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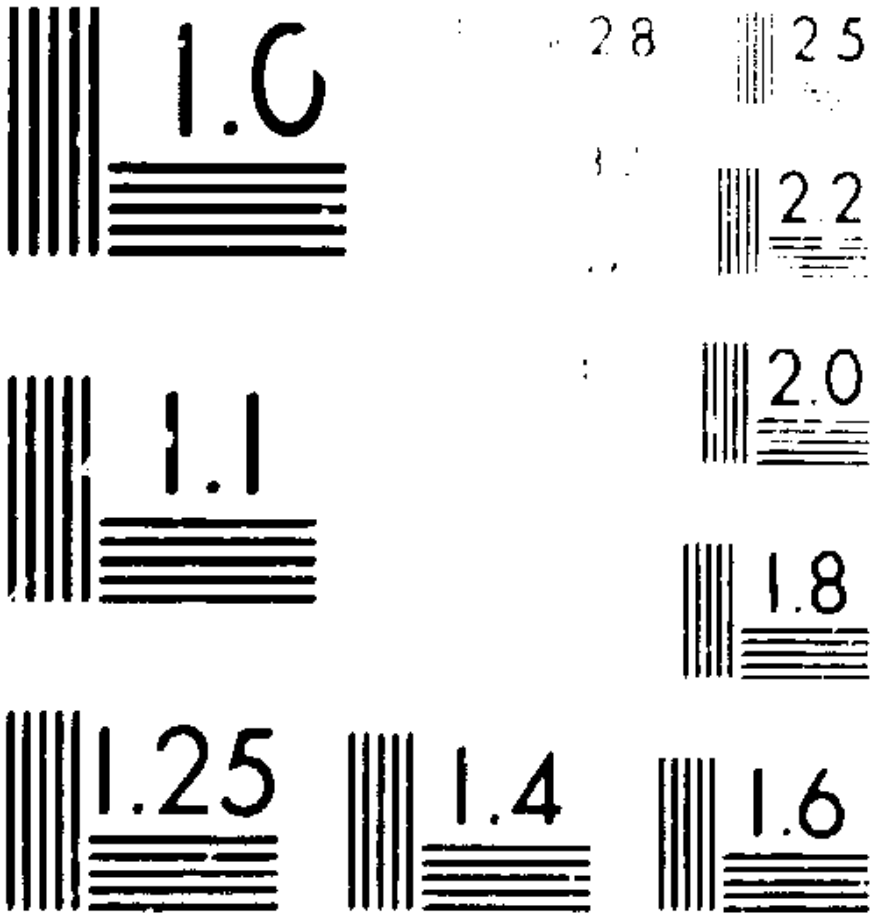
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WATER USE AND EFFLUENT TREATMENT PRACTICES FOR THE MANUFACTURE OF THE 26 PRIORITY DRUGS IN THE UNIDO ILLUSTRATIVE LIST *

prepared by the
Division for Industrial Studies

R. Coughlin

542

* Presented to the Second Consultation on the Pharmaceutical Industry, Budapest, Hungary, 22-25 November 1983.

V.83 56924

EXPLANATORY NOTES

All process water, including aqueous solutions, should be at least of Drinking Water quality unless labelled "purified" where Purified Water is recommended. Purified Water should also be used to prepare final dosage forms not intended for injection. Water for injection should be used to prepare injectable dosage forms. Preparation of dosage forms is not shown in the flow sheets. (Figures 1 - 9).

DEFINITIONS

BOD_5 or BOD: Biochemical oxygen demand. The 5-day, 20°C, BOD_5 test is widely used to determine the pollutional strength of waste water in terms of the oxygen required to oxidize or convert the organic matter to a nonputrescible end product. The BOD_5 test is a bioassay procedure that measures the oxygen consumed by living organisms while utilizing the organic matter present in the waste water under conditions as similar as possible to those that occur in nature.

COD: Chemical oxygen demand. The COD test is an alternative to the BOD_5 test. It is widely used and measures the quantity of oxygen required to oxidize the materials in waste water under severe chemical and physical conditions. The major advantage of the COD test is that only a short period (3 hours) is required to conduct the test. The major disadvantage is that the test does not indicate how rapidly the biologically active material would be stabilized in natural conditions.

TOC: Total organic carbon. An estimate of the concentration of organic matter in the waste matter in the waste water. The organic carbon in the sample is oxidized at high temperature. The amount of CO_2 produced is measured by an infra-red analyzer.

MLSS: In the treatment of waste water by the activated sludge process, the activated sludge together with the raw waste water is called mixed liquor, and the sludge solids in the system are known as mixed liquor suspended solids (MLSS).

MLVSS: Mixed liquor volatile suspended solids (g volatile sludge solids/l aeration tank volume).

O & M: Operation and maintenance (i.e. plant running costs).

ACKNOWLEDGEMENT

This study was prepared with the assistance of Robert Coughlin, chemical engineer.

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RECOMMENDATIONS

A. For the Pharmaceutical Manufacturer

1. The pharmaceutical manufacturer should carry out the strictest quality control for the various process waters used in pharmaceutical manufacture, formulation and packaging.

2. The plant should be designed with separate sewer systems for sanitary sewage, rain water run-off and process effluent and a separate collection system for unrecovered waste solvents. This will maximize opportunities for recycling and re-use and minimize waste treatment costs and pollution discharges.

3. In semi-arid regions all possibilities for water re-use should be explored. For example, (a) cooling waters should be recycled, (b) recycling of steam to be used as boiler make-up water should be an established practice, (c) process waste waters should receive at least secondary treatment plus disinfection so that they can be used for certain non-contact product uses (cleaning animal pens, for example), (d) rain water run-off should be stored for re-use.

4. Adherence to rules of good practice throughout the plant will provide a close check on raw materials and products and reduce spills, inadvertent discharges and spoiled batches. Waste loads, and therefore treatment costs, can thus be lowered substantially. (a) Each significant step in the process, such as the selection, weighing, and measuring of components, the addition of ingredients during the process, weighing and measuring during various stages of processing, and the determination of the finished yield, should be performed by a competent and responsible individual and checked by a second competent and responsible individual. (b) All containers, lines, and equipment used during the production of a batch of a drug should be properly identified at all times to indicate accurately and completely their contents and, when necessary, the stage of processing of the batch.

5. Solvent recovery:(a) For reasons of economy as well as environmental protection, solvent recovery and re-use should be routinely practiced in the manufacture of all drugs where solvents are utilized (nearly all of the 26 drugs in the UNIDO illustrative list). This practice can reduce foreign exchange outlays for fresh solvent purchases.(b) Unrecoverable waste solvents should never be discharged into process waste waters.(c) Residue from solvent recovery operations and unrecoverable waste solvents should be cleanly incinerated. Means of energy utilization from this operation should be investigated.

6. Effluent discharges: (a) Waste waters from a pharmaceutical manufacturing operation to be discharged into a public waterway should undergo a minimum treatment consisting of primary sedimentation followed either by lagooning where land is cheap and space permits or by other secondary treatment such as a trickling filter. (b) If waste waters from a pharmaceuticals manufacturing plant are to be discharged to a sewer system for treatment at a municipal sewage treatment plant, the factory should carry out equalization, neutralization (if necessary) and primary settling as minimum pretreatment measures before discharge to the sewer.

7. Fermentation wastes:(a) Recovery of by-products from spent fermentation broth should be investigated, such as evaporation to form a syrup suitable for animal feed.(b) If by-products are not recoverable, then a well designed anaerobic treatment process should be considered because of possibilities for energy recovery and greatly decreased amounts of sludge production.

8. Non-recyclable solid wastes should be disposed in a secure land fill designed to prevent contamination by seepage into ground or surface water.

9. Certain metal catalysts such as Raney nickel should be regenerated whenever possible. When not feasible, the material should be separated as a solid waste and not permitted to enter the waste water stream.

B. For the Government

1. The government should ensure that the highest standard of process water quality control is maintained through (a) intermittent inspection and sampling and (b) providing back-up analytical services to the industry.

2. The government should be specifically informed about any proposed effluent discharge from a pharmaceutical plant.

3. The government should establish and enforce effluent standards which are appropriate for the situation.

C. Training

1. Pharmaceutical training programmes should always include water quality control practice and environmental protection components. For example, any pharmaceutical study tour for officials from developing countries should include viewing water treatment, solvent recovery, waste water treatment and water recycling operations with necessary technical briefing.

2. UNIDO training programmes dealing with environmental protection should include a visit to a pharmaceutical plant so that environmental officials from government and industry see first hand good water use and effluent treatment practices in the industry (Such a visit is included in the UNIDO training programme on environmental assessment and management aspects of air and water pollution from industry, given annually at the State University of Ghent, Belgium.)

INTRODUCTION

This report reviews and elucidates water use and effuent treatment practices important for the manufacture or formulation and packaging of twenty-six drugs which have been identified
by UNIDO as important for developing countries.

These drugs are listed in Table 1 and are contained in the model list of essential drugs compiled by the World Health Organization Expert Committee[1/]. The selection of these drugs conforms with criteria set forth by the UNIDO Panel of Industrial Experts for the Production of Drugs in Developing Countries[2/]. The list has been endorsed by the First Consultation Meeting on the Pharmaceutical Industry[3,4/] and the meeting on cooperation among developing countries organized by the National Council of Pharmacists in Morocco in cooperation with UNIDO[5/].

The present report is concerned with treatment of wastes arising from the manufacture of these 26 drugs as well as standards and criteria for process water to be used in the manufacture of these drugs. For example water which has been purified by deionization which removes much of the dissolved impurities is certainly not sterile; it has been reported[6/] that in deionized water initially containing 90 organisms per ml the microbial count increased to a million organisms per ml after only 24 hours. Beyond sterility considerations water used to prepare injectable drugs also must be free of pyrogens which are molecular fragments (often lipopolysaccharides from microbial cell walls) which cause a rise in temperature when administered to man.

Special procedures are required to prepare non-pyrogenic water and they are also discussed in this report.

Special consideration is given in this report to waste beers from fermentation processes and to the very high strength wastes which can arise when organic solvents find their way into wastewaters. There is a separate section on recovering and purifying such solvents for re-use. Aside from these introductory pages the report contains the following sections:

- Outlines of Typical Manufacturing Processes for the 26 drugs
- Water Supply for Drug Manufacture, Formulation and Packaging
- Solvent Recovery
- Wastewater Treatment Practices and Technology
- Two Case Studies of Actual Water Use and Effluent Treatment Practices

This study is the second in a series of contributions designed to meet the objectives of the Industrial Water Use Section of ECOSOC Resolution 1979/70 (UNIDO Industrial Development Board document ID/B/262, 19 March 1981). It has been prepared especially for the UNIDO Second Consultation on the Pharmaceutical Industry, Budapest, Hungary, 22-25 November 1983.

THE TWENTY-SIX ESSENTIAL DRUGS

Introduction

This section of the report gives a very brief description of one possible manufacturing process for each drug. The information herein has been largely drawn from the patent literature and other publications. It should not be considered authoritative regarding any particular manufacturing process and it has been assembled only to show how various wastes may arise in illustrative processes as well as process water requirements. It should also be pointed out that for many of the twenty-six drugs alternative processes can be used for manufacture; furthermore, taken together, these 26 drugs represent many different types of technology; for example: chemical synthesis, fermentation, isolation of natural products, blood fractionation and the like. Finally, many new processes are in the research development, and pilot plant stages based on emerging biotechnology and genetic engineering. An exhaustive treatment for even one drug is beyond the scope of this report.

These manufacturing processes are usually highly proprietary and, therefore, will probably be developed and operated under a license or joint venture with a present manufacturer who owns the technology. The processes reviewed briefly in this section for each drug have been culled from the technological and patent literature and should be looked upon only as representative and typical - but not necessarily the actual methodology that would be adopted for actual production. A special effort has been made to point out process water requirements and where and how waste waters may arise. The UNIDO consultations on the Pharmaceutical Industry identified nine essential drugs (marked with an asterisk in Table 1) to be considered for production in developing countries starting from raw materials or intermediates. Therefore flow sheets are provided for these drugs to supplement the explanations of the manufacturing processes. The flow sheets have been prepared by applying experienced engineering judgement to patent disclosures or similar published information. The major intention is to show process water requirement and how waste waters can arise and not to present detailed engineering flow sheets for actually installed processes. The literature which has been consulted to develop this information is referenced for each drug by the footnote numbers given in Table 1.

Table 1

Illustrative list of 26 essential drugs for which facilities for the local manufacture of active ingredients should be established in developing countries.

ANALGESICS

1. *Acetylsalicylic acid[7]
2. Paracetamol[8]

ANTI-INFECTIVE DRUGS
Antihelminthic drugs

3. Mebandazole[9]
4. Benzyl Penicillin[10]

Antibacterial drugs

5. *Ampicillin[11]
6. Benzyl Penicillin[12]
7. Erythromycin[13]
8. *Sulphadimidine[14]
9. *Tetracycline[15]

Antifilarial drugs

10. *Diethylcarbamazine[16]

Antileprosy drugs

11. *Dapsone[17]

Antimalarial drugs

12. *Chloroquine[18]
13. Primaquine[19]

Antituberculosis drugs

14. *Ethambutol[20]
15. *Isoniazid[21]
16. Streptomycin[22]

CARDIOVASCULAR DRUGS
Antihypertensive drugs

17. Hydralazine[23]
18. Propranolol[24]
19. Reserpine[25]

DIURETICS

20. Furosemide[26]

ANTI-DIABETICS

21. Insulin[27]

ORAL CONTRACEPTIVES

22. Ethinylostradiol + levo-norgestrel[28]

IMMUNOLOGICALS

23. Blood and Blood fractions[29]

VITAMINS

24. Ascorbic acid[30]
25. Hydroxocobalamin[31]
26. Retinol[32]

* Nine essential drugs to be considered for production in developing countries starting from raw materials or intermediates

