward
Neutralization	26.0	44.3
Equalization	20.1	28.6
Activated sludge	16.9	20.5
Settleable solids removal	13.3	NA
Primary sedimentation	12.0	NA
Aerated lagoon	7.5	4.9
Primary clarification	3.9	9.8
Chlorination	3.6	2.5
Polishing ponds	3.2	NA
Waste stabilization pond	2.9	2.5
Trickling filter	2.9	2.0
Multimedia filtration	2.3	6.1
Steam stripping	1.9	5.7
Evaporation	1.9	NA
Secondary clarification	1.6	20.9
Granular activated carbon	1.3	3.3
Oxidation	1.0	2.0
Dissolved air flotation	1.0	NA
pH adjustment	NA	50.0
Phase separation	NA	12.3

(Source: USEPA TDD. 1998, Table 3-9, 3-53) NA – Not Available from Survey data.

The total of the percentage in both the columns is not equal to 100 because some industries use more than one treatment technologies while some industries do not operate any onsite treatment unit.

The major onsite wastewater treatment technologies (USEPA Technical Development Document, 1998, 7-1) are as follows:

1. pH adjustment or neutralization
2. Equalization
3. Advanced biological treatment
4. Cyanide destruction
5. Multi-media or Multi-layer filtration
6. Polishing pond treatment
7. Steam stripping and steam stripping with rectification
8. Granular activated carbon adsorption
9. Air stripping
10. Incineration

1. pH Adjustment/Neutralization:

Effectiveness of most of the pharmaceutical wastewater treatment technologies depend on the pH of the wastewater stream and these treatment technologies work best at a certain specific pH range. Therefore, pH adjustment or neutralization is usually done prior to many wastewater treatment operations. In any type of sedimentation process, pH adjustment or neutralization is important because solubility of most of the constituents in pharmaceutical wastewater is pH dependent. pH adjustment units usually consist of a mixing tank, stirring equipment and feed system for chemicals. pH is adjusted in the

mixing tank by adding either acids or alkali, depending on the desired pH. The pH of final discharge is usually adjusted to between 6 and 8.5. (Guyer, H. 1998; 103)

Advantage:

- pH adjustment is used as a pretreatment technology, prior to many physical, chemical and biological wastewater treatment processes to improve their effectiveness.
- pH adjustment is very much important for maintaining structural integrity of the membrane in filtration unit.
- pH adjustment is also useful in reducing total solid content of wastewater stream through precipitation of many compounds whose solubility is pH dependent.

Limitation:

- This is a chemical addition process. Therefore, this process increases total chemical load of the wastewater.
- Some of the pH adjusting compounds (like NaOH) are expensive.

2. Equalization:

In any particular production day in a pharmaceutical industry, wastewater flow rate from different production units will vary according to the speed of the processes and thereby, sometimes overload and affect the performance of different wastewater treatment units. For example, biological and chemical treatment units work best at a constant inlet wastewater flow rate because it guarantees adequate process retention time. Similarly in

other wastewater treatment process like gravity sedimentation i.e. polishing pond treatment, fluctuation in the influent flow rate disturbs solid settling process and reduces treatment unit effectiveness. Therefore, equalization of wastewater flow rate through a wastewater treatment unit is very important for overall performance of the unit.

The equalization of flow prevents surges i.e. short term, high volumes of incoming flow and controls the flow through each stage of the treatment system, allowing adequate time for the physical, biological and chemical processes to take place. Equalization unit consists of large tanks or basins where a certain percentage of daily wastewater streams is held to stabilize flow turbulence and is then discharged at a constant flow rate to downstream treatment units.

Advantage:

- Flow equalization eliminates or at least minimizes shock loadings throughout the downstream of wastewater treatment processes, thereby enhances performance of those treatment processes.
- Flow equalization prevents system overloading.
- Equalization tanks consolidate smaller volumes of wastewater streams so that, for batch treatment systems, full batch volumes are available.

Limitations:

- Flow equalization unit requires large land areas which increases capital cost.
- Additional operational cost may be required for odor control.

3. Advanced Biological Treatment:

Advanced biological treatment is a very useful method of degrading various organic constituents in pharmaceutical wastewater and hence, is widely used in pharmaceutical manufacturing industries to treat BOD₅, COD, and TSS of wastewater stream. In fact, by using this method, BOD₅ and COD of wastewater stream can be reduced by 90% and 75% respectively, in respect of their values in untreated wastewater. (USEPA Technical Development Document. 1998, 7-11)

Biological treatment of wastewater can be carried out either in presence of oxygen which is also called aerobic treatment or in absence of oxygen which is also called as anaerobic treatment. Again, under the aerobic biological treatment methods, different technologies are available like activated sludge process, surface impoundments, trickling filters, rotating biological contractors (RBC), sequencing batch reactors (SBR) and others, out of which, only first four methods are in common use in pharmaceutical manufacturing industries. Among these four methods, the basic mechanism of activated sludge process and surface impoundment process is the suspended growth technique in which microorganisms are kept suspended within the liquid being treated and thus, allowed to come into contact with the suspended and dissolved organic and nonmetallic inorganic wastes. The basic mechanism of trickling filter and rotating biological contactors is the fixed-film technique in which microorganisms are allowed to grow on a supporting medium and form a biological slime layer and as the wastewater passes through the unit, suspended and dissolved organic and nonmetallic wastes come in contact with the slime

layer and decompose into carbon dioxide, water, nitrate, sulfate, organic byproducts and cellular biomass. In both suspended growth and fixed film techniques, oxygen, nitrogen and phosphorous are supplied to maintain the microbial load in the units. (Guyer, H. 1998; 151-6)