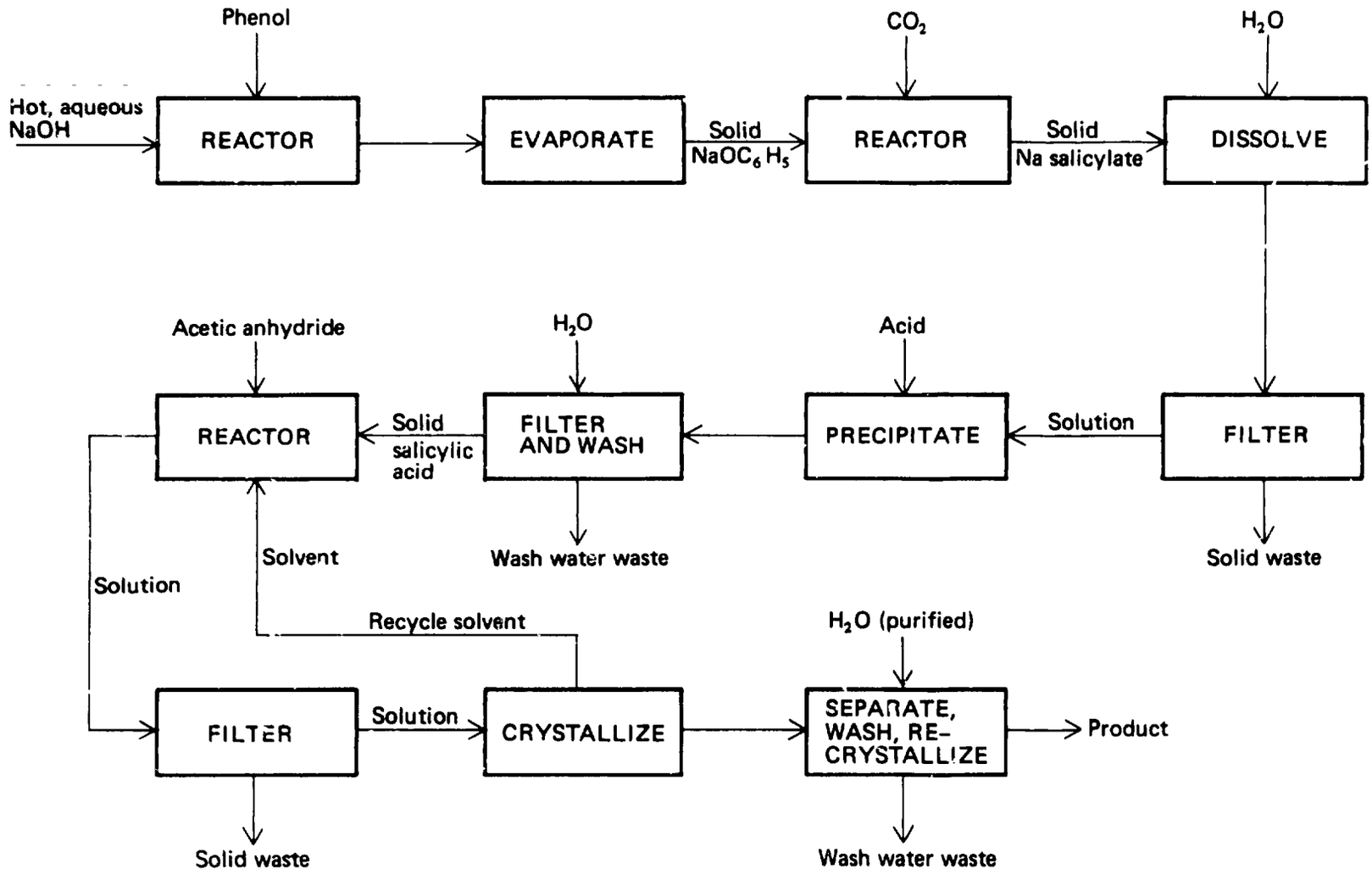
1. Acetylsalicylic Acid or aspirin is manufactured by acetylating salicylic acid using acetic anhydride. A process flow sheet is shown in Figure 1. The salicylic acid is synthesized from phenol by reacting it with hot aqueous NaOH in an autoclave; the solution is then evaporated and dried and the solid intermediate, sodium phenoxide, is reacted with pressurized CO_2 to produce the sodium salt of salicylic acid. This product is dissolved in water and the resulting solution is filtered and then acidified to precipitate salicylic acid. The salicylic acid intermediate is then acetylated with acetic anhydride. These two chemicals are reacted in glass-lined or stainless steel vessels at temperatures maintained below 90°C. After about three hours the product solution is filtered and then chilled to about 0°C to induce crystallization of the product. The crystals are separated, washed and dried; the mother liquor is recycled for re-use in the reaction. Most variations of the process employ an organic solvent as part of the reaction mixture.

This process produces minimal wastewaters such as washing of the crystals, washings from cleaning vessels and lines and, of course, spillage. The solid waste from the initial filtration of the reaction product (before crystallization) can be disposed by landfill or burying. Wastewaters are biologically treatable and not particularly hazardous. Mother liquors from precipitations are generally recycled.

2. PARACETAMOL or N-acetyl-p-aminophenol

This drug is manufactured by electrolytic reduction of nitrobenzene to p-aminophenol followed by acetylation with acetic anhydride to form the final product. Following the electrolysis of nitrobenzene in aqueous solution acidified with H_2SO_4, the product solution, which now contains p-aminophenol, is neutralized with $CaCO_3$ or $Ca(OH)_2$. The precipitate of $CaSO_4$ formed by neutralization is filtered from the solution in the next step this solid precipitate can be disposed by burying or landfilling. The filtrate solution is next extracted with an immiscible solvent such as heptane or toluene to remove impurities and then contacted with activated carbon to remove additional impurities. After the active carbon is filtered the p-aminophenol

Figure 1. Acetyl Salicylic Acid Process Flow Sheet



is acetylated by adding acetic acid and acetic anhydride to the aqueous filtrate. After reaction the acetylated product is crystallized by chilling the solution to 8-10°C and the solid product, N-acetyl-p-aminophenol is removed by filtration.

Contaminated solvent from the solvent-extraction step is regenerated by distillation.

The waste residuum from the distillation process should be incinerated. Solvent requirements amount to about two liters per kilogram of paracetamol product ; most of this solvent can be recovered and re-used.

The contaminated active carbon is regenerated for re-use by washing it sequentially with hot dilute caustic, hot dilute acid and a water rinse. These washing constitute waste-water streams. Another waste water stream is the filtrate and washings from the final product filtration. These wastewaters are generally biologically treatable and none are hazardous.

3. Mebendazole or methyl N- 5(6)-benzoyl-2-benzimidazolyl carbamate is prepared as follows:

A.) 4-chloro-3-nitrobenzene, sulfolane, methanol and ammonia are reacted for 8-12 hours at 125°C at autogenic pressure.

B.) The reaction mixture from step A is vacuum-evaporated to a semisolid residue which is subsequently boiled in a dilute HCl solution. After cooling, the precipitated product is filtered and dissolved in chloroform and the chloroform phase dried and evaporated. The intermediate product, 4-amino-3-nitrobenzophenone, is recrystallized from toluene.

C.) The intermediate product is then mixed with methanol and concentrated HCl and hydrogenated at normal pressure and room temperature using a 10% Pd-on-charcoal catalyst added to the mixture. After hydrogenation,

the catalyst is filtered off, the solvent evaporated and the residue is crushed and slurried in propanol, filtered, washed with propanol and dried yielding the intermediate product 3,4-diaminobenzophenone hydrochloride.

D.) S-methylisothiourea sulfate is diluted with water and methyl chloroformate added while keeping the mixture cooled by an ice bath. Then while keeping the temperature below 20°C a NaOH solution is added very slowly followed by acetic acid.

E.) The intermediate product from step C is suspended in water and added to the mixture arising from step D. Sodium acetate is then also added and the mixture is heated to 85°C and stirred and held at this temperature for about 45 min. After cooling, the precipitated reaction product, mebendazole, is filtered, washed with water and ethanol, dried and crystallized from a mixture of acetic acid and methanol.

Strong aqueous wastes arise from steps B and E, but these are biologically treatable. Solvents from steps B, C, and E should be re-used with intermediate purification as needed. The catalyst from step B should be re-used until it is no longer active at which time is should be returned to the manufacturer.

4. Benzylpencillin or penicillin G is a B-lactam antibiotic produced by fermentation of Penicillium chrysogenum. Growth medium in flasks is innoculated with the microorganism and incubated while shaking. After several days the contents of a flask are transfered into a larger amount of growth medium in a seed tank which is aerated for several days to encourage further growth.

The contents of the seed tank (800 liters) are then used to innoculate medium in a larger fermenter (60-80,000 gal) equipped with means for introducing sterile solutions to help growth, control pH and foam formation and encourage the production of penicillin G. For this last purpose sterile phenylacetic acid is often metered continuously into the large fermenter.

After about seven days the contents of the large fermenter are filtered to remove the cells of P. chrysogenum leaving the penicillin G in the cell-free liquid. The penicillin is extracted from the aqueous liquid into amyl or butyl acetate using a series of extractor units. The penicillin is then extracted back into an aqueous buffer solution where it forms the potassium salt which is then purified by crystallization from a butanol-water solution. Steps of redissolution, filtration, recrystallization, etc. are then involved in formulating the penicillin into a sterile injectable drug.

Several sources of wastewater include the waste fermentation broth after solvent extraction of the penicillin and solvent stripping of the acetate solvent as well as the water phases from recrystallizations and washing the filtered solid penicillin. The solvents are recovered and re-used but small amounts of distillation residuum will arise from solvent recovery. This material should be incinerated if possible because it is a very high strength waste if added to the wastewaters. The wastewaters are non-hazardous and can be treated biologically. The filtered cell mass (called Mycelium waste) can be buried, put in a landfill or used as a soil conditioner-fertilizer.

5. Ampicillin or α-aminobenzylpenicillin is made from 6-aminopencillanic acid (or 6-APA) by a series of chemical-synthesis steps. The 6-APA itself is made by a fermentation process essentially identical to that described above for manufacturing benzylpenicillin except that phenylacetic acid is not added during the process. There is also an enzymatic process for manufacturing 6-APA.

The adduct to be added to 6-APA is synthesized by protecting the amino group of phenyglycine by forming the carbobenzoyl derivative. This intermediate is then converted to the mixed carbonic anhydride by treating it with ethyl chloroformate. The resulting compound is condensed with 6-APA to form an amide which is catalytically hydrogenated to form ampicillin.

Ampicillin manufacture entails generation of wastewaters just the same as for benzylpencillin alone, but with additional waste waters formed during the conversion of 6-APA to the -aminobenzylpenicillin product. Such

additional wastewaters are biologically treatable and represent a small increment beyond the waste water produced from the manufacture of benzylpenicillin or 6-aminopenicillanic acid (6-APA). A simplified flowsheet for ampicillin is shown in Figure 2.

6. Benzylpenicillin has been covered above as drug number 4.

7. Erythromycin is a macrocylic lactone manufactured by fermentation of Streptomyces erytheus. The spent cell growth is filtered from the fermentation broth and the drug is extracted from the aqueous filtrate into a solvent such as ethyl acetate or butyl acetate. The drug is then extracted back into aqueous acid solution. Further purification may be accomplished by repeated extractions (with appropriate pH adjustment). Thereafter the drug can be crystallized from acetone-water mixtures.

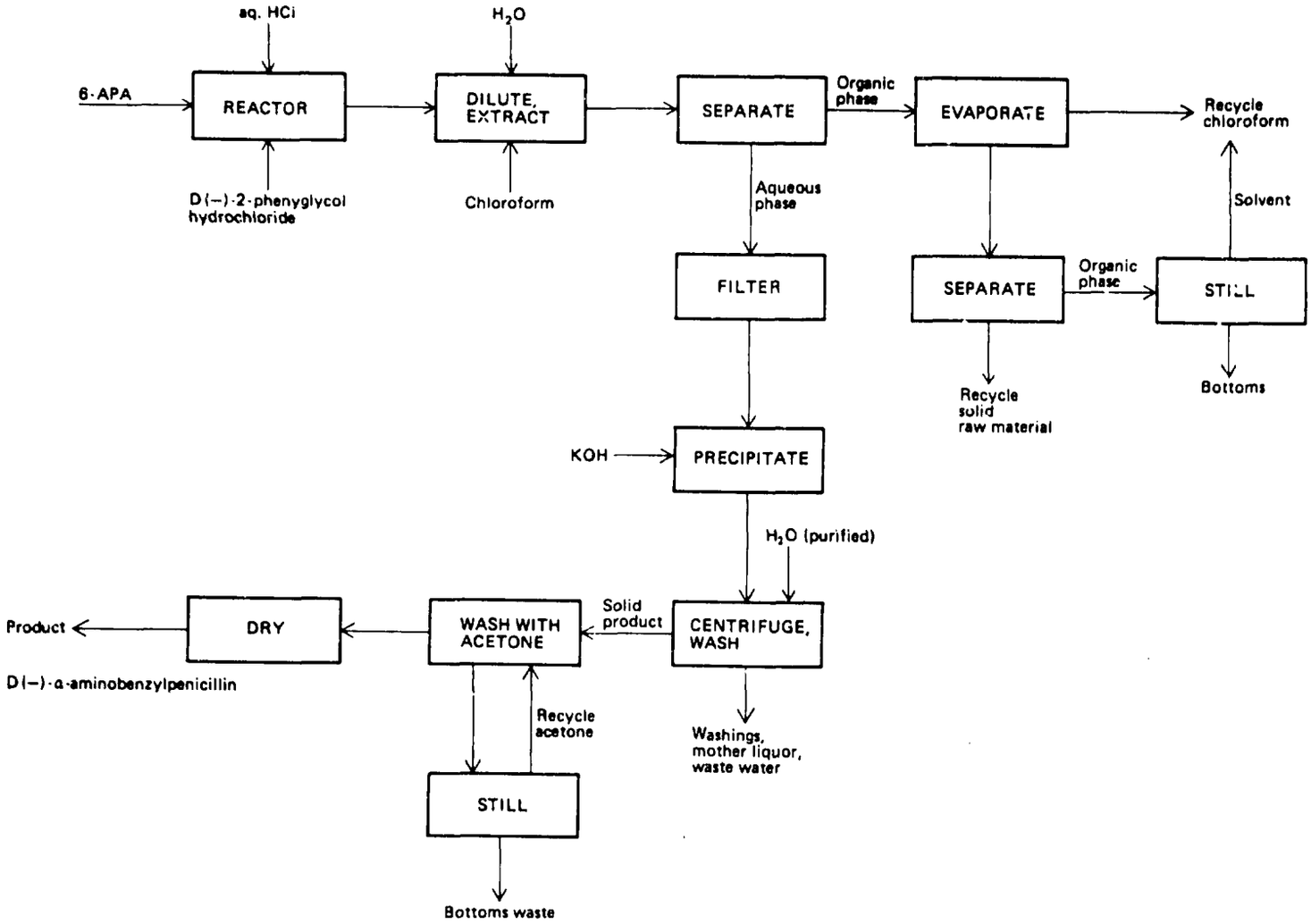
The wastes produced are entirely parallel to the case of benzylpenicillin above: mycelium, solvent-recovery bottoms, biologically treatable wastewaters from extracted fermentation broth and purification operations.

8. Sulphadimidine or sulphamethazine

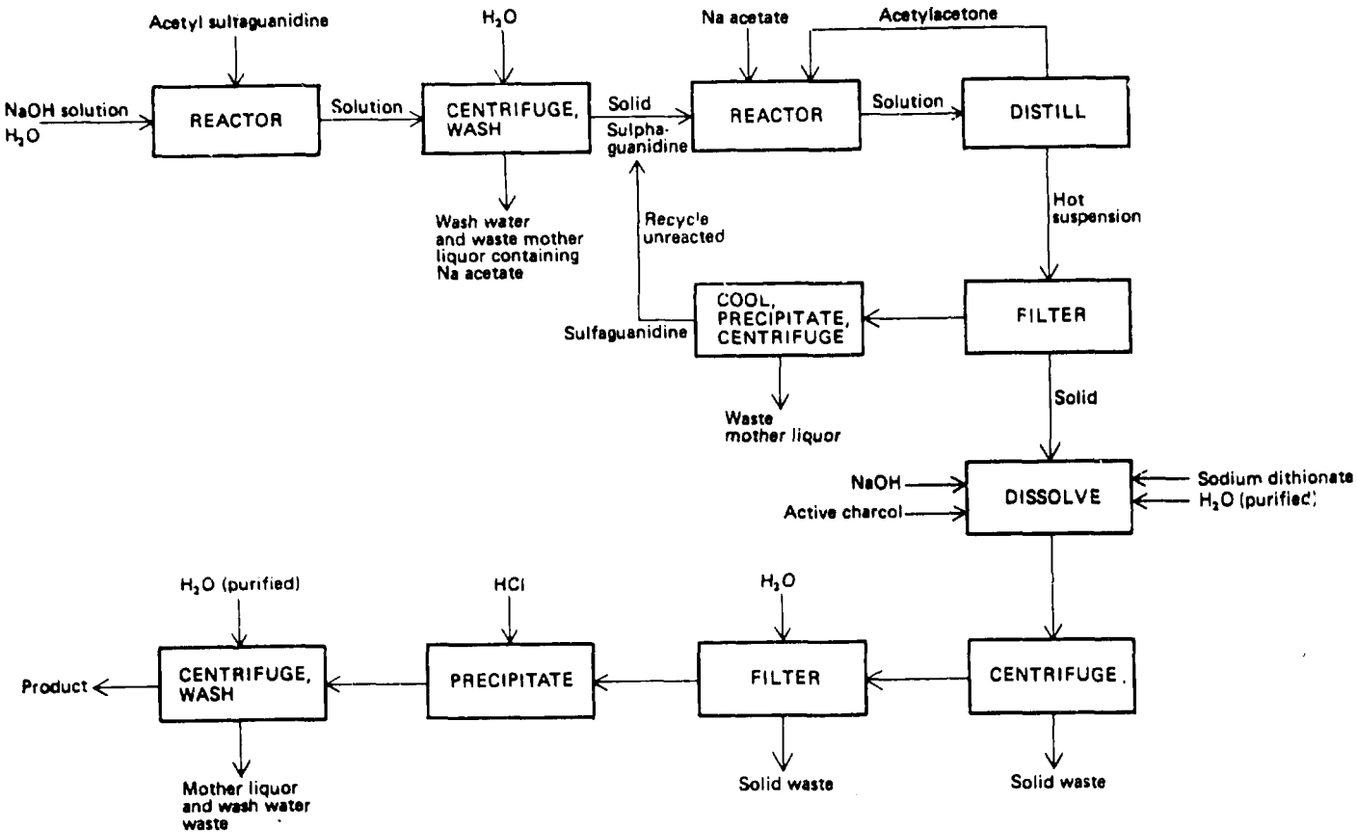
The manufacturing process begins by condensing acetylsulphanilyl chloride (ASC) with guanidine in the presence of sodium hydroxide form p-aminobenzenesulphonamidoguanidine, usually called sulphaguanidi The solution is then acidified with acetic acid and sodium acetylac added. The reaction is allowed to proceed with stirring up to about 24 hours at about 100°C. Then the mixture is cooled to about 60°C and the solid sulphadimidine product filtered and washed with 80°C water. Some of the unreacted SG can be recovered by further cooling the filtrate.

The major wastewater sources are the filtrate and the washings from the final product. These are generally biologically treatable. Wastes are not hazardous. Figure 3 shows a simplified flowsheet.

Figure 2. Ampicillin Process Flow Sheet



3. Sulphadimidine Process Flow Sheet



To prepare injectable formulations of this drug additional purification is necessary with attendant generation of wastewaters. Specially purified, pyrogen-free water is also required to prepare injectable forms.

9. Tetracycline is often manufactured by chemical modification of chlortetracycline also called aureomycin which is produced by fermentation. It can also be produced directly by fermentation.

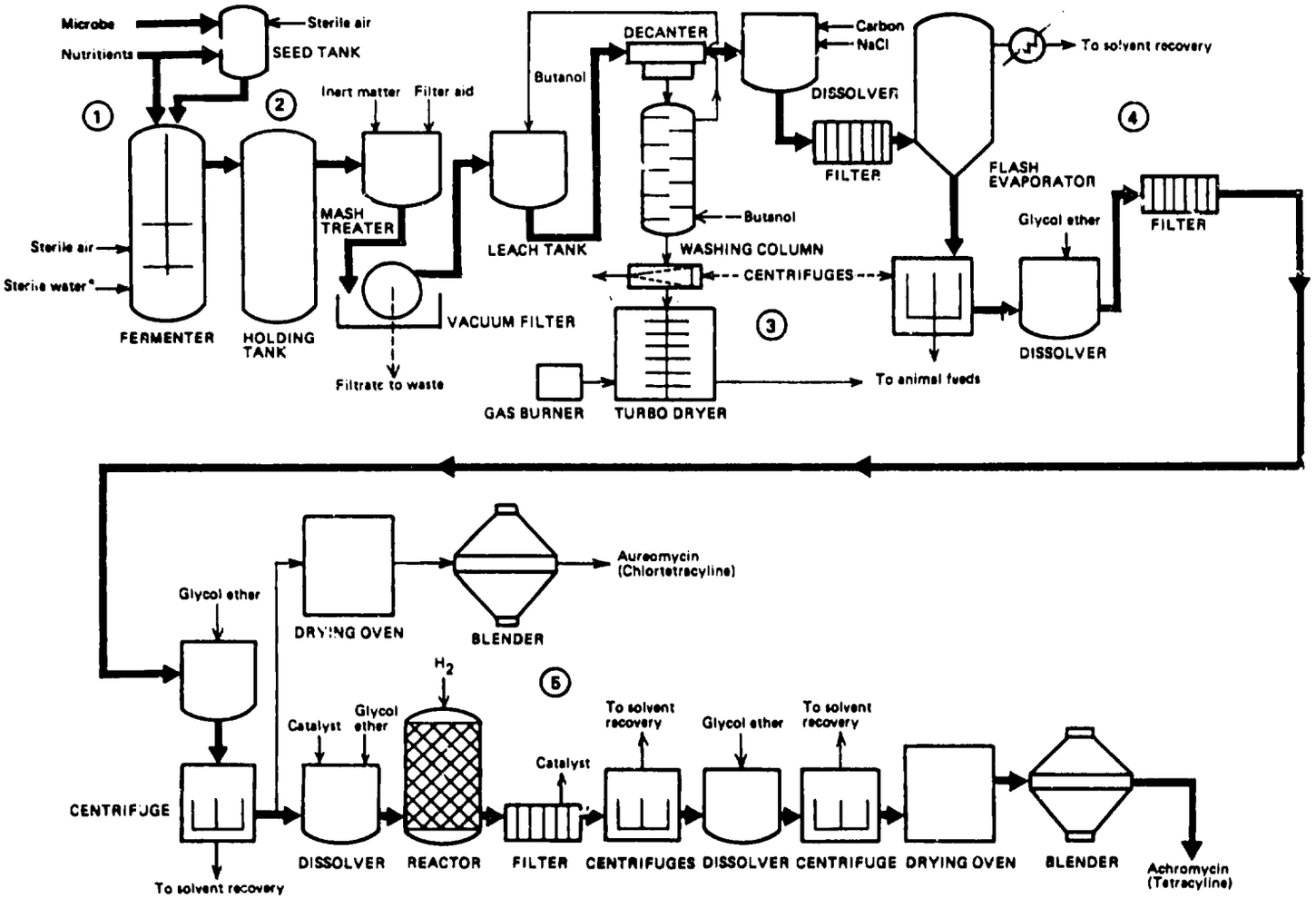
Chlortetracycline is isolated from the fermentation culture broth of Streptomyces aureofaciens. Submerged fermentation is conducted in the usual way (see Benzylpencillin) but the product recovery and purification are somewhat different. After fermentation appreciable quantities of chlortetracycline are present as precipitated metal chelate salts. Before filtering the cell mass from the broth, these precrystallized salts are solubilized by acidifying the mixture to pH 3. After the mycelium is filtered, the crude chlortetracycline is precipitated from the filtrate broth as an alkylsulfonate salt by addition of an alkylsulfonic acid. The salt is then suspended in 2-ethoxyethanol and brought into solution by adding triethylamine to a pH of about 8. This alkaline solution is then filtered to remove insoluble impurities and colored impurities are removed by contacting the solution with activated carbon. After decoloration the pH is adjusted to 0.8 using HCl to precipitate the hydrochloride salt of chlortetracycline.

To make tetracycline, basic solutions of the chloro-compound are hydrogenated using Pd-on-carbon as a catalyst. The HCl liberated by this reaction is neutralized by the base. A typical solvent for this reaction is 2-methoxyethanol. The crude product is precipitated by adding water and purified by recrystallization from aqueous methanol.

Another variation of the foregoing process is shown in Figure 4 where butanol and ethylene glycol monoethylether are used as solvents.

Tetracycline can also be manufactured by direct fermentation using a mutant strain of Streptomyces aureofaciens.

Figure 4. Tetracycline Process Flow Sheet



*Sterile water for fermentation is usually prepared from drinking water

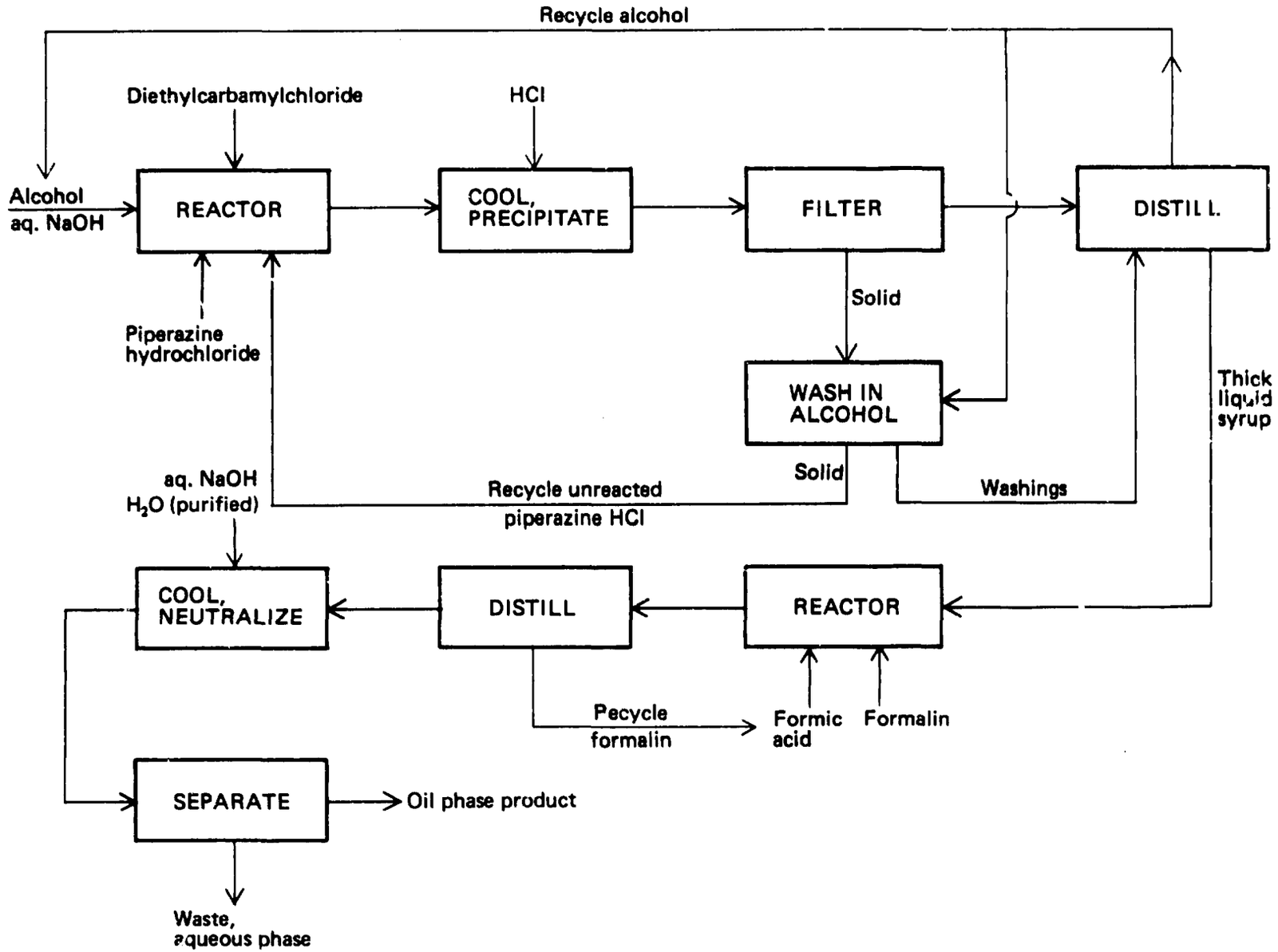
It is evident that the wastes from fermentation, recovery and purification will be rather similar to those arising from benzylpenicillin manufacture. In addition some additional treatable wastewater may arise from hydrogenerating the chloro-compound to tetracycline.

10. Diethylcarbamazine or 1-diethylcarbamyl-4-methylpiperazine is synthesized by the reaction of piperazine with diethylcarbamyl chloride in alcohol to form an intermediate, 1-diethylcarbamyl-piperazine. This intermediate is then reductively methylated using formaldehyde and formic acid. The first reaction is conducted at 45-50°C with cooling to remove reaction heat. After reaction the mixture is acidified with concentrated HCl with cooling and then chilled to 20°C to precipitate unreacted piperazine (as the hydrochloride) which is filtered, washed with alcohol and re-used. The filtrate and washings are then distilled to remove alcohol which can be re-used, leaving behind a thick syrup which is mixed with formic acid, heated to about 80°C and formalin added. Thereafter the mixture is refluxed for an hour at 105°C and then batch distilled to a boiling temperature of 150°C. The residue is then cooled to 30°C, and neutralized with cooling using sodium hydroxide solution. The product is separated as an oil from the aqueous waste solution, dried and further purified.

The major waste water stream is the aqueous phase separated from the product oil. If the ethanol is all recycled there are no hazardous wastes. Some salt may separate from the aqueous waste but it should be included in the wastewater stream. Additional wastes may be produced by further purification by crystallization or distillation; such wastes should be incinerated if possible. Figure 5 gives a simplified flowsheet for the manufacture of this drug.

11. Dapsone (4,4-diamino-diphenyl sulfone) can be manufactured starting either with p-chloronitrobenzene or chlorobenzene. By the first route p-chloronitrobenzene is condensed with potassium xanthate to form 4,4-dinitro-diphenyl sulfide which is then oxidized to the corresponding sulfane. This dinitro compound is then catalytically reduced using Raney

Figure 5. Diethyl Carbamazine Process Flow Sheet



nickel and hydrogen to give the diamino compound which is the Dapsone product. In the other method chlorobenzene is chlorosulfonated and the resulting compound is then used to alkylate additional chlorobenzene in a Friedel Crafts reaction. The 4,4-dichloro compound which results from the alkylation is then reacted with ammonia to give the corresponding diamino compound, Dapsone, by ammonolysis. Figure 6 gives a simplified flowsheet for the process beginning with p-chloronitrobenzene.

The wastewaters from either process route will contain salts and organic solvents mostly from purification which can be handled in the usual ways and ultimately sent to biological treatment after solvent stripping. Other organic solvents not in wastewaters must also be recovered and re-used.

Spent Raney Ni catalyst should be recovered and reclaimed and not permitted to enter the natural environment. Spent Friedel Crafts catalyst can be buried in the form of hydrated aluminum oxide after hydrolysis.