The essential parts of an activated sludge treatment system are an equalization basin, a primary clarifier, an aeration basin, a secondary clarifier, and a sludge recycle line. Prior to aeration step, settleable solids are removed in a settling tank which acts as primary clarifier. Oxygen, recycled sludge, and nutrients are added to the aeration basin to maintain the microorganism population. Microorganisms are kept suspended in the aeration basin by the flow of oxygen, supplied by aerators. The secondary clarifier is necessary to control the amount of suspended solids to be discharged and the sludge is also obtained from this clarifier for recirculating to the aerated basin. For optimum performance of the activated sludge system, equalization of flow, pH, temperature, and pollutant loads is very important. (USEPA Technical Development Document.1998, 7-12)

Biological waste products and expired microorganisms are the primary constituents of the generated sludge which is further treated to reduce overall volume prior to disposal. The commonly used treatment methods are sludge thickening and sludge dewatering. Gravity separation, dissolved air flotation, or centrifugation technique is used for sludge thickening and filtration techniques like filter press, vacuum filter etc. is used for sludge dewatering. Nutrient-to-microorganism ratio, sludge production rate, percent BOD₅ of effluent TSS, sludge retention time etc. are the some important

parameter of activated sludge treatment system. Advanced biological treatment method, when combined with nitrification, is also useful to reduce ammonia content of the wastewater. This can be achieved by incorporating two sets of autotrophic¹⁸ microorganisms in biological treatment units. One set of microorganisms i.e. Nitrosomonas bacteria, converts ammonia to nitrites while the other one i.e. Nitrobacter bacteria, converts nitrites to nitrates. Nitrification capability can be determined through biological monitoring of both of the ammonia oxidizing bacteria and nitrite oxidizing bacteria. It also can be determined by analyzing the nitrogen balance between the amount of ammonia and that of the nitrite and nitrate (USEPA Technical Development Document. 1998, 7-13).

Advantage:

- Activated sludge process produce a very clean effluent within a reasonable period of time.
- Activated sludge process is not usually affected by external temperature conditions.
- Surface impoundment process is the cheapest method of organic waste treatment.
- Potentially toxic chemicals can be treated biologically by surface impoundment process as the toxic chemicals get diluted due to large volume of the treatment unit.
- Wastewater streams containing large variations of content can be effectively treated by Sequential batch reactor (SBR).

¹⁸ Autotrophic microorganism - An organism that makes its own food (as in plants)

- Rotating biological contractor (RBC) can tolerate large surges in wastewater concentrations.
- Rotating biological contractor (RBC) requires low energy for operation.

Limitations:

- Activated sludge process requires high amount of energy for operation.
- Surface impoundment process is less effective during winter season as the process is sensitive to temperature fluctuations.
- Rotating biological contractor (RBC) requires high installation cost and high operational cost. (Guyer, H. 1998; 153-6)

4. Cyanide Destruction

Cyanide compounds are highly toxic, not only to human beings but also to aquatic life as they disturb their reproductive cycle and developmental stages. These compounds also have neurotoxic effect. Thereby, removal of cyanide compounds or cyanide ions from pharmaceutical wastewater is very important. Cyanide destruction methods are used for this purpose. Cyanide destruction is a chemical treatment method by which cyanide is converted to either inactive nitrogen gas or ammonia. Three chemical treatment methods are widely used in pharmaceutical industries for cyanide destruction. These are alkaline chlorination, hydrogen peroxide oxidation and basis hydrolysis method. All of these three methods are batch operating methods. The choice of treatment method depends upon the nature of cyanide compounds present in the wastewater stream.

The alkaline chlorine treatment unit usually consists of two reaction vessels and an equalization tank for storing of accumulated wastewater during treatment operation (USEPA Technical Development Document.1998, 7-18). This reaction is a two step process and is carried out separately in two reaction vessels. In the first step, sodium hypochlorite reacts with cyanide ions of the wastewater stream and oxidizes cyanide to cyanate ion (and also cyanogen chloride which is hydrolyzed to cyanate ion). In the second step, this cyanate ion further oxidized by hypochlorite ion to nitrogen gas and carbon dioxide. Temperature, pH and red-ox potential are important factors for the effectiveness of this treatment process.

The hydrogen peroxide treatment unit usually consists of a reaction vessel, hydrogen peroxide storage vessel, equalization tank, and feed systems for chemicals (USEPA TDD.1998, 7-18). In the reaction vessel, hydrogen peroxide oxidizes the cyanide ion to produce cyanate and water. The cyanate then hydrolyses over time depending on the pH to give carbon dioxide and an ammonium salt or carbonate and ammonia. To accelerate the reaction speed, sometimes copper sulfate is used as a catalyst. Temperature and pH are important factors for the effectiveness of this treatment process.

The basic hydrolysis treatment unit usually consists of a reaction vessel, storage vessel and feed system for chemicals and heat exchanger (USEPA TDD.1998, 7-18). In this process, cyanide ion reacts with water in presence of a base like sodium hydroxide

and produces formate and ammonia. Temperature and pH are important factors for the effectiveness of this treatment process.

Advantages:

- Alkaline chlorination process, in presence of heat, with an extended retention time results in complete destruction of total cyanides of wastewater stream.

Limitations:

- Alkaline chlorination process cannot effectively oxidize stable iron, copper, and nickel cyanide complexes.
- Hydrogen peroxide method requires high pH.
- Hydrogen peroxide method is slow and requires copper catalyst to accelerate the reaction rate.
- Cyanide destruction processes involve high operational and maintenance cost.

5. Multi-media or Multi-layer Filtration

BOD₅ content of wastewater is, in part, due its Total Suspended Solid (TSS) content and this part of the total BOD₅ content can be reduced by reducing the amount of particulate matter of wastewater through filtration technologies. To reduce TSS in wastewater, particularly multi-layer or multi-media filtration technology is used in pharmaceutical industries. This method is also useful in dewatering of sludge. As the name implies, this filtration unit is composed of a series of different types of filtering media. These typically

consist of layers of activated charcoal, anthracite or hard coal, assorted rocks or gravels, garnet or fine sand. These layers are arranged in descending order of their granule size i.e. layer with the coarsest granular material is at the top of the filtering bed while the finest granular material is at the bottom of the bed to facilitate the flow of wastewater from inflow to outflow direction of the bed. The waste stream enters at the top of the filter bed and as the wastewater percolates through the upper porous layers, the larger suspended particles are trapped in and on to the upper porous layers of the bed. Smaller particles, not trapped, continue into the lower layers of the bed. As the particle size in the lower layers becomes smaller progressively, the space between the particles is reduced, thereby trapping increasingly smaller suspended particles and thus increasing the capacity of the filtration unit. As the wastewater passes through this filtering bed, suspended solids are removed from the wastewater by any or a combination of straining, impaction, sedimentation, interception and adsorption process. (Guyer, H. 1998; 72)

Multimedia filtration is a batch process and the filtration is continued until the solids concentration increases to an unacceptable level in the effluent of the filtration unit. Under such a condition, cleaning of the bed is done by backwashing of the filtering media with a strong stream of clean water which is introduced at the bottom of the bed. This process agitates or fluidized the filtering bed materials where the trapped solid particulate matters get released from the bed and the concentrated wash water is pumped off and is either returned to the biological treatment system or sent for further processing.

Wastewater flow rate, hydraulic loading rate, and filter medium depth are the important factors to be considered for effective operation of the multimedia filtration unit (USEPA TDD. 1998, 7-15).

Advantages:

- Multi-media filtration systems are able to filter a wastewater stream with a very high amount of turbidity or suspended solids.
- Multi-media filtration units filter wastewater streams at a much higher flow rate than a single-media filtration unit.
- Multi-media filtration units have a longer running time than a single media filtration unit.
- Multi-media filtration units require less backwash water per unit volume of filtrate as the bed can hold more turbidity than that of a single media filtration unit because suspended solids are trapped and held throughout the entire bed depth.
- A very high degree of clarity is achieved because pore size of the filtration bed decreases as the wastewater stream passes towards bottom of the bed. (Guyer, H. 1998; 73)

Limitations:

- Multi-media filtration process involves high labor cost.

6. Polishing Pond Treatment

Sedimentation technology is also used in pharmaceutical industry to reduce TSS content of wastewater stream. Polishing pond treatment process uses sedimentation technology

where a wastewater stream that enters at one end point of the pond is allowed to remain there for a pre-designated period of time, during which suspended solid (TSS) materials settle to the bottom of the pond due to gravitational force and the supernatant wastewater stream flows out the other end point of the pond (Guyer, H. 1998; 153-4). This process also reduces some TSS associated BOD₅ content of the wastewater stream due to removal of TSS from the wastewater stream.

This is a batch process. The water retention time and wastewater stream velocity are the important factors for the maximum effectiveness of this treatment technology because these two factors should be set as such to allow maximum settling of TSS out of the wastewater stream. The standard retention time is 14 to 15 days. The depth of the polishing pond should be small to avoid anaerobic condition. The polishing pond usually requires two liners and a leak detection system. (USEPA Technical Development Document. 1998, 7-17)

Advantage:

- Simple in operation.

Limitations:

- Application of polishing pond is limited to wastewater stream containing materials that are not restricted from land disposal.
- Polishing pond treatment requires the use of large amount of land areas.

(Guyer, H. 1998; 153-4)

7. Steam stripping and steam stripping with rectification

Another important wastewater treatment technology in pharmaceutical manufacturing industries is steam stripping and/or steam stripping with rectification. This method works on the basic principle of relative volatility differences between organic chemicals and/or inorganic gases like ammonia, and water, thereby separates organic chemicals and/or ammonia from wastewater stream as it passes through the unit. This method is very useful in treating a variety of wastewater streams, containing a single to a complex mixture of the volatile constituents. The unit is installed immediately after the wastewater generating unit for maximum effectiveness of the treatment operation.

Steam stripping and steam stripping with rectification can be conducted as either a batch or continuous operation in a packed tower or fractionating column (sieve tray or bubble cap) with more than one stage of vapor-liquid contact. In a steam stripping column, the wastewater feed enters near the top of the column and then flows downward by gravity, countercurrent to the steam which is introduced at the bottom of the column. In a steam stripping with rectification column, the wastewater feed enters lower down the column to allow for a rectification above the feed. In the rectification section, a portion of the condensed vapors are refluxed to the column to counter currently contact the rising vapors. This process concentrates the volatile components in the overhead stream.

Steam may either be directly injected or re-boiled, although direct injection is more common. The steam strips volatile pollutants from the

wastewater, which are then included in the upward vapor flow. As a result, the wastewater contains progressively lower concentrations of volatile compounds as it moves toward the bottom of the column. The extent of separation is governed by physical properties of the volatile pollutants being stripped, the temperature and pressure at which the column is operated, and the arrangement and type of equipment used.

The difference between steam stripping columns and steam stripping with rectification columns is the location of the feed stream. Stripping columns have a feed stream located near the top of the column while steam stripping with rectification columns have a feed stream located further down the column. Pollutants that phase separate from water can usually be stripped from the wastewater in a steam stripper (a column without rectifying stages). Pollutants that are not phase-separable, such as methanol, need a column with rectifying stages to achieve a high concentration of the pollutants in the overhead stream.

The typical construction material for steam stripping and steam stripping with rectification columns in the pharmaceutical manufacturing industry is stainless steel. If a wastewater stream is highly corrosive, a more corrosion-resistant material, such as Hastelloy or Teflon®-lined carbon steel, may be required for construction of the column. The majority of pharmaceutical manufacturing facilities which currently use steam stripping and/or steam stripping with rectification columns to treat their wastewater use stainless steel.