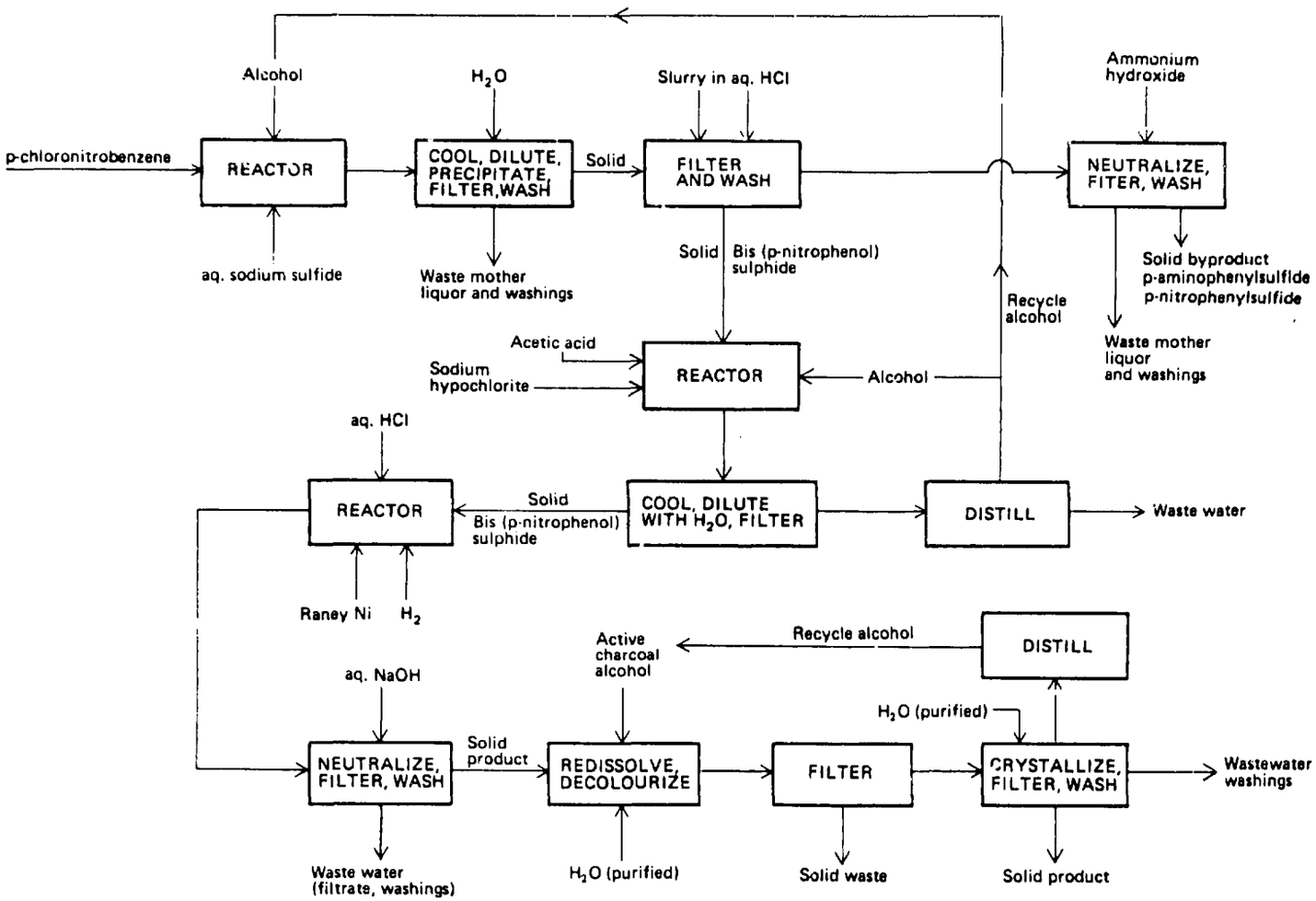
12. Chloroquine or 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline

This drug is prepared by refluxing a mixture of 4,7-dichloroquinoline and 4-diethylamino-1-methylbutylamine at 160-180°C for several hours. The hot reaction mixture is then dissolved in aqueous acetic acid. The mixture is then neutralized with NaOH solution and then the chloroquine product is extracted from the aqueous phase into ether.

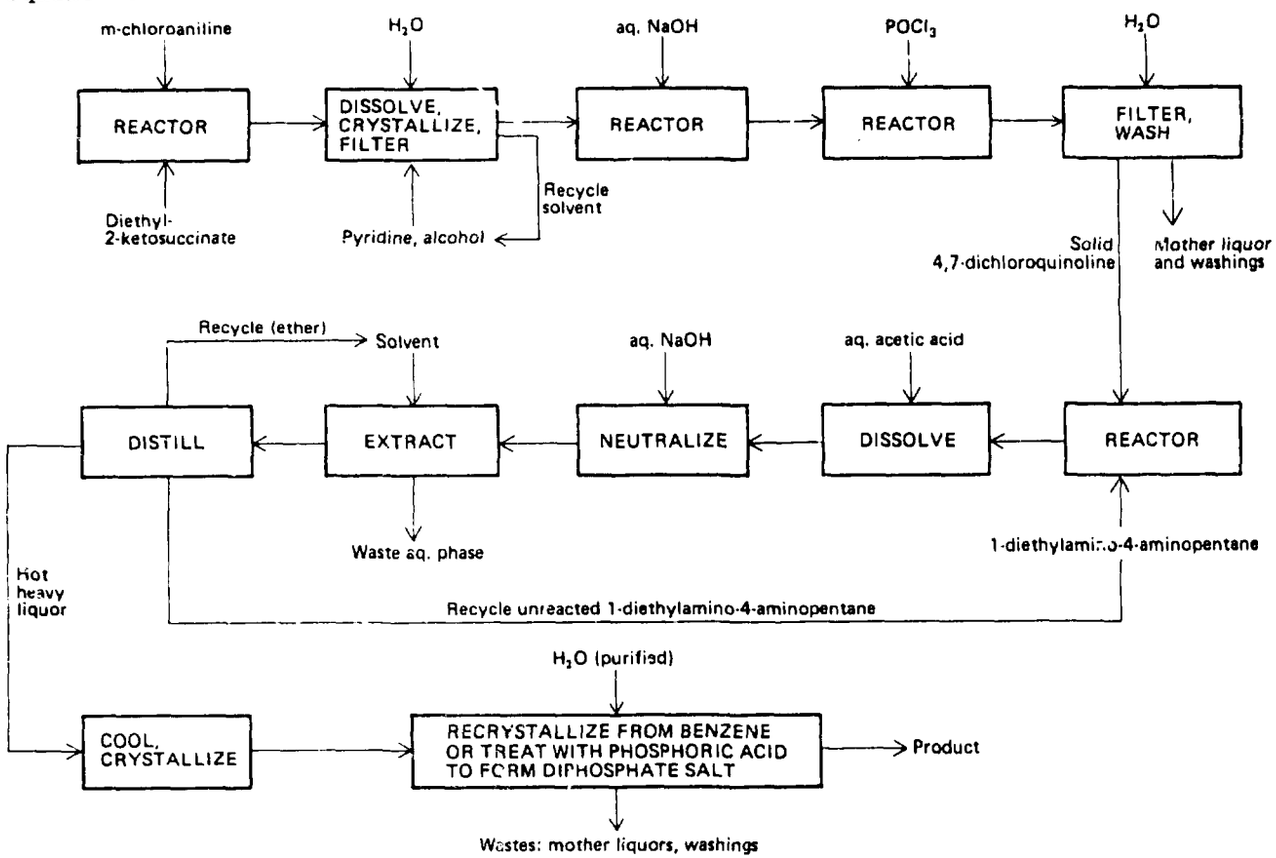
The ether solution is dried and then the ether is removed by distillation. The residue is then vacuum-distilled (160-170°C at 0.5 torr) to recover the excess 4-diethyl-1-methylbutylamine. Finally, the remaining product, chloroquine, is purified further by distillations or crystallization from a solvent.

The major wastewater is the aqueous reaction solution remaining after the product has been extracted therefrom into ether. Solvent recovery of the ether and the crystallization solvent are integral parts of the process. Recovery of the crystallization solvent will produce a residuum which should be incinerated. Figure 7 presents a simplified flowsheet for this drug.

6. Dapsone Process Flow Sheet



7. Chloroquine Process Flow Sheet



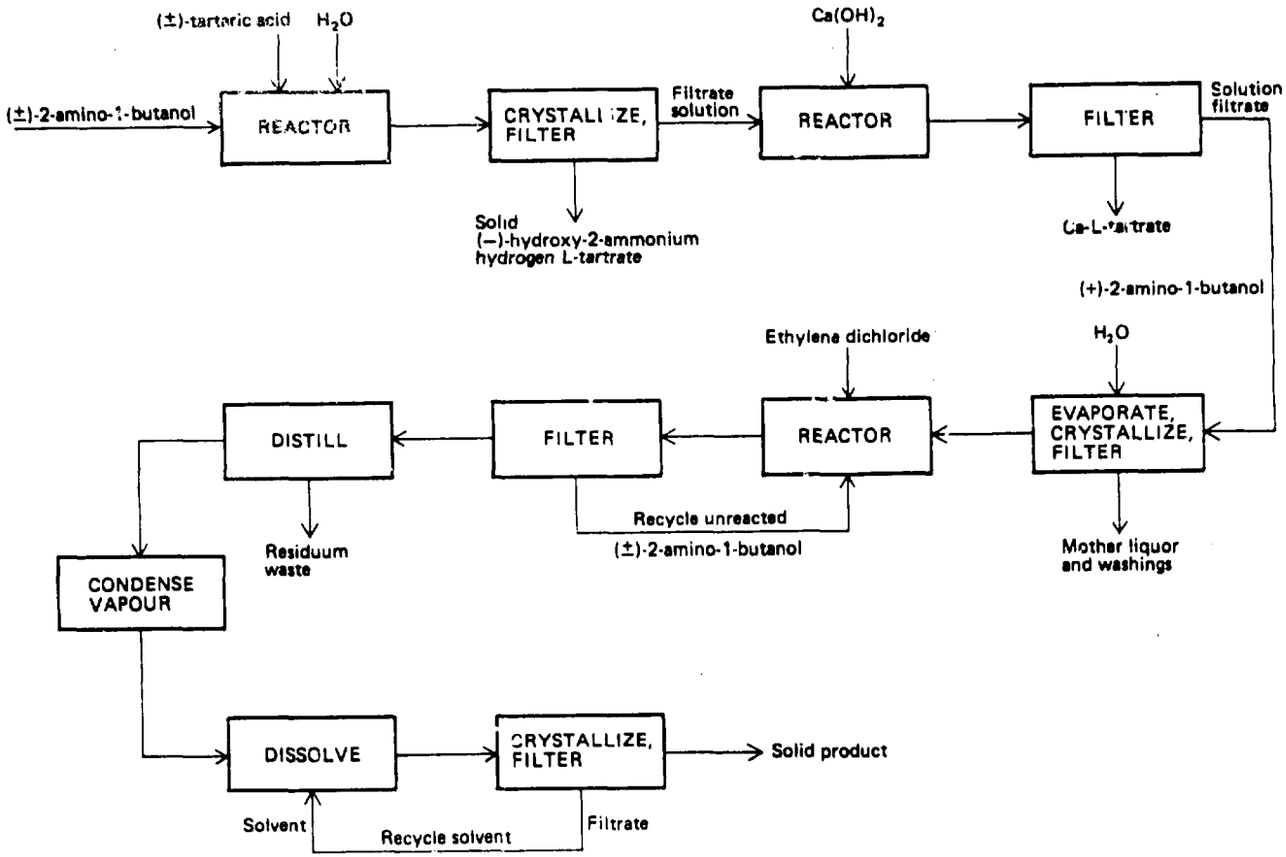
13. Primaquine or 6-methoxy-8-(4-amino-1-methylbutylamino)-quinoline

Potassium phthalimide is refluxed with 1,4-dibromopentane in acetone; then precipitated KBr is filtered off and the acetone and excess dibromopentane removed by distillation, leaving behind an oil (4-bromo-1-phthalimidopentane), which is purified by vacuum distillation. This intermediate oil is refluxed with 6-methoxy-8-aminoquinoline in ethanol. After cooling, ether is added and the precipate (6-methoxy-8-aminoquinoline hydrobromide) is filtered and washed with ether. The filtrate is washed with K_2CO_3 solution, then washed and dried. Ether is removed from the filtrate by distillation, then alcohol is added to the dark residue and the resulting solution boiled with decolorizing charcoal, filtered and then cooled to crystallize the intermediate [6-methoxy-8-(4-phtalimido-1-methybutylamino)-quinoline]. This latter compound is hydrolyzed to the final product by refluxing it with hydrazine in alcoholic solution. The drug is then extracted into ether and precipitated as the diphosphate by adding an alcoholic solution of phosphoric acid.

Most of the aqueous waste will be in the form of residuum after ether and alcohol are distilled from waste solutions. This residuum should be incinerated if possible. Otherwise it can be mixed with large volumes of wastewater (e.g. sanitary sewage) for dilution. A major solid waste is active carbon from the decolorization step; this should also be incinerated.

14. Ethambutol is the dextrorotatory form of 2,2'-(ethylenediimino)-di-1-butanol. It is prepared by briefly heating ethylene dichloride with excess (+)-2-amino-1-butanol. The latter (+)-isomer is obtained in an optical resolution process that involves crystallization from an aqueous solution of the adduct formed with the appropriate isomer of tartaric acid. Waste streams include the filtrate from the last step and calcium tartrate formed upon recovery of the (+)-2-amino-1-butanol from the adduct. Ordinarily, little if any solvent recovery is required but calcium tartrate or calcium sulfate might be formed as a solid waste. A simplified flowsheet is given in Figure 8.

8. Ethambutol Process Flow Sheet



15. Isoniazid (isonicotinic acid hydrazide or 4-pyridinecarboxylic acid hydrazide) is easily made by reacting isonicotinic acid and hydrazine. To a mixture of isonicotinic acid and 60% hydrazine-water solution 1-pentanol is added in order to remove water by azeotropic distillation. The mixture is refluxed for several hours during which an azeotropic mixture of H_2O and 1-pentanol is distilled away. The mixture is cooled to precipitate the product, isoniazid, which can be further purified by crystallization from ethanol or butanol.

The major potential sources of pollution from this process are the solvents which should be recovered and re-used. Residua from solvent recovery should be incinerated. Figure 9 shows a simplified flowsheet.

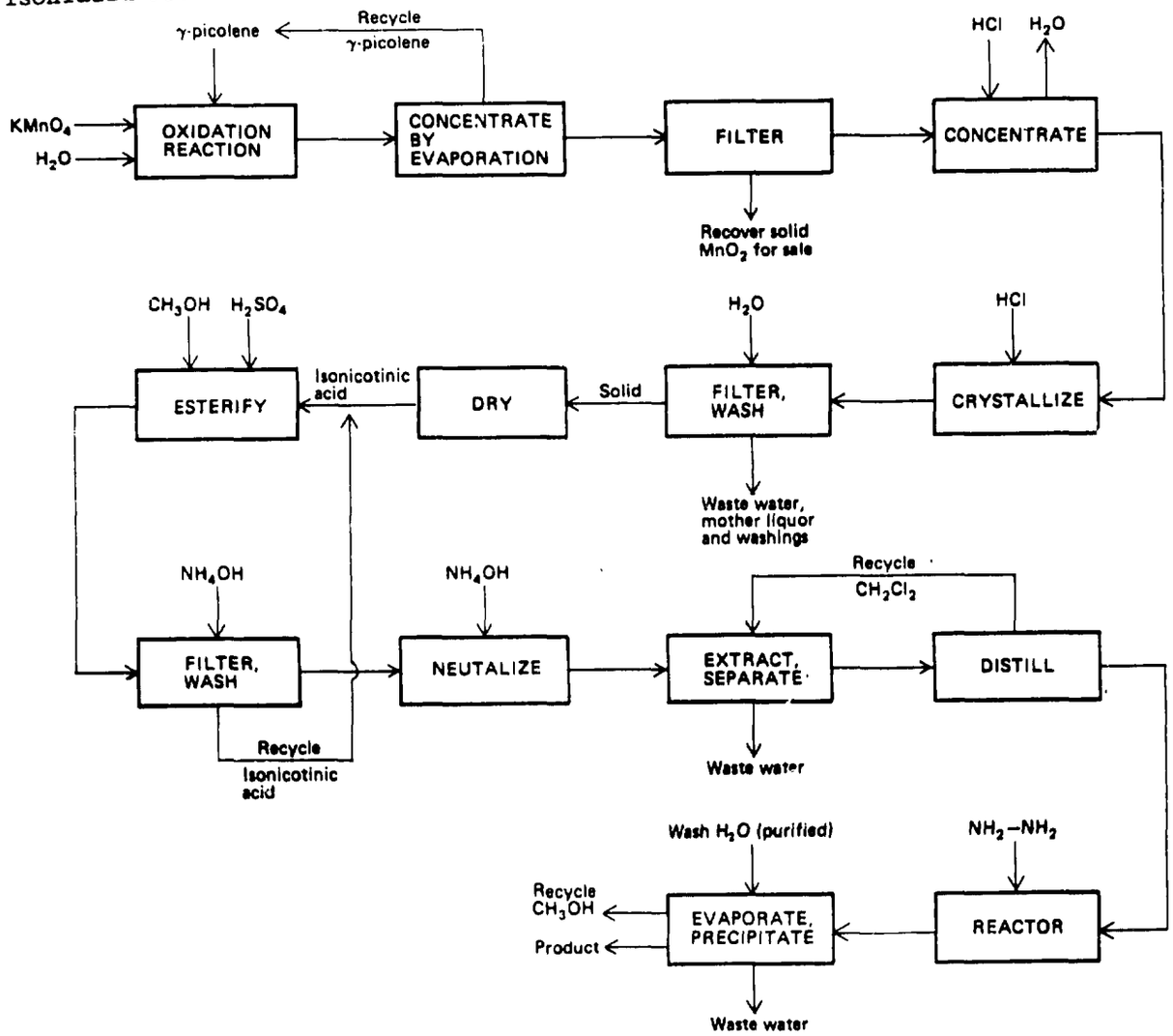
16. Streptomycin is produced by fermentation of Streptomyces griseus which secretes only part but not all of the antibiotic into the fermentation broth. The portion of the streptomycin remaining in the cells can be released by treating them with dilute acid.