Salts and other pollutants may contribute to scaling and corrosion inside the column. Timely maintenance should be provided to deter scaling problems. Generally, columns with smaller diameters are packed while columns with larger diameters have trays. Typical column packings are Pall rings, Rashing rings, Berl saddles, and Intalox saddles. The key design parameters for stripping columns are the steam-to-feed ratio and the number of trays or equilibrium stages in packed columns. These parameters are calculated using the equilibrium ratio of the least strippable contaminant in the wastewater stream and the removal efficiency required to treat the contaminant to the desired concentration. Typical ranges for steam-to-feed ratios vary from 1:3 to 1:35, and the typical number of trays or equilibrium stages vary from 2 to 20 (USEPA Technical Development Document.1998, 7-19; 21).

Advantages:

- The main advantage of steam stripping is that, unlike air stripping, resultant off-gas stream is usually condensed and the contained constituents is recovered or incinerated.
- Steam stripping removes both volatile organic and volatile inorganic constituents of wastewater stream.

Limitations:

- Steam stripping is operated at higher temperatures and some times results in heat stress in the surrounding environment.
- Steam stripping process involves high operational and maintenance cost.

8. Granular Activated Carbon Adsorption

Adsorption is one of the surfaces phenomenon by which dissolved or suspended materials can be removed from a gas or a liquid stream through bond formation with the bonding sites of a solid adsorbent surface. Different types of adsorbents like, activated carbon, silica gel, alumina etc. are available for this purpose but, granular activated carbon is considered the best among all of these adsorbents due to its hydrophobic nature, high internal surface area and high surface bonding affinity to most of the other compounds. Therefore, granular activated carbon adsorption method is widely used to reduce BOD₅, COD and organic constituents of pharmaceutical wastewater.

Activated carbon is prepared by destructive distillation of carbon containing materials like coconut shell, wood etc and then either it is powdered or broken down to granule size to increase its internal surface area.

In wastewater treatment unit, either activated carbon is packed into columns or bed of activated carbon is prepared into large enclosed tanks. Enclosed tanks are more common in wastewater treatment and more than one tank is use in series to ensure maximum effectiveness of the treatment process. When wastewater passes through these columns or tanks, its constituents come in contact with the surface of activated carbon and get adsorbed on to the surface of the activated carbon due to bond formation with the surface bonding sites. As the time goes on, the surface area of the upper layer of activated carbon bed becomes saturated and consequently, the adsorption zone moves downward to the lower level. This process continues until almost all of the activated carbon in the bed

becomes saturated and the constituents of wastewater, being treated, appear in the effluent of treatment unit at a higher value than the acceptable limit. At this point, the activated carbon is called spent. This spent activated carbon can be regenerated by destructive distillation or by backwashing with steam or by chemical treatment. After a few cycle of regeneration, adsorbing capacity of the activated carbon goes down below the acceptable level and then it is disposed off. (Guyer, H. 1998; 88-89)

The effectiveness of wastewater treatment by granular activated carbon adsorption process depends on three important factors. These are wastewater TSS concentration, saturation loading and hydraulic loading. (USEPA Technical Development Document.1998, 7-24)

Advantages:

- Low space is required for GAC.
- One major advantage of Granular Activated Carbon technology is its ability to remove a wide variety of toxic organic compounds to non-detectable level (99.99%)
- Low operational and maintenance cost.

Limitations:

- GAC unit works best at low suspended solids concentration of wastewater.
- Bacterial growth in granular carbon beds generates hydrogen sulfide which creates odors and corrosion problems.
- GAC adsorption is highly sensitive to pH, temperature, and flow rate of wastewater.

- Wet spent carbon from GAC unit is highly corrosive and abrasive creates land disposal problem. (EPA Wasterwater Technology Fact Sheet, Sept. 2000)

9. Air Stripping

Air stripping technology is very useful in removing volatile organic compounds (VOCs) as well as volatile inorganic compounds like ammonia, from pharmaceutical wastewater stream. Air stripping is carried out either in a countercurrent, packed column or in an aeration tank. In these treatment units, wastewater is sprayed by a spray nozzle at the top of the unit. As the wastewater descends through the treatment unit, air is forced upward through the unit, stripping off the volatile compounds and then the volatile compounds are carried out of the system at the top of the unit with air stream. Internal baffles inside the treatment unit increase surface area of the wastewater and thereby, increase wastewater-air contact and thus maximize volatilization of volatile compounds from wastewater. Effluent of these treatment units is discharged at the bottom of the units. (USEPA Technical Development Document. 1998, 7-28)

Advantages:

- Air stripping removes both volatile organic and volatile inorganic constituents of wastewater stream.
- Air stripping is a cost-effective method of wastewater treatment.

Limitations:

- It removes volatile contaminants from wastewater stream but, discharges the same contaminants into the surrounding atmosphere.
- At low temperature, air stripping is less efficient and there is a possibility of freezing within the tower. (USEPA Technical Development Document.1998, 7-28)

10. Incineration

Incineration is used in pharmaceutical industries where diverse toxic or very toxic wastewater streams are produced due to chemical multi-products production operations and these wastewater streams cannot be routed to a conventional wastewater treatment plant. Different types of incinerators are available for this purpose like rotary-kiln, fluidized bed, multiple/stepped hearth etc. Among this, fluidized bed and multiple hearth incinerators are more common in pharmaceutical industries. An acid gas scrubber is used to control Hydrochloric acid that is generated during incineration. In this process, organic and inorganic contaminants of wastewater are thermally destroyed to ash and the resultant water vapor is discharged to air. (USEPA Technical Development Document.1998, 7-29)

Advantage:

- Incineration is the most effective way of complete destruction of all contaminants of wastewater stream.