Streptomycin can be recovered from solution by adsorption on active carbon followed by elution with acidic aqueous methanol, and precipitation as a salt. Further purification can be done by chromatography and crystallization of the complex formed between streptomycin hydrochloride and calcium chloride.

Waste waters produced will be quite similar to those arising from benzylpenicillin or tetracycline. Solvent recovery of methanol from the eluent will be necessary but, other than this, the solvent recovery requirement will not be as large as in the case of tetracycline and benzylpenicillin.

17. Hydralazine (1-hydrazinophthalazine) is manufactured by condensing the half-aldehyde corresponding to phthalic acid (1-carboxybenzaldehyde) with hydrazine, reacting the product with phosphorus oxychloride to form a chlorinated intermediate. This latter product is then reacted with hydrazine to form the final product.

Figure 9. Isoniazid Process Flow Sheet



Only aqueous wastes containing hydrochloric and phosphoric acids should arise. It may be necessary to recover some solvent used for purification by recrystallization.

18. Propranolol or 1-isopropylamino-3-(1-naphthyloxy)-2-propanol

This drug is manufactured by heating isopropylamine and 1-chloro-3-(1-naphthoxy)-2-propanol under autogenic pressure at 70-80°C for up to 10 hours. After cooling aqueous HCl is added and the mixture washed with ether. Then the aqueous phase is decolorized with active carbon followed by neutralization with NaOH solution. The precipitate is filtered, washed with water, dried and crystallized from cyclohexane.

Wastewater arises in the form of filtrate from the final filtration step. Solvent recovery should be conducted for the ether washings and the crystallization-purification solvent, cyclohexane. Residuum from the distillation operations should be incinerated. Spent active carbon from decolorization should also be incinerated.

19. Reserpine is an alkaloid drug extracted from the powdered roots of Rauwolfia plants (Rauwolfia serpentina). Two solvents are used: a methanol-water solvent for the initial extraction; the product is then exchanged into an immiscible chlorinated solvent. Both solvents are recoverable in part but small amounts of these solvents become waste. Further purification of the reserpine alkaloid can produce yet another solvent waste. These waste solvent residues should be incinerated if possible; otherwise they can be biologically treated provided they are diluted sufficiently with lower strength wastewater.

The solid waste which arises from this process can be buried (landfilled) or incinerated.

20. Furosemide or N-furfuryl-1-carboxy-3-sulfonamido-4-chloroaniline is manufactured as follows: 1,3-dichlorobenzoic acid is reacted with chlorsulfonic acid to give the 5-sulfonyl chloride compound which is converted to the sulfonamide. The last compound is reacted with furfurylamine to give the final product. Various wastewaters containing salt will be produced. Waste solvents may also be produced from purification steps.

21. Insulin Practically all commercial insulin is prepared from the pancreas of beef or swine, although various types of synthetic and genetically engineered insulin can be expected to penetrate the market gradually. The animal glands are macerated and then extracted with an aqueous solution of alcohol and acid. After centrifugation, neutralization with ammonia, and filtration, the mixture is again acidified to pH=3. Then evaporation and heat treatment separate solvent for recycle and cause the precipitation of fats which are skimmed from the solution. After another filtration step the insulin is purified by NaCl precipitation, isoelectric precipitation and, finally, precipitation as zinc insulin crystals.

There are numerous wastes from this process. The extracted glands from the centrifugation step should be sold as animal feed, the protein and filter aid from two filtration steps should be buried in a landfill. The small amount of waste from solvent recovery should be incinerated and the fats sold. Wastewaters which from the various precipitation processes can be treated biologically after steam stripping.
Pyrogen-free water must be used to prepare insulin in injectable form.

22. Ethinylestradiol is prepared from estrone using potassium acetylide as reagent. The acetylide is prepared in liquid ammonia from potassium and acetylene. To this is added a solution of estrone in ether and dioxane. After reaction and evaporation of the NH_3, ether and then dilute H_2SO_4 solution are added. The ether phase is then separated and washed, dried and evaporated in vacuum. The residual oil is dissolved in methanol, but water is added and, upon cooling, the product crystallizes. The crystals are washed and recrystallized from methanol and water.

The major waste waters are potassium sulfate solution and methanol solutions. Recovery of the methanol should be practiced as economical. Evaporated NH_3 should be condensed and re-used in the process.

23. Blood and blood fractions from human blood plasma contain important proteins such as fibrinogen or antihemophilic globulin (to counter hemorrhaging), gamma-globulins (to prevent hepatitis, measles, chicken pox and tetanus), thrombin (to coagulate blood) and albumin (for treating shock).

Whole blood is obtained from human donors or from placentas following childbirth ; then the cells are removed by centrifugation leaving behind the plasma which can be used as is or processed further into various protein fractions. The blood cells can be used for therepy or discarded as a waste but in more recent practice they are returned to the donor as part of the donation process.

Protein is precipitated from blood serum by adding ethanolic acetate buffer in various steps depending on the method used and the fractions sought. After the final precipitation the diluted fraction which can contain about 40% ethanol must be steam stripped to recover the alcohol[it can then be treated biologically. Other wastes include diatomaceous earth filter aid (12kg per 500 l of plasma) and placentas, if used. The former solid waste can be buried, the latter incinerated.

24. L-Ascorbic acid or vitamin C is manufactured from D-glucose which is first hydrogenated to sorbitol that is then oxidized to L-sorbose. To protect all but the C_1 hydroxyl groups the sorbose is condensed with a ketone such as cyclohexanone and then the C_1 hydroxy is oxidized to the corresponding carboxylic acid. This compound is hydrolyzed to remove the ketone to form 2-keto-L-gluconic acid which is then esterified using methanol and HCl. Upon heating the ester the L-asorbic acid product is formed. It can be purified by recrystallization.

Waterwaste arises when the product is removed from the reaction mixture. It should be biologically treatable provided it is not contaminated with heavy metals that might be used as catalysts. The ketone solvent is regenerated after oxidation of the C_1 hydroxyl groups and should be recovered and re-used. Some solid waste may arise from spent catalysts. Wherever possible such wastes should be reclaimed and the catalytic metals re-used.

25. Hydroxyocobalamine or the hydroxy form of vitamin B_{12} is manufactured by fermentation. Many different micro-organisms produce this vitamin and in some instances it can be obtained as a byproduct from fermentation broths arising from the production of antibiotics (e.g. benzylpenicillin). A typical microbe for producing vitamin B_{12} is Streptomyces olivaceus and cobalt salts are added to the fermentation medium to maximize production because the vitamin contains complexed cobalt as part of its molecular structure. After about 2-4 days when the available nutrients have been consumed, lysis of the mycelium begins. This process is speeded up by adjusting the pH to about 5 using H_2SO_4 and heating. This frees the cobalamin from the mycelium. A reducing agent such as Na_2SO_3 may be added to retard oxidation.

After the broth is filtered to remove cells the filtrate liquid is treated with cyanide to convert all the vitamin B_{12} cobalamins to the cyano form cyanocobalamin. This form is then absorbed from solution onto a solid absorbent such as charcoal, Fuller's earth or bentonite. The cyanobalamin is then eluted from the adsorbent using a variety of possible soultions such as hydrochloric acid, aqueous organic bases, water-acetone, aqueous sodium cyanide or sodium thiocyanate. The vitamin is then extracted into an organic solvent such as cresol, amylphenol or benzyl alcohol. The vitamin can also be precipitated as the copper or zinc cyanide-cyanocobalamine complex. Catalytic hydrogenation in aquo is then used to substitute a hydroxyl for the cyano group thereby forming hydroxycobalamine.

Wastewaters produced by vitamin B_{12} manufacture are typical for fermentations. Solvent recovery will also be required. An added complication can be introduced by the posrible presence of cyanide in the wastewaters ; for this reason these waters must be diluted with lower-strength sewage before sending them to biological treatment processes.

26. Retinol or Vitamin A is manufactured from B-Ionone, a well known compound in the perfume industry which has 13 carbon atoms. The synthesis involves adding one carbon atom to make a C_{14} compound, then adding six carbon atoms to make the C_{20} backbone structure of Vitamin A.

Step A. B-Ionone is condensed with monochloracetic acid ester and sodium ethylate for several hours with stiring and cooling. Then methanolic NaOH solution is added and further reaction ensues for about two hours at 5°C. Then the mixture is diluted with water, extracted with ether and the ether phase washed and dried. The ether is then evaporated and the residue distilled under vacuum. The fraction which boils from 100-102° C at 0.5 torr is the C_{14} aldehyde intermediate.

Step B. The C_6 side chain is prepared separately using a Grignard reagent formed from magnesium and ethyl bromide in ether. This is then reacted with 1-hydroxy-3-methylpent-2-ene-4yne under reflux for several hours. The mixture is cooled and to it is added the C_{14} aldehyde intermediate from step A dissolved in ether, followed by additional refluxing for several hours. The reaction mixture is cooled and poured over a mixture of NH_4Cl and ice. The hydrolyzed C_{20} condensation product is then extracted into ether and the ether phase washed and dried.

After the ether is evaporated, the unreacted C_6 compound is distilled from the residue in high vacuum (0.5 torr) at 80°C. The remaining residue is then dissolved in petroleum ether and extracted into aqueous methanol. Further purification follows by diluting the methanol solution with water and extracting the C_{20} product back into petroleum ether which is then washed, dried and evaporated to give the C_{20} condensation product.

Step C. The C_{20} product from Step B is partially hydrogenated in methanol using a Pd-on-carbon catalyst. After filtering the catalyst and diluting with water the product is extracted into petroleum ether which is washed, dried and evaporated to give the hydrogenated C_{20} intermediate.

Step D. The C_{20} product from Step C is dissolved in a mixture of benzene and pyridine, reacted with acetyl chloride, cooled with ice and then the organic phase is washed with dilute H_2SO_4 and $NaHCO_3$, dried and evaporated to give a C_{20} - acetate intermediate.

Step E. The C_{20} - acetate from Step D. is dehydrated in petroleum ether using iodine to form the acetate of Vitamin A. The organic phase is washed with various aqueous reagents and the unreacted intermediates extracted into aqueous methanol. The petroleum - ether phase is then dried and vacuum - evaporated to yield the vitamin -A- acetate product.

Step F. The acetate form from Step E can be saponified with KOH to produce the alcohol form of vitamin A.

The wastes from the various steps include an aqueous salt waste from Step A, an aqueous waste containing magnesium, bromide, chloride and ammonium ions from Step B, as well as aqueous washings from Steps D and E and potassium acetate solution from Step F. Various amounts of organic compounds will be included in these wastewaters. In many of the steps waste solvents will be generated - these must be recovered and re-used. Step B may produce a solid waste of $Mg(OH)_2$.

WATER SUPPLY FOR DRUG MANUFACTURE, FORMULATION AND PACKAGING

Introduction

Before discussing water treatment and the rigorous water-purity requirements specific to certain drug manufacture, formulation and packaging operations, the categories of water requirements common to all industrial manufacturing processes are reviewed. Drug manufacturing, formulation and packaging also requires these types of process water in addition to the highly purified and tightly controlled process water that comes in contact with the pharmaceutical preparations themselves.

After giving a discussion of ordinary water requirements immediately below, a subsequent section will treat the very demanding and specific, rigorous requirements for the process waters that will actually contact the pharmaceutical raw materials, intermediate substances, and the final drug formulations.

General Water Requirements for Drug Manufacture, Formulation and Packaging

The water use in any industrial process falls within one of four basic groups:

1. Cooling water
2. Process water
3. Steam generation and boiler make-up
4. Sanitary and service use.

Each of these groups have a different potential of re-use based on the nature of the water use.

1. Cooling Water

On the average, 60-70% of all industrial water use in the industrialized countries is for cooling. If one includes electric power generation as an industry, cooling water accounted for 90% of all water use in the United States in 1977. The two types of cooling are non-contact and contact cooling. In non-contact cooling, cooling takes place via heat exchangers directly or with an intermediate cooling cycle. Oftentimes waste heat is the only result of the cooling process. However, on other occasions chemicals are added to prevent corrosion or fouling and these are sources of pollutants. Contact cooling water may become contaminated from by-products of production processes, trace substances from the raw material or final products or other chemicals such as additives and catalysts. Therefore both waste heat and chemical pollutants will generally be present in the used contact cooling water.

Water recycling for cooling purposes has the greatest potential for water savings within industry, although not without a considerable cost. Cooling towers, with natural or mechanical draft, wet or dry, or cooling ponds, with spray units or large surface area, exist for recycling cooling water. These technologies for recycling of cooling water have been widely employed in water short areas for a number of years. Even with recycling some "make up" water is needed to prevent salt build-up. Small amounts of cooling water must be released as "blow-down" and fresh make-up water provided to replace the blow-down and the water evaporated during the cooling process. New technologies are being developed for using lower quality water for cooling purposes. Other process effluents may be thereby re-used and higher quality water saved for other uses.

Re-use of other process water as a source of cooling water is not as wide-spread as recycling. This is due in part to the extensive treatment which would be necessary for many of the process effluents before they would reach the quality required for the cooling system.

2. Process Water

Process water is that part of industrial water use that is directly involved in the production process except for non-contact cooling and non-contact steam. In the pulp and paper industry it includes the water used in the removal of bark from pulp wood, moving the ground wood and pulp from one process to another, in cooking of wood chips for removal of lignins, and in washing the pulp. In the chemical industry water is used as a solvent, cleaner, transporter or as a cooling liquor when chemicals such as sodium sulfite and sodium hydroxide are dissolved in water. The food industry uses water for cleaning, cooking and canning. In many industries, residuals, by-products, and other wastes are removed via water, creating heavily polluted waste waters. The ability of water to remove waste material is a process use also.

There are very specific purity requirements for process water for drug manufacture, i.e. for the process water which comes into contact with raw materials, intermediate chemicals and final formulated products. These very rigid and specific purity requirements are discussed in the next section.

Conserving process water can take two forms: recycling or re-use. Re-use of process water may be via the cascade or series method in which the water is used from one process stage to the next with final waste water treatment occurring after the last process. If a process requires a higher quality water than the effluent of the last process, the effluent will be treated. The volume of discharge of waste water would be determined by the largest waste using process.

The recycling approach to process water conservation requires a closed or partially closed system where the effluent of a process is treated and used directly, or after mixing with raw water as intake water for the same process. There are other indirect benefits to recycling and re-use than water savings. In the process of treating the process effluents, valuable raw materials, solvents, and by-products can be recovered or waste material may be removed at a cost less than would be possible in an end-of-the-pipe waste water treatment plant.

3. Boiler Make-Up

Boiler make-up water is primarily used for steam generation for process use. Steam condensate or boiler water is discharged (blowdown) when steam becomes contaminated due to contact with raw materials or by-products or to prevent damage to the boiler tubes from corrosion or salt build-up. The amount of water discharged as blowdown must be replaced and is called boiler make-up water.

There are three major uses of the steam generated within an industrial plant:

(a) For non-contact process heating, where the steam is usually generated at pressures of 125-650 psig.

(b) For power generation to drive steam turbines, compressors, and pumps associated with various processes. The steam for this use normally requires superheating and is generated at pressures from 650-1,500 psig.

(c) For use as a dilutant, stripping medium, or a source of vacuum using stream jet injectors. This steam comes in contact with the raw materials in the production process. The pressures required for these uses are much lower than for the other two uses and in many instances, the source of this steam is the exhaust of the steam from the other uses.