- Complete incineration destroys chemical properties of hazardous wastes.

Limitations:

- High working temperature creates thermal stress in the surrounding environment.

Product Stewardship

Product stewardship is a broad term and is a product-centered concept of reducing environmental impacts of a product throughout its life cycle, through shared responsibility of manufacturer, retailers, users and disposers. As per EPA –

In most cases, manufacturers have the greatest ability, and therefore the greatest responsibility, to reduce the environmental impacts of their products. Companies that are accepting the challenge are recognizing that product stewardship also represents a substantial business opportunity. By rethinking their products, their relationships with the supply chain, and the ultimate customer, some manufacturers are dramatically increasing their productivity, reducing costs, fostering product and market innovation, and providing customers with more value at less environmental impact. Reducing use of toxic substances, designing for reuse and recyclability, and creating take-back programs are just a few of the many opportunities for companies to become better environmental stewards of their products. (EPA Product Stewardship, July 2007)

To address the issues of pharmaceuticals and other personal care products in the environment, pharmaceutical manufacturers should have to take on new responsibility for

reducing the environmental impacts of their products. Currently, pharmaceutical manufacturers are exercising different product stewardship programs like formulation alteration or modification, pharmaceuticals mail-back program, pharmacy take-back program etc. In fact, all of these product stewardship programs are proactive approaches to address the PPCPs issues. All these approaches are very important as majority of this PPCPs issue is due to fecal excretion of non-metabolized or incomplete metabolized portion of drug formulations, improper method of disposal of unused prescription and non-prescription drugs or personal care products present in household wastewater.

Formulation alteration or modification

When a drug is administered through any of the local routes (like gastrointestinal tract, vagina, bronchi, eye, ear etc.) or systemic routes (like parenteral, rectal, sublingual etc), it undergoes four basic processes within the body. These are absorption, distribution, metabolism and excretion. That means, drug is absorbed first into the blood or lymphatic system, then is generally distributed to target organ(s) and produce desired effect(s); then goes to liver and metabolized there to inactive form(s) and finally, excreted through kidney. Exception is there, like some drugs after absorption into the system, first go to the liver and metabolized to more reactive form(s) and then go to the target organ(s) to produce the desired effect(s). However, all of these four processes are very important consideration for product stewardship approaches because disturbance in any of these processes or incompleteness of any of these processes results in excretion of active constituent(s) of drug formulation(s) into the environment.

If drugs are not completely absorbed into the system then non-absorbed portion excretes as such from the body; if the absorbed portion is not completely metabolized inside the body then the non-metabolized portion of the active constituents excrete as such into the environment; some time metabolized portions that excrete through kidney is more toxic in nature than the parent compounds. If drugs are not distributed properly into the system then it results in incomplete metabolism and excretion of active constituents from the body. Therefore, pharmaceutical industries are working on drug formulations for alteration or modification of formulations and/or modification of chemical structure of active constituents of drug, to increase drug absorption, to increase drug metabolism, to increase drug distribution and their target is to achieve 100% in all of drug absorption, distribution, metabolism processes to ensure that drug constituents are being excreted into the environment in least possible amount in their biologically most inactive form(s).

Digoxin is used in cardiac disease like cardiac arrhythmia, ischemic heart disease etc. When Digoxin is administered orally, ~70% is absorbed into the blood, of which 25% binds to plasma proteins and transported to and localized in heart, skeletal muscle, liver and kidney; a small fraction is metabolized in liver to inactive products and is primarily excreted unchanged by glomerular filtration in kidney, has a total body clearance of ~ 150mL/min and a plasma half life ($t_{1/2}$) of ~ 40 hours. Therefore, each single tablet of digoxin contributes active constituent to the environment to some extent through human fecal excretion. Moreover, the total amount of digoxin in each tablet should be the sum of the amount required to achieve the minimum effective concentration (MEC) in blood and the amount that is excreted unchanged from the body.

Therefore, this incomplete absorption and/or incomplete distribution and/or metabolism of drug not only gives rise to PPCPs issue but also, causing destruction of natural resources (as the active constituent of digoxin tablet is digitalis glycoside which is extracted from digitalis plants) and at the same time, increases the drug price in the market. So, modification of digoxin tablet formulation or modification of digitalis glycoside structure could enhance lipoprotein solubility of the active constituent, thereby increases drug absorption; similarly, it could increase drug-protein binding and thereby, increases drug distribution and drug-receptor binding at the target site(s). Therefore, less amount of drug will be required to incorporate into the dosage form to get the same effect while excretion of active constituent into the environment will be less. In this way, product stewardship could help to solve all of the above mentioned issues. Under certain condition or disease state like vomiting, there is incomplete absorption of drugs that results in discharge of active constituents into the environment. This is not controllable through product stewardship.

Pharmacy take-back program

Another major source of PPCPs in the environment is improper household disposal of expired or unwanted prescription or Over-The-Counter (OTC) drugs by flushing them down the toilet or drain. Although it is an improper method of disposal of drugs containing different bio-reactive constituents but, it has become a traditional method and is widely being used now-a-days.

The best method of disposal of household expired or unwanted prescription or Over-The-Counter (OTC) drugs is to return these medications to nearby pharmacies,

through pharmacy take-back program, for destruction. As per Daughton (The Green Pharmacy, 2003) –

It is designed to accept the free return of all prescription and OTC medications (and certain other medically oriented products); it does not, however, accept physician samples.

Besides local pharmacies, now-a-days pharmaceutical industries also have been started to participate in this program to collect both pharmacies' own in-stock expired drugs and that collected by these pharmacies from consumers through pharmacy take-back program, and to destroy these drugs in a proper manner.