Steam purity is of prime importance for i) boilers with superheaters, ii) boilers that supply power generation turbines, iii) steam that is used directly in a process (contact steam). The purity need for contact steam depends upon the process requirements while the purity of non-contact steam depends upon the pressure needed.

Recycling of steam to be used as boiler make-up water is established practice in industry. The exhaust steam is condensed to water, discharging the heat of vaporization as waste heat, as heat used for other processes or to preheat raw intake water to save energy. The condensate may have to be treated depending on the use to which it is put (contact or non-contact for example).

Re-use of process steam can be done by re-using the steam itself by recovering the heat capacity, or both. The exhaust of high pressure steam processes can be used as a source of steam for low pressure steam processes without any treatment. This takes full advantage of the properties of the steam. The exhaust from the last steam use can be condensed, treated if necessary, and re-used as boiler make-up. The condensate, if not re-used for boiler make-up, could be re-used for other industrial uses. Two relatively recent developments use waste steam as a waste treatment aid. Waste heat evaporation and vapor-compression evaporation are techniques that evaporate some of the waste water stream producing distilled water and concentrate the pollutants which makes for more efficient final treatment.

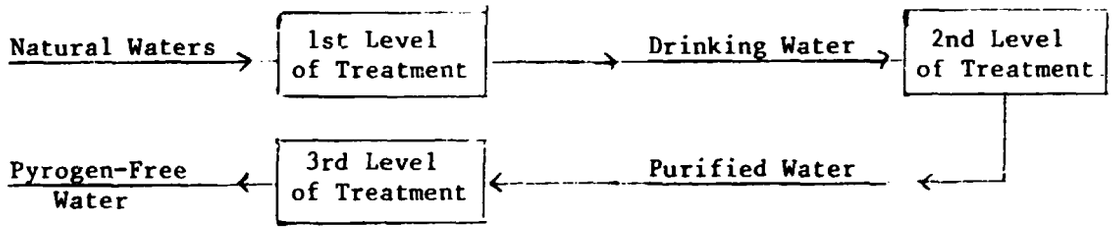
4. Sanitary and Service Use

Sanitary uses are those water needs for the employees such as showers, toilets, food preparation, and drinking water. These uses are usually dependent upon the number of employees, although in some industries, such as mining or steel mills, there is more water use by the employees. Service water is that related to the maintenance, cleaning, or preparation of the plant or support services not related to the industrial production processes. Examples are dust control of access roads and parking lots of a cement factory, or washing of trucks, or irrigation of landscaping surrounding the plant.

In industrial plants sanitary water tends to be supplied from the local water system due to the quality standards required by local health codes. The sanitary wastes are discharged to biological treatment plants employed by industry or discharged to the municipal treatment plant. There is little recycling of sanitary waste due to the high quality standards required for drinking water and the availability of low cost municipal water, but there are many possibilities for re-use. There is more recycling of service water since it is used in larger quantities and need not meet such strict quality. There is some re-use of process water effluents for service water with little or no treatment due to the low quality requirement for some service water uses.

Rigorous Process Water Requirements Specific to Drug Manufacture

Rigorous standards for water purity and quality are logical requirements for water used in manufacturing drugs. These water-purity requirements are more demanding for process water for drug manufacture than for ordinary drinking water, even for drugs to be administered orally. For drugs that will be injected, the standards are still stricter and require that the water be free from pyrogenic substances. These different levels of purity are further emphasized and illustrated by what may be considered a typical sequence of water treatment:



Definitions of Water Purity

In order for water to be safe for drinking (potable water) it must meet certain criteria for microbiological counts, color, turbidity, pH, dissolved oxygen, toxic impurities, taste, odor and temperature. For example, surface water criteria for public water supplies published by the U.S. Department of the Interior in 1968 are given in Table 2. Table 3 gives the maximum contaminant levels for drinking water promulgated by the U.S. Safe Drinking Water Act of 1974.

The rules of the United States Pharmacopeia (USP) may be taken as representative of most developed nations and WHO regarding water to be used for manufacturing drugs. According to USP, "Drinking Water" which meets the U.S. Environmental Protection Agency regulations (essentially those specifications of Table 3) may be used for the preparation of USP drug substances but NOT for the preparation of dosage forms.

Table 2

Surface Water Criteria for Public Water Supplies

Criteria	Maximum Permissible Level (ppm Unless Otherwise Indicated)
Physical:	
Color (Pt-Co Standard)	75
Odor	variable
Temperature	< 85° F
Turbidity	variable
Microbiological:	
Total Coliform	< 10,000/100 ml
Fecal Coliform	< 2000/100 ml
Inorganic:	
Alkalinity	variable
Ammonia	0.5 (as N)
Cadmium	0.01
Chloride	250
Chromium, hexavalent	0.05
Copper	1.0
Dissolved oxygen	> 4
Iron	0.3
Lead	0.05
Nitrates plus nitrites	10 (as N)
pH	6.0-8.5
Phosphorus	variable
Sulfate	250
Total dissolved solids	500
Zinc	5
Organic:	
Cyanide	0.20
Oil and grease	virtually absent
Phenol	0.001
Pesticides (variable with type)	< 0.05

Table 3

Maximum Contaminant Levels in Drinking Water
(1974 Safe Drinking Water Act)

Inorganic Chemicals, mg/l		Organic Chemicals, mg/l	
Arsenic	0.05	Carbon chloroform	
Barium	1.0	extract	0.7
Cadmium	0.01	Pesticides:	
Chromium	0.05	Chlordane	0.003
Cyanide	0.2	Endrin	0.0002
Fluoride	1.2-2.4	Heptachlor	0.0001
Lead	0.05	Heptachlor epoxide	0.0001
Mercury	0.002	Lindane	0.004
Nitrate (as N)	10.0	Methoxychlor	0.1
Selenium	0.01	Toxaphene	0.005
Silver	0.05	2,4-D	0.1
		2,4,5-TP	0.01

Other Parameters	
Turbidity	< 1 turbidity unit (TU)
Coliform bacteria	< 1/100 ml
Total bacteria	< 500/ml

Water which has been rendered suitable for pharmaceutical purposes by distillation, by ion-exchange treatment, by reverse osmosis, or by another suitable process is termed "Purified Water" by the USP. "Purified Water" is suitable for the preparation of dosage forms not intended for injection. "Purified Water" should not be used in pharmaceutical preparations intended for parenteral administration; instead, water so intended must meet still higher standards of purity which are in three categories· "Water for injection", "Bacteriostatic Water for Injection" or "Sterile Water for Injection". "Purified Water" is prepared from water meeting the standards for drinking water ; it contains no added substance and meets rigid specifications for chemical purity. These standards are given in Table 4. The various methods of production of Purified Water can offer numerous possibilities for contamination. Purified Water produced by distilling Drinking Water is sterile, provided the condenser is sterile. On the other hand, ion-exchange columns and reverse osmosis units afford sites for microorganisms to lodge and attach where they can multiply and eventually enter the product water. Such processes, therefore, require frequent monitoring and this becomes especially important following periods of shut-down for a few hours or more.

Water for Injection is prepared, according to USP regulations, by distillation or by reverse osmosis and contains no added substance. The major specification is freedom from pyrogenic substances as confirmed by the USP rabbit-injection test. The USP specifications for Water for Injection are also given in Table 4. Other more specific categories of Water for Injection are "Bacteriostatic Water for Injection" and "Sterile Water for Injection". The specifications for these latter two are given in Table 5. These two latter categories arise because "Water for Injections" prepared by one of the prescribed methods may not be sterile, e.g. if the condensor of the still or the reverse osmosis unit is not aseptic. "Sterile Water for Injection" is "Water for Injection" that is sterilized and suitably packaged. After the "Sterile Water for Injection" is

Table 4

U.S.P. Specifications

Purified Water

Purified Water is water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the federal Environmental Protection Agency with respect to drinking water. Purified Water contains no added substance.

Caution: Do not use Purified Water in preparation intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.

Packaging and storage. Preserve in tight containers.
Labeling. Label it to indicate the method of preparation.
pH (791). Between 5.0 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.30 ml of saturated potassium chloride solution to 100 ml of Purified Water.
Chloride. To 100 ml add 5 drops of nitric acid and 1 ml of silver nitrate TS: no opalescence is produced.
Sulfate. To 100 ml add 1 ml of barium chloride TS: no turbidity is produced.
Ammonia. To 100 ml add 2 ml of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in *High-purity Water* (see under *Reagents* in (661)) [0.3 ppm].
Calcium. To 100 ml add 2 ml of ammonium oxalate TS: no turbidity is produced.
Carbon dioxide. To 25 ml add 25 ml of calcium hydroxide TS: the mixture remains clear.
Heavy metals. Adjust 40 ml of Purified Water with 1 N acetic acid to a pH of 3.0 to 4.0 (using short-range pH indicator paper), add 10 ml of freshly prepared hydrogen sulfide TS, and allow the liquid to stand for 10 minutes: the color of the liquid, when viewed downward over a white surface, is not darker than the color of a mixture of 50 ml of the same Purified Water with the same amount of 1 N acetic acid as was added to the test specimen, matched color-comparison tubes being used for the comparison.
Oxidizable substances. To 100 ml add 10 ml of 2 N sulfuric acid, and heat to boiling. Add 0.1 ml of 1.0 N potassium permanganate, and boil for 10 minutes: the pink color does not completely disappear.
Total solids. Evaporate 100 ml on a steam bath to dryness, and dry the residue at 105° for 1 hour: not more than 1 mg of residue remains (0.001%).
Bacteriological purity. It complies with the federal Environmental Protection Agency regulations for drinking water with respect to bacteriological purity (40 CFR 141.14; 141.21).

Water for Injection

Water for Injection is Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution: Water for Injection is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter protect it from microbial contamination.

Table 4--Continued

Packaging and storage. Preserve in tight containers. It may be stored at a temperature below or above the range in which microbial growth occurs. Pyrogen. When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* (151). Other requirements. It meets the requirements of the other tests under *Purified Water*, with the exception of the test for *Bacteriological purity*.

Table 5

U.S.P. Specifications

Bacteriostatic Water for Injection

Bacteriostatic Water for Injection is Sterile Water for Injection containing one or more suitable antimicrobial agents.

Note: Use Bacteriostatic Water for Injection with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Packing and storage. Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type II glass, of not larger than 30-ml size.
Labeling. Label it to indicate the name(s) and proportion(s0 of the added antimicrobial agent(s).
Antimicrobial agent(s). It meets the requirements under *Antimicrobial Preservatives--Effectiveness* (51), and meets the labeled claim for content of the antimicrobial agent(s), as determined by the method set forth under *Antimicrobial Agents--Content* (341).
Pyrogen. When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* (151), the test dose being 5 ml per kg, injected very slowly.
Sterility. It meets the requirements under *Sterility Tests* (71).
pH (791). Between 4.5 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.30 ml of saturated potassium chloride solution to 100 ml of Bacteriostatic Water for Injection.
Chloride. It meets the requirements of the test for *Chloride* under *Sterile Water for Injection*, allowance being made for chloride derived from any chloride-containing added substance declared on the label.
Other requirements. It meets the requirements of the other tests under *Purified Water*, with the exception of those for *Ammonia, Oxidizable substances*, and *Bacteriological purity*.

Sterile Water for Injection

Sterile Water for Injection is Water for Injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage. Preserve in single-dose containers, preferably of Type I or Type II glass, of not larger than 1-liter size.
Labeling. Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without its first having been made approximately isotonic by the addition of a suitable solute.
Pyrogen. When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* (151).
Sterility. It meets the requirements under *Sterility Tests* (71).
Ammonia. For Sterile Water for Injection in glass containers of up to 50-ml size, dilute 50 ml with 50 ml of *High-purity Water*(see under *Reagents* in (661)), and use this dilution as the test solution; for larger sizes, use 100 ml of the test solution add 2 ml of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in *High-purity Water* (see under *Reagents* in (661)) (0.6 ppm for Sterile Water for Injection packaged in containers of up to 50-ml size; 0.3 ppm for larger sizes).

Table 5--Continued

Chloride. To 20 ml in a color-comparison tube add 5 drops of nitric acid and 1 ml of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 ml of *High-purity Water* (see under *Reagents* in (661)) containing 10 g of Cl (0.5 ppm), viewed downward over a dark surface with light entering the tubes from the sides.

Oxidizable substances. To 100 ml add 10 ml of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers of up to 50-ml size, add 0.4 ml of 0.1 N potassium permanganate, and boil for 5 minutes; for larger sizes, add 0.2 ml of 0.1 N potassium permanganate, and boil for 5 minutes: the pink color does not completely disappear.

Total solids. Proceed as directed in the test for *Total Solids* under *Purified Water*. The following limits apply for Sterile Water for Injection in glass containers: up to and including 30-ml size, 0.004%; from 30-ml up to and including 100-ml size, 0.003%; and for larger sizes, 0.002%.

Other requirements. It meets the requirements of the other tests under *Purified Water*, with the exception of the test for *Bacteriological purity*.

protected from microbial contamination by the addition of one or more suitable anti-microbial agents it is called "Bacteriostatic Water for Injection".

Regular testing of purified water for pyrogenicity must be performed. The standard USP test involves injecting a water sample into a rabbit and monitoring its body temperature -- a test which requires up to three days. More rapid assays of pyrogenicity can be obtained using a procedure which is based on reaction of an amoebocyte lysate obtained from Limulus polyphemos.

It should be emphasized that most pyrogens are lipopolysaccharides from bacterial cell walls, are quite stable thermally, and cannot be eliminated by the standard sterilization techniques of autoclaving or filtration through microporous media. These toxins can range in size from a molecular weight of about 20,000 up to aggregates of about 0.1 micrometer.

Water Purification Technology

Ion-Exchange generally takes place between ions on a solid resin held in a column and ions in the water to be purified which flows through the column packed with the particles of ion-exchange resin. Dissolved minerals and undesired metallic ions can be removed from water by this process which is similar to adsorption or sorption and is reversible. The ion-exchange resins are polymers containing functional ionic groups within a porous internal structure. If the polymeric backbone of these resins is represented by R then we can represent the reactions of typical cationic or anionic resins as follows:

Strong base (quaternary ammonium) anion exchangers·

$$R_3R'NOH + Cl^- \rightleftharpoons R_3R'NCl + OH^-$$

$$2\ R_3R'NCl + SO_4^{2-} \rightleftharpoons (R_3R'N)_2SO_4 + 2\ Cl^-$$

Weak base (amine) anion exchangers·

$$RNH_3OH + Cl^- \rightleftharpoons RNH_3Cl + OH^-$$

$$2\ RNH_3Cl + SO_4^{2-} \rightleftharpoons (RNH_3)_2SO_4 + 2\ Cl^-$$

Strong acid (sulfonic) cation exchangers·

$$RSO_3H + Na^+ \rightleftharpoons RSO_3Na + H^+$$

$$2\ RSO_3Na + Ca^{2+} \rightleftharpoons (RSO_3)_2Ca + 2\ Na^+$$

Weak acid (carboxylic) cation exchangers·

$$RCOOH + Na^+ \rightleftharpoons RCOONa + H^+$$

$$2\ RCOONa + Ca^{2+} \rightleftharpoons (RCOO)_2Ca + 2\ Na^+$$

Ion exchange columns are operated under non-equilibrium conditions. After they have reached equilibrium with the feed water they are regenerated usually with solutions of acid (for cation exchange resins) or base (anion exchange resins). The ion-exchange operation is usually conducted in fixed beds of resin. The resin first becomes saturated near the feed point and the zone of saturation then progresses through the column; when it reaches the other end of the column the unwanted ions are said to break through and the resin must then be regenerated.

Some representative publications describing ion exchange purification processes are references 33 through 36.

Reverse Osmosis and Ultrafiltration

These are membrane-permeation processes in which the solvent (water) passes through the membrane but dissolved species do not. Thereby, these operations differ from dialysis in which dissolved solutes pass through the membrane. The driving force for solvent or water permeation is a pressure difference between liquid on either side of the membrane.