Pharmaceuticals mail-back program

This is similar to pharmacy take-back program with the exception that under this program, instead of returning back to pharmacies, consumers are able to free return of their expired or unwanted prescription or Over-The-Counter (OTC) drugs directly to the participating pharmaceutical industries by postal mail services.

The drawback of this program is that the postage requirements for mailing back the drugs discourage people to participate in the program.

II. Case Studies

The websites of the following pharmaceutical companies have been visited to identify their respective approaches toward PPCPs in the environment.

1. 3M Pharmaceuticals
2. Abbott Laboratories
3. Albert David Ltd
4. AstaZeneca International
5. Bristol Mayer Squibb
6. GlaxoSmithKline
7. Patheon, Inc.
8. Pfizer
9. Sandoz
10. Wyeth Pharmaceuticals

The different approaches that the pharmaceutical industries are using to address the issues of PPCPs, have been given in the following table:

Table 5

Approaches	Number of Industries Using this Approach	Total Percentage (%)
End-of-Pipe Wastewater Treatment	10	100
Product Stewardship	8	80
Combination of both the above	8	80

The different technologies that the pharmaceutical industries are using have been given in the following table (this information has been collected both from case studies and interview):

Table 6

Technology		Number of Industry Using This Technology	Total Percentage (%)
pH adjustment or Neutralization		10	100
Equalization		8	80
Advanced Biological Treatment	With Nitrification	6	60
	Without Nitrification	3	30
Cyanide Destruction	Alkaline Chlorination	1	10
	Hydrogen Peroxide Oxidation	1	10
	Basic Hydrolysis	0	00
Multi-Media Filtration		6	60
Polishing Pond		1	10
Steam Stripping	With Rectification	0	00
	Without Rectification	1	10
Granular Activated Carbon Absorption		7	70
Air Stripping		3	30
Incineration		2	20
Product Stewardship	Formulation Modification	8	80
	Structural Modification	6	60
	Pharmacy Take-Back	2	20
	Pharmaceutical Mail-Back	1	10

The total number in the first column is greater than 10 and the total of the percentage in the second column is greater than 100 because some of those industries use more than one treatment technologies.

All of the industries that use either fermentation or chemical synthesis or both are using at least Advanced Biological Treatment technologies; some of them are using a combination of Advanced Biological Treatment and Effluent Filtration or Advanced

Biological Treatment and Polishing Pond, while the rest is using a combination of Advanced Biological Treatment and Effluent Filtration and Polishing Pond. All other industries that use either biological/natural extraction or mixing-compounding-formulating or both are using at least Advanced Biological Treatment technologies; some of them are using a combination of Advanced Biological Treatment and Effluent Filtration.

Bristol-Myers Squibb (Sermoneta, Italy) is using a system comprised of an advanced biological reactor with nitrification/denitrification combined with advanced ozone oxidation as a part of their wastewater treatment approaches while Pfizer (Ringaskiddy, Ireland), the GlaxoSmithKline (Carrigaline, Ireland) and Abbott Pharmaceuticals (Puerto Rico) are using ZeeWeed membrane bioreactors for reliable and effective treatment of wastewater, avoiding some problems experienced with conventional settlement technology. Wyeth Pharmaceuticals (Newbridge, Scotland) is using a combination of membrane bioreactor and ozone treatment system to treat wastewater stream onsite. AstraZeneca also treats many of its wastewater streams using onsite biological treatment units. 3M Pharmaceuticals and Sandoz (New York) use filtration technology as a main part of their wastewater treatment while Patheon, Inc. (Whitby, Canada) use a combination of Steam Stripping and onsite biological treatment unit to treat their wastewater stream. Albert David Ltd. use cyanide destruction and air stripping system in combination with onsite biological treatment system to treat wastewater treatment. Albert David Ltd. also uses onsite polishing pond to treat their wastewater streams.

Most of these 10 industries are also using product stewardship approaches. The specific product stewardship programs are formulation modification, structural alteration, pharmacy take-back program and pharmaceuticals mail-back program. Formulation modification is the most common program that industries are using to reduce environmental impacts of their products while some industries are concentrating on pharmacokinetic properties of drug molecules and are trying to reduce environmental impacts of their products through structural modification of the active ingredients. A very few of them have participated in pharmacy take-back program and one of them has started pharmaceutical mail back program as a part of their product stewardship approaches.

III. Interviews:

According to responses to the Detailed Questionnaire of the interviews:

- * All of the ten pharmaceutical manufacturing facilities reported using pH adjustment or neutralization treatment of their wastewater stream as a pretreatment, prior to other physical, chemical and biological wastewater treatment processes to improve their effectiveness. Advanced biological treatment process is highly pH sensitive and so, pH adjustment is necessary before advanced biological treatment of wastewater. Also pH plays an important role in solubility of many wastewater contaminants and pH adjustment helps to

remove these contaminants through precipitation. However, this is a chemical addition process and different neutralizing chemicals are added during the process that increases total chemical load. CaO, Ca(OH)₂, NaOH etc. are usually used to raise pH while HCL, SO₂ gas, H₂SO₄ etc. are normally used to lower pH of the wastewater stream. Some facilities are using liquefied CO₂ in place of H₂SO₄. NaOH is expensive and CaO is very cheap and easily available. Therefore, CaO is the most preferred agent for treating acidic wastewater stream. Eight of the ten pharmaceutical manufacturing facilities reported using flow equalization unit to consolidate smaller volumes of wastewater streams so that, for batch treatment systems, full batch volumes are available and at the same time, to eliminate or at least to minimize shock loadings throughout the downstream of wastewater treatment processes to prevent system overloading.

- * Nine of the ten pharmaceutical manufacturing facilities reported using advanced biological treatment unit to remove organic and inorganic contaminants of their wastewater stream. Activated sludge is the most preferred process as it produces a very clean effluent within a reasonable period of time and not affected by external temperature conditions. Although surface impoundment is the cheapest method and can tolerate a large amount of potentially toxic chemicals, it is not preferred due to large amount of expensive land space requirement. Sequential batch reactor (SBR) and Rotating biological contractor (RBC) are not preferred due to high installation and high operational costs. Now-a-days, many industries are preferring membrane bioreactor technology for reliable and effective

treatment of wastewater, avoiding some problems experienced with conventional activated sludge process. Bristol Mayer Squibb (Sermoneta) is using a system comprised of an advanced biological reactor with nitrification/denitrification combined with advanced ozone oxidation to reduce hard COD. The GlaxoSmithKline (Carrigaline) is using a system consists of an equalization tank, pretreatment screening, a combination bioreactor and filtration tank equipped with fine bubble diffused aeration for aerobic biological treatment and ZeeWeed UF membranes. As per Mr. Simon of GlaxoSmithKline – “We use MBR technology as it offers a proven alternative to conventional approaches to the treatment of PWW, which poses particular problems for conventional treatment technology due to variations in feed-water strength and potential shock loading, and high dissolved solids content leading to floc destabilization and subsequent biomass leakage, resulting in a deterioration in treated effluent quality. Moreover, this generates an effluent permeate of consistently high quality, superior in performance to CAS alternatives. This MBR technology has proved valuable in achieving reliable and cost-effective treatment for our global pharmaceutical industry.” Pfizer (Ringaskiddy) is using membrane bioreactor technology effectively overcomes the problems associated with poor settling of sludge in conventional activated sludge processes. Abbott Pharmaceuticals (Puerto Rico) is using membrane bioreactors as MBR process combines the unit operations of aeration, secondary clarification and filtration into a single process, producing a high quality effluent, simplifying operation and greatly reducing space requirements.

- * Two of the ten pharmaceutical manufacturing facilities reported using cyanide destruction process to remove cyanide compounds or cyanide ions from their wastewater stream. Alkaline chlorination is the most preferred process as within an extended retention time and in presence of heat, it results in complete destruction of total cyanides of wastewater stream. Hydrogen peroxide method is not preferred as it requires high pH and reaction rate is slow, requires copper catalyst to accelerate the reaction rate and copper recovery increases operational cost.

- * Six of the ten pharmaceutical manufacturing facilities reported using multi-media filtration system as it is able to filter wastewater stream with a very high amount of turbidity or suspended solids and a very high degree of clarity is achieved because pore size of the filtration bed decreases as the wastewater stream passes towards bottom of the bed. It is preferred over single media filtration system as it filters wastewater stream at a much higher flow rate and has a longer running time than a single media filtration unit. As per Mr. Bill N. of 3M Corporate Communication – “We use a number of different technologies depending on the facility. The most common technology for treating waste water at 3M is a filter technology.”

- * One of the ten pharmaceutical manufacturing facilities reported using polishing pond to remove suspended solids from their wastewater stream. Although the

operation is very simple but, polishing pond is not preferred due to large amount of expensive land space requirement.

- * One of the ten pharmaceutical manufacturing facilities have been reported using stream stripping process to remove volatile contaminant of their wastewater stream. This process is preferred over air stripping in that, unlike air stripping, resultant off-gas stream is usually condensed and the contained constituents is recovered or incinerated.

- * Seven of the ten pharmaceutical manufacturing facilities reported using granular activated carbon adsorption to remove dissolved or suspended organic and inorganic contaminant of their wastewater stream. It is a highly preferred process of wastewater treatment due to its low space requirements and low operational and maintenance cost requirements.

- * Two of the ten pharmaceutical manufacturing facilities have been reported using incineration process for complete destruction of all contaminants of wastewater stream and 3 of the 10 pharmaceutical manufacturing facilities have been reported using air stripping to remove volatile organic and inorganic contaminant of their wastewater stream. Although air stripping is a cost-effective method but is not preferred as it discharges volatile contaminants into the surrounding atmosphere.

- * Eight of the ten pharmaceutical manufacturing facilities have been reported being involved with different product stewardship programs. All of them, who have participated in product stewardship, are doing research on formulation modification or alteration in order to substitute eco-toxic ingredients like different additives in dosage forms i.e. binding agent, dissolution agent, disintegrating agent, preservatives, emulsifying agents etc. from their formulations with biologically inert substances or eliminate these at all. 6 out of these 8 industries are involved in research on structural modification of drug molecules in order to improve pharmacokinetic properties of those molecules, thereby ensuring more effectiveness of the drugs and less fecal excretion into the environment. Two of these eight industries have participated in pharmacy take-back program to assist pharmacies in proper disposal of the expired or partially used prescription and non-prescription drugs, collected from local residents. One of these industries has also started pharmaceutical mail-back program to collect expired or partially used prescription and non-prescription drugs directly from the customer and dispose the same in an environmentally friendly manner. As per Mr. Simon of GlaxoSmithKline “We have voluntarily started to collect unwanted medicines from customers through pharmacy take back program and pharmaceuticals mail back program to make sure that drugs are not being disposed in an improper manner by the customers. In near future, we have a plan to recover active ingredients from these unused medicines to reduce our overall production costs”.

IV. Analysis:

From both the case studies and interview, it has been found that all pharmaceutical industries are involved in onsite wastewater treatment operation to some extent. They do pH adjustment and filtration at minimum. The wastewater treatment technologies vary from unit to unit according to the type of chemical used and the type of pharmaceutical manufacturing process in place. As the wastewater treatment technologies are chemical specific or process specific, therefore the question of determining the best treatment technology is not relevant here.