Membrane filters operate to a large extent by a sieving effect, but ordinary filters such as cloth or paper are usually not effective for these applications because they trap particles within a fibrous

structure that eventually gets plugged and thereby reduces the flow rate of liquid through the filter. Ultrafiltration or reverse osmosis membranes, on the other hand, have tiny pores which exclude ions or macromolecules and prevent them from entering the porous structure of the membrane. In further contrast to filtration, the impure solution flows parallel to the membrane surface while only a part of the solvent flows through the membrane.

Usually the membrane is fabricated in the form of hollow fibers which can withstand large differential pressures with a relative strength dependent on the ratio of the outside to the inside diameters. The hollow fibers are ordinarily held as a parallel bundle within a shell in a configuration similar to that of a shell-and-tube heat exchanger. Water is pumped at high pressure through the shell on the outside of the fibers, the purified permeate flows through the fiber walls into the interior of the hollow fiber tubes under a driving force created by a pressure difference which can range from several hundred psi to more than a thousand psi. Corresponding fluxes through the fiber membranes range from about 15 - 25 gal/ft^2-day (0.006 - 0.01 m^3/m^2-day).

Reverse osmosis is generally used to remove ionic impurities from water whereas ultrafiltration is aimed at the removal of dissolved macromolecules which often do not bear a charge. Although the distinction is somewhat arbitrary, ultrafiltration is usually reserved for a separation where the solute molecules are more than an order of magnitude larger than the solvent molecules and the osmotic pressure difference of the solvent across the membrane is small and often negligible. Whereas ultrafiltration may be viewed more as a purely sieving process based on molecular size and shape, reverse osmosis is believed to involve an affinity or adsorption between solvent and membrane by which the adsorbed solvent layer tends to exclude solute molecules from the pores which are only about twice as wide as the adsorbed layer. Pores of about 13Å diameter will usually provide about 97% or more salt rejection.

An interesting aspect of membrane technology is the thin-skinned or "anisotropic" membrane. The separation process is controlled by the skin with its submicron pores, whereas the supporting layer has pores considerably larger than a micron. The supporting layer provides mechanical strength but does not control the separation process.

Operating costs for membrane systems depend on the nature and difficulty of the separation to be performed. They usually fall in the range of $0.20 and $5.00 per 1,000 gallons.

Useful references for membrane purification processes are numbers 37-40.

Important distinctions between UF and RO should be noted. The U.S.P. definition of water for injection (WFI) specifies that WFI must be produced by distillation or RO; the inclusion of RO as an acceptable process has been relatively recent. However, the U.S.P. specifies production processes only in the case of WFI and other types of water (e.g. U.S.P. Purified Water) may be produced by UF.

Distillation

This is the most widely practiced method for preparing Purified Water and Water for Injection. The principle is simply that dissolved non-volatile impurities remain in the liquid and are not carried over into the vapor which is pure and is condensed to a purified water. In practice, purifying water by distillation is far more complex than boiling a teakettle because microscopic water droplets tend to get carried into the vapor taking with them small amounts of impurities. Even tiny amounts of carried-over impurities can spoil the purity of the water; this is especially true for pyrogens only small amounts of which can render the product water pyrogenic and unsuitable for use in preparing injectable drugs.

Three design principles are frequently used to provide good separation between vapor and liquid droplets : (1) use low vapor velocities, (2) make the vapor follow a direction-changing path around baffles which remove entrained water droplets, and (3) make the vapor follow a circular or spiral pathway which tends to remove the higher-density droplets by centrifugal action. A low vapor velocity design is usually achieved by a slow heating rate and use of large vapor spaces for disengagement of entrained droplets; this entails a high capital investment per unit production capacity and, therefore, is almost never used for a continuous, high-production-rate still where low capital investment is a criterion. More usually, high vapor velocity designs are used to minimize capital investment. Moreover, other features are also built into the design to maximize the amount of distillate produced per unit of energy expended and, therefore, minimize operating costs. The common method of optimizing the energy usage are called vapor compression, thermocompression and multiple-effect distillation.

Vapor compression is applied to the vapor produced from a conventionally heated first stage. The mechanical energy delivered to this vapor by a compressor superheats it; this permits the superheated vapor to boil an equivalent amount of water in another stage where the compressed, superheated vapor from the first stage condenses. In this way, a given amount of steam applied to the first stage is used to produce significantly more distillate with an assist from a mechanical compressor. This usually brings about energy savings and reduced operating costs.

Thermocompression is applied to the vapor from a first stage ; this produces a superheated steam that can be used to boil a second stage. Thermocompression is achieved using a steam-jet ejector. A water-jet ejector using distillate applies a vacuum to the second stage and permits the distillate to be delivered above atmospheric pressure.

Delivery of distillate above atmospheric pressure, which is accomplished by either the mechanical, vapor-compression system or the steam-jet thermocompression system, minimizes possible internal contamination of the distillation system by potential backwards migration from the point of distillate withdrawal. Thermocompression offers the added advantage of eliminating the need for the mechanical compressor used in the vapor-compression system.

Using high-pressure steam and pressurized feed water permits multiple-effect evaporation with the first effect above atmospheric pressure and each subsequent effect at successively lower temperatures down to the last effect at about one atmosphere.

The steam from the first effect condenses in the tubes of the second effect thereby causing boiling of the water in the second effect at a pressure lower than the boiling pressure in the first effect. Three effects (stages) are common with more effects employed occasionally.

The Zyclodest distillation system is a variation of the vapor-compression design. The major difference is that this system employs a closed-loop flow system "energy loop" for absorbing the energy and exchanging it with the product fluid which flows in a separate, isolated "product loop". The water in the energy loop is re-used continually as it changes from liquid to vapor, is mechanically compressed, and then condenses as it exchanges its latent heat into the boiling water in the seperate, isolated "product loop".The Zyclodest system operates under pressure and can deliver hot or cold condensate under pressure.

Useful descriptions of distillation systems as applied to generating pharmaceutical-grade water may be found in references 41 and 42.

A Typical Water-Purification System

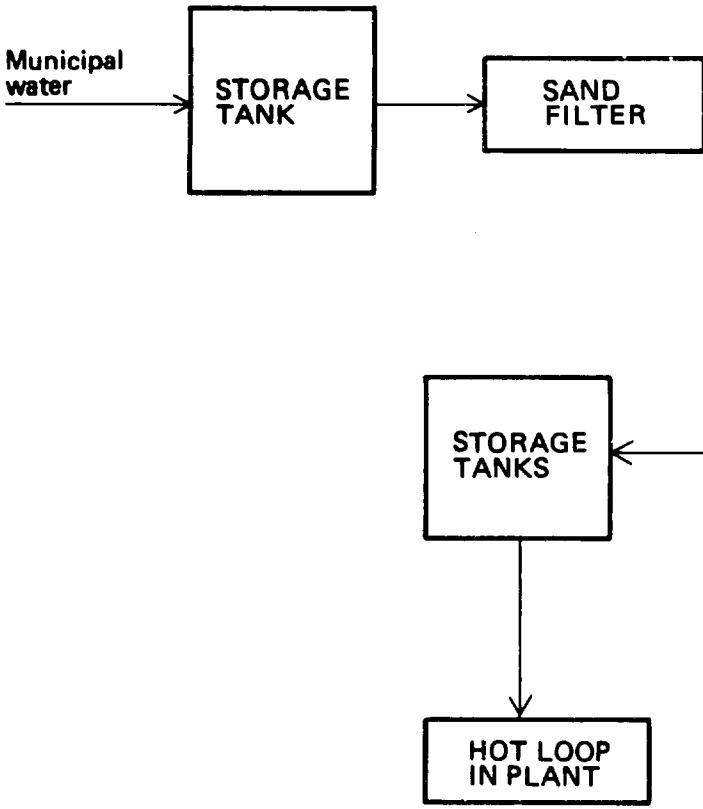
The diagram shown in Figure 10 represents an actual purification system installed by a large U.S. drug company at a manufacturing plant it built in Puerto Rico during the 1970's. The source of the water was a local municipal water supply. This local supply in Puerto Rico was judged to be somewhat less reliable than the municipal water systems which supplied other plants of the same company in the continental United States. For this reason the treatment system of Figure 10 is somewhat more elaborate than ordinarily used by this company. Some important features of the system shown are the Finn-Aqua multi-stage distillation system which produces pyrogen-free water and the hot loop for delivering hot, non-pyrogenic water at numerous locations throughout the manufacturing plant. The ultrafilter just upstream of the distillation unit was found to be necessary to prevent silica from entering the stills where it tended to build up and block the stages thereby causing carry over of pyrogens and deterioration of water purity.

The general scheme of Figure 10 should be considered representative only. The individual processing steps that must be used and the size of the units relative to their throughput will depend greatly upon the condition of the water supply. In case there is no acceptable municipal water supply available near the site of a pharmaceutical manufacturing plant to be built in a developing country it may be necessary to build a much more elaborate water purification system than that shown in Figure 10.

Economics

Tables 6 and 7 taken from reference 41 give tables of comparative operating costs for several different sizes and types of stills. The two different tables are based on two different sets of assumptions given at the bottom of each table. These assumptions

Figure 10. Water Purification Flow Sheet



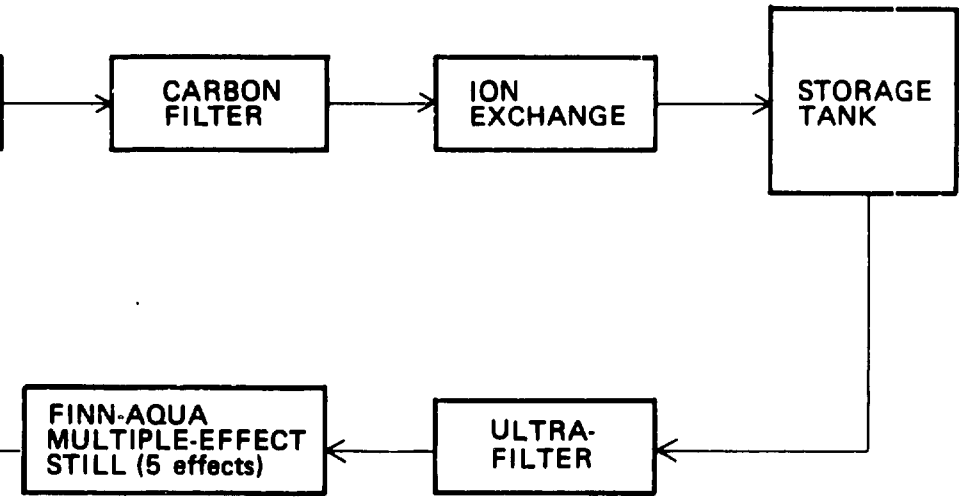

CARBON FILTER
ION EXCHANGE
STORAGE TANK
ULTRA-FILTER
FINN-AQUA MULTIPLE-EFFECT STILL (5 effects)

Table 6

Operating Cost (in dollars) per 1000 gal. of Product Water

Still Size (GPH)	Single Effect	Thermo-compression	Vapor Compression	Multiple Effect	Zyclodest
50	60.96	15.84	16.58	29.81 (3-effects)	16.26
100	60.96	15.84	16.58	29.81 (3-effects)	16.26
300	60.96	15.84	16.58	23.69 (4-effects)	16.26
900	n/a*	15.84	16.58	16.66 (6-effects)	16.26
1200	n/a	n/a	16.58	16.66 (6-effects)	16.26
1800	n/a	n/a	16.58	16.66 (6-effects)	n/a
2400	n/a	n/a	16.58	11.96 (8-effects)	n/a
3000	n/a	n/a	16.58	11.96 (8-effects)	n/a

Utility costs: steam = $4.50/1000 lb; electricity = $.10/kWh; feedwater = $4.85/1000 gal.; cooling water = $4.00/1000 gal.

*Not available.

Table 7

Operating cost (in dollars) per 1000 gal. of Product Water

Still Size (GPH)	Single Effect	Thermo-compression	Vapor Compression	Multiple Effect	Zyclodest
50	46.36	7.75	6.78	13.99 (3-effects)	6.41
100	46.36	7.75	6.78	13.99 (3-effects)	6.41
300	46.36	7.75	6.78	11.12 (4-effects)	6.41
900	n/a*	7.75	6.78	7.82 (6-effects)	6.41
1200	n/a	n/a	6.78	7.82 (6-effects)	6.41
1800	n/a	n/a	6.78	7.82 (6-effects)	n/a
2400	n/a	n/a	6.78	5.61 (8-effects)	n/a
3000	n/a	n/a	6.78	5.61 (80effects)	n/a

Utility costs: steam - $2.50/1000 lb; electricity = $.04/kWh; feedwater = $1.85/1000 gal.; cooling water = $1.00/1000 gal.

*Not available.

are costs of steam, electricity, feedwater and cooling water. The spread in these assumed costs cover a range of costs for purified water (drinking water) that is used as a feed for the stills.

Table 8 is taken from a brochure of a U.S. manufacturer of hollow-fiber ultrafiltration systems (Amicon Corporation) offered for removing pyrogens from water. This table gives a comparison among several different types of systems, including operating costs and comparative capital cost. The operating costs given for distillation are significantly lower than those given in Tables 6 and 7 and this may be the result of excluding the cost of feedwater or cost of cooling water or using different cost values.

Drinking Water Sources

The foregoing description of a water-purification system (Figure 10) was based on using drinking water purchased from a municipal water system as feed. In case such a drinking-water source is not available purchase of a packaged water treatment plant should be considered. A cost evaluation of such package treatment plants was conducted by U.S.E.P.A.[43] which cites the following cost comparison (1977 dollars) of plants of the same capacity (1 million gal per day):

	Conventional Municipal Plant	Packaged Plant
Construction Cost:	$1.124 million	$0.488 million
Annual treatment, oper. and maint. cost:	$62,570	$40,410

These data can be used to estimate costs of drinking water as follows:

For Conventional Plants (assume 8% p. a simple interest and 40 yr. life)

Capital Cost: $\frac{1.24 \times 6.96 \times 12}{365}$ = $0.28/1000 gal.

O & M Cost: $\frac{62,570}{365 \times 1000}$ = $0.17/1000 gal.

Table 8

Comparison of Ultrafiltration with Other Methods of Pyrogen Removal

	Hollow Fiber UF	Distillation	Thermo-comp. Distillation	Reverse Osmosis	Charged Filters
Usability					
for water	Yes	Yes	Yes	Yes	Yes
for product	Yes	No	No	No	Yes
Sanitary design	Good	Good	Good	Fair	Good
Removal efficiency	10	10	10	10	10 -10
Approximate operating cost, U.S. $ per 1,000 L	0.50-0.80	10-15	1-2	1-2	2.50-10
Approximate capital cost 800 L/hr system	$8,000	$60,000	$140,000	$20,000	$5,000

For Packaged Plants (assume 8% p.a. simple interest and 20 yr. life)

Capital Costs: $\frac{0.488 \times 8.37 \times 12}{365}$ = \$0.13/1000 gal.

O & M Costs: $\frac{40,410}{365 \times 1000}$ = \$0.11/1000 gal.

That these costs are somewhat low may be attributed to taking capital costs equal to construction costs only. Another U.S.E.P.A. report[44/] gives total costs for a 1 mgd package plant as \$ 0.47/1000 gal. treated (Oct. 1978 dollars).