All of the pharmaceutical industries, contacted for the purpose of this research, believe that product stewardship is the best approaches to address the issue of PPCPs on a long term basis. Product stewardship is not economically feasible in all the cases and end-of-pipe wastewater treatment is the best option there. However, two of these ten pharmaceutical industries who are not currently involved in any of the product stewardship approaches, have a plan to become actively involved in near future, in addition to their end-of-pipe wastewater treatment activities because all the pharmaceutical industries believe that neither end-of-pipe wastewater treatment activities nor the product stewardship approaches could alone address the issues of PPCPs in the environment; but that a combination of these two approaches could address the issues more effectively.

Conclusion:

Proactive approach, if economically feasible, is always preferred over reactive approach as it provides a long term solution to the problem. Moreover, proactive approach gives more economic benefit on a long-term run than that of reactive approach. The same concept is also true in case of addressing the issues of PPCPs in the environment. In this case, proactive approach like different product stewardship methods is considered better than reactive approach like different wastewater treatment methods. However, none of these two approaches could alone address the issues of PPCPs in the environment; rather a combination of different product stewardship approaches with some kind of wastewater treatment methods could address the issues more effectively.

As the major sources of PPCPs in the environment are human excreta and improper disposal of unwanted medicine, different product stewardship approaches have been proved very effective in addressing the issues. Besides formulation modification and structural modification of drug components, pharmacy take-back program could also play a major role in addressing the issues but, lack of incentive resists people from participating into this program. In fact, expired or unwanted medicines in acceptable condition (i.e. such a physical condition of the formulation that does not show any sign of contamination or deterioration or any other kind of changes) could be collected either through pharmacy take-back program or through pharmaceuticals mail-back program from customers for the purpose of recovering active ingredients of drug formulation, thereby saving the cost of expensive active ingredients for the next batch(s) of medicine which, in turn, could allow the Pharmaceutical companies to provide some incentive, in

the form of price discount, to their customers to encourage them to participate more and more in Product Stewardship programs. This concept has been praised by Mr. Simon of GlaxoSmithKline and he also believes that this concept could be proved beneficial to Pharmaceutical Companies.

For the purpose of this paper, a few of the renowned pharmacies like CVS pharmacy, Rite Aid pharmacy, Duane Reade pharmacy and Sunnyside Pharmacy have been contacted and as per their statistics, only 2% of their total customers (assuming that 50% of total customers have unwanted medicines) have participated in pharmacy take-back program. The pharmacy personnel believe that this percentage could be increased by providing some kind of incentives to the participants and particularly, the Sunnyside pharmacy likes the concept mentioned in the above paragraph because that concept could help pharmacies to provide 1-2% discount to the participants on the price of their next purchase of the similar category of drugs which could act as an incentive and would encourage people to participate more and more into the product stewardship program. Therefore, how this concept will work? People return unwanted i.e. expired medicines to the pharmacies. Expired medicine does not mean that it has reduced efficacy or no efficacy, rather in most of the cases, it has full efficacy as unexpired medicine. In fact, pharmaceutical manufacturers set this expiry date as 1/10th of the actual shelf life of the formulation to avoid any deformity in the formulation like color change, phase separation etc. Therefore, pharmaceutical manufacturer could collect these expired medicines in acceptable condition from consumers through pharmacies and could extract the active ingredients of those formulations and also could use these active ingredients in the

manufacture of fresh batches of medicines. In this way, pharmaceutical manufacturer could save the cost of active ingredients of formulations (if the extraction cost is less than the cost of procuring active ingredients from other sources) which could, in turn, allow them to provide discount to the participating customers on the price of their next purchase of the similar category of drugs. As for example, if a customer returns an antimicrobial drug of quinolones group to a participating pharmacy, the pharmacy will issue a discount coupon to that customer and upon producing this coupon to a participating pharmacy, the customer will get a discount on the price of their next purchase of any quinolones group of antimicrobial preparation. This discount money will inspire more people to participate in the pharmacy take-back program. In this way, pharmaceutical industries could also actively participate in the pharmacy take-back program and both, pharmaceutical industries and their ultimate consumer could be benefited and at the same time, problem of improper household disposal of unwanted medicine could be solved. In the similar way, pharmaceutical mail-back program could also be very effective in addressing the issues of PPCPs in the environment.

Regarding participation issue related to pharmacies, there is no legislation till to date for pharmacies to participate in pharmacy take back program; rather the approach is totally voluntary, but it can be hoped, this would become legislation in the near future. In addition to all of the above mentioned approaches, educating people about the issues of PPCPs is another very useful product stewardship approach that some pharmaceutical companies and pharmacies have voluntarily started e.g. Sunnyside pharmacy distributes a quarterly environmental awareness leaflets within the local community for fostering the

environmental awareness among the general public. If other pharmaceutical companies and pharmacies come forward to take such a voluntary initiative, then dealing with the issues of PPCPs would be much easier in future.

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Appendix A:

Detailed Interview Questionnaire

Company: _____

Name: _____

Title: _____

Department/Unit: _____

Date: _____

- What are the most recent approaches from company's perspective to address this issue?
- Why they have chosen any particular approach?
- Why they are not using any other approaches?
- What onsite wastewater treatment technologies they are using? What is their limitation(s)?
- What they think about the best way to address the issue of PPCPs?
- What they are thinking to do in near future regarding the issue of PPCPs?
- Are they doing so actually to protect our environment, or just due to some regulatory concern to look the company doing better?

Appendix B:

Website of Pharmaceutical Industries Visited for Case Study Purpose:

3M Pharmaceuticals – www.3M.com

Abbott Laboratories – www.abbott.com

Albert David Ltd – www.albertdavidindia.com

AstaZeneca International – www.astazeneca.com

Bristol Mayer Squibb – www.bms.com

GlaxoSmithKline – www.gsk.com

Patheon, Inc. – www.patheon.com

Pfizer – www.pfizer.com

Sandoz – www.sandoz.com

Wyeth Pharmaceuticals – www.wyeth.com