SOLVENT RECOVERY

Introduction

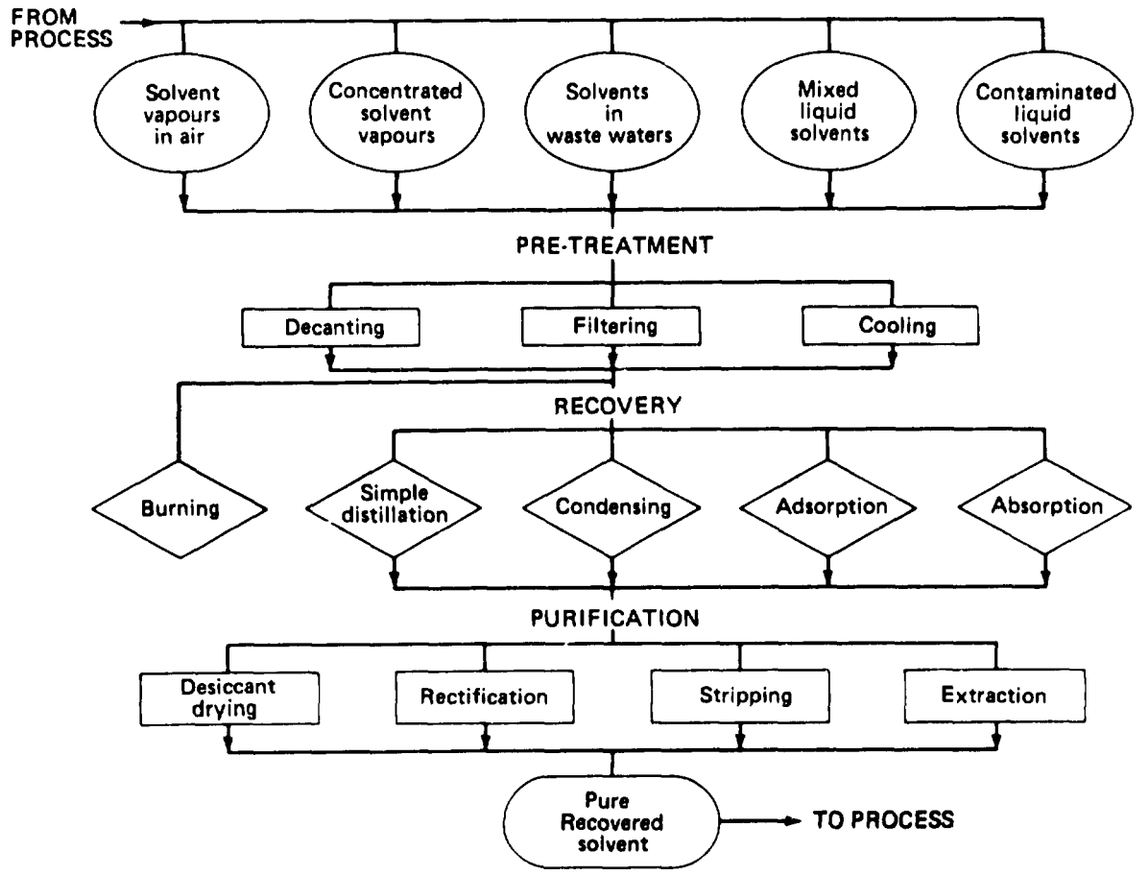
Recovery of waste solvents from chemical processes is not only good policy for protecting the environment ; it is also a sensible business policy in view of the high prices and shortages of solvents. In terms of modern requirements for wastewater effluents, there is no such thing as a water-immiscible solvent; even toluene, soluble in water only to the extent of 0.05% can cause the organic carbon content of wastewaters to exceed acceptable levels in most instances.

Figure 11 is taken from two important references in solvent recovery (ref. 45 and 46). This diagram is generally applicable and encompasses recovery of solvents from air and solvent vapors as well as solvents from wastewater and purification of liquid mixtures of solvents. The methods of solvent collection are applied to the recovery of solvent vapors or for removing solvents from air. Good practice in design and operation of pharmaceutical manufacturing plants will mean that solvents will be recovered from vapors as well as from wastewaters and other liquid wastes. The major problem is the purification of solvents for re-use and that will be the major concern of this section of the report.

Purification of Solvent Mixtures

Purification is usually accomplished by fractional distillation or, in the case of complex mixtures, by some combination of liquid-liquid extraction and decanting together with fractional distillation. A large number of process schemes and equipment arrangements are used, depending on the complexities of the mixture, on the relative volatilities and the solubilities of the components of the mixture. For example, distillation is usually not economical for removing small amounts of high-boiling impurities from water because too much water would have to be vaporized

Figure 11. Alternative Solvent Recovery Processes



instead the impurities can be extracted from the water phase into an immiscible low-boiling solvent and the solvent can then be purified by distillation and reused. Small amounts of phenol, glycol and dimenthyl formamide can be removed from water this way.

Special procedures must be used when azeotropes are encountered. These azeotropic compositions are those for which a liquid and its equilibrium vapor have the same composition -- a situation which renders ordinary distillation ineffective for separating the components.

Fractional distillation can involve two types of operation: enrichment (often called rectification) and stripping. A typical fractional distillation column consists of a vertical sequence of stages for contacting liquid and vapor, with the rectification section above the point of feed introduction and the stripping section below it. In the rectification section heavier components are condensed into a decending liquid phase from a countercurrent ascending vapor phase, thereby enriching or purifying the vapor which is condensed at the top of the column. A portion of the condensed overhead product is returned as "reflux" to the top of the column while the balance is withdrawn as overhead product. In the stripping section the descending liquid gives up lighter components to rising vapors. The liquid which is removed from the bottom of the column contains the heavier components from which the lighter components have been stripped.

Binary Mixtures -- No Azeotrope Problems

When no azeotropes are formed, or where azeotropes are acceptable as products, a continuous fractionation column can be used to separate the more volatile component as the overhead product and the less volatile component as the bottom product. For small scale, low volume or intermittent operation, or when the feed contains solids, a batch still may be preferred. The purity of the products will depend on the relative rates of feed, products withdrawal, reflux rate, reboiling rate and number of contacting stages in the column. Example systems which do not form azeotropes and can therefore be separated this way are:

methanol-water, dimethylformamide-water, and hexane-toluene. An example of an azeotropic composition that is sometimes acceptable is the 95% ethonol-5% water formed as an azeotropic overhead product at atmospheric pressure with those components. When the bottom product is water or contains water, direct steam injection can be used instead of a reboiler. This is sometimes referred to as steam-stripping of a volatile solvent from water; the solvent vapors may be further purified in an enriching section above the feed point.

When a binary mixture forms two phases that are relatively pure (very low mutual solubility) it may be sufficient merely to decant one phase from the other, provided the solubility of one component in the other is less than the acceptable contamination. Possible examples are toluene-water and heptane-water, although to get greater purity the more complex methodology of the next paragraph can be used.

Binary mixtures which form two phases with significant mutual solubility usually have an azeotropic composition within the two-phase region. Such mixtures can be purified using two stripping columns and a decanter for a water-solvent system. If the feed is richer in water than the azeotrope it is fed to the water column as shown; if the feed is richer in solvent, however, it is fed to the solvent-stripping column instead. No rectifying sections are shown in this scheme because the decantation step as shown is more efficient as long as the two phases can be so separated. When only one product need be purer than the composition of the decanted layer, then only one corresponding stripping column is required.

Binary Single-Phase Azeotropes

Azeotropic behavior can be modified by changing the pressure or the number of components present, and both these techniques can be used in practice to shift or to eliminate an azeotrope in order to purify the components. For example, when methylethyl ketone (MEK) and water are distilled at one atmosphere an azeotrope is formed which contains 35%

water. If this azeotropic product is then distilled in a second column operated at 100 psia the azeotrope is shifted to 50% water and dry MEK can be produced at 100 psi (absolute) from a 35% water feed while the high-pressure azeotrope (50% water) is recycled from the high pressure column back into the feed to the atmospheric column.

"Azeotropic distillation" refers to the method of adding a third component to the binary mixture to form a ternary azeotrope that separates into two layers. The layer enriched in the third component (called an "entrainer") is totally refluxed. The other layer is enriched in one of the binary components and is mixed with the feed whereas the other binary component can be taken from the bottom of the column. The entrainer must be readily distillable from this bottom product. An example is the use of benzene as an entrainer for the azeotropic distillation of water-ethanol mixtures.

"Extractive distillation" employes a third component or "solvent" which does not form an azeotrope with either feed component. The solvent is added to the distillation column to alter the relative volatility of the original pair allowing one component to distill overhead. The solvent leaves the column as a bottom product with the other component and this mixture is then separated in a second column. Some examples are: acetone-methanol (water solvent), ethanol-water (ethyene glycol solvent) and tetrahydrofuran-water (dimethylformamide solvent).

Another method of circumventing azeotropes is to add salt to reduce the vapor pressure of the component in which the salt is more soluble. For example, potassium acetate can be so used in separating ethanol from water (ref. 47).

Still another method is to separate an azeotrope by extraction of one of its component into an immiscible solvent. The two resulting phases can then be purified by separate distillations. An example is separation of a methanol-methylene chloride azeotrope by extracting the former component into water.

Chemical action can also be used to nullify azeotropic behavior by altering the volatility of one component. A good example is the use of solid sodium hydroxide to remove water from an organic solvent in the form of an immiscible aqueous solution. This produces an organic solvent of a purity greater than the azeotropic composition but the caustic solution must be evaporated so the sodium hydroxide can be reused.

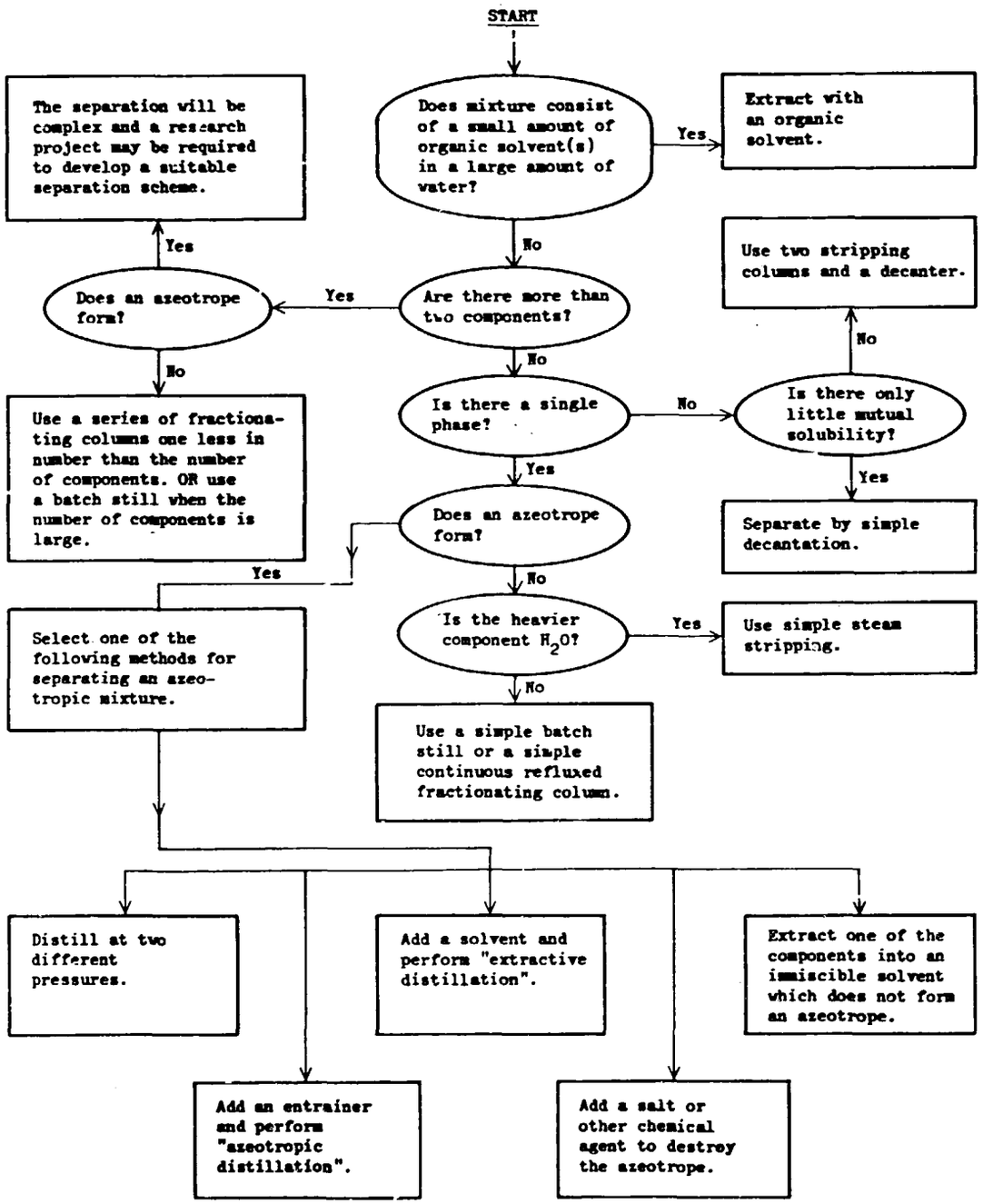
Multicomponent Mixtures

When no azeotropes form a series of distillation columns can be used in series. The number of columns needed is one less than the number of components to be separated. When the number of components is large it may be less expensive to use batch distillation because only one apparatus is required for any number of products. If batch distillation times of at least 12 hours can be used the cost of start up and shut down can be relatively unburdensome and batch systems up to about 10000 gal. capacity are common.

Usually multicomponent systems are rather complex and several binary and multicomponent azeotropes can occur. Two liquid phases are also possible and complete separations of such complex systems may be extraordinarily difficult. In the worst cases it may not be technically or economically feasible to separate more than several impure fractions of different boiling-point ranges, as is done in refining petroleum to make fuels. In such cases each different mixture may require laboratory experimentation to develop a purification process because insufficient data will be available for design calculations. Such processes can entail combinations of continuous and batch distillations, decanting, multistage extraction and chemical treatment. For example, methanol-toluene-water can be separated by combined distillation decantation and separate stripping steps; MEK-toluene-water can be separated by combined single-stage extraction, continuous distillation and batch distillation[ethanol-ethyl acetate-water involves three binary azeotropes and requires multistage fractional extraction, binary distillation and azeotropic distillation. Figure 12 illustrates, in the form of a decision tree, the kind of thinking which underlies the development and design of a solvent separation/purification system.

Charts for installed costs for both carbon adsorption recovery systems and for distillation purification equipment can be found in Reference 46. The costs shown are in December 1975 dollars (a Marshall & Stevens Process Industries Average Index of 451) but they can be brought up to July 1982 (Marshall & Stevens Index - 775) by multiplying by the ratio 775/451).

Figure 12. Decision tree for solvent separation



DECISION TREE FOR SOLVENT SEPARATION

WASTES AND WASTE WATER TREATMENT

Introduction

Drug manufacturing is often considered in terms of several different generic types of operation: synthesis of certain drugs by chemical means, production of certain drugs by fermentation operations, extraction of drugs from botanical raw materials, production of biological drugs from human blood fractions, animal sera and the like and formulation and packaging of drugs. Most drug manufacturing operations usually take place in multipurpose plants that can be used to synthesize a number of different drugs in different time periods. Moreover, drugs synthesized by microbes during fermentation processes usually require one or more subsequent chemical-synthetic steps to convert the microbial product into the form that is ultimately packaged and sold. Drug raw materials extracted from botanicals usually also require similar chemical finishing steps. So do the so-called biologicals. Finally, it is not unexpected that formulation and packaging of drugs would be done at the same industrial location where production is accomplished.

Often the wastes produced by each type of pharmaceutical operation are discussed and characterized separately in written reports. Nevertheless it is common practice for the wastewaters from several different types of operation at the same plant site to be mixed together and purified by treating the mixture. On the other hand, solid wastes and solvent wastes should be kept segregated and disposed of separately.

Each type of drug-manufacturing operation will produce wastewaters and dirty or "used" organic solvents. To the extent possible, the organic solvents should be recovered, purified and re-used; they should be kept out of and, where necessary, stripped from the wastewaters. The reasons for segregating the organic solvents are manyfold; not only is it good economic practice to recover and re-use expensive organic solvents, but these solvents contribute enormously to the pollution content of wastewaters if they are not removed. For example, a typical ketone solvent has a BOD of about two million mg/ml. The stronger the wastewater, the more costly it is to purify by any treatment.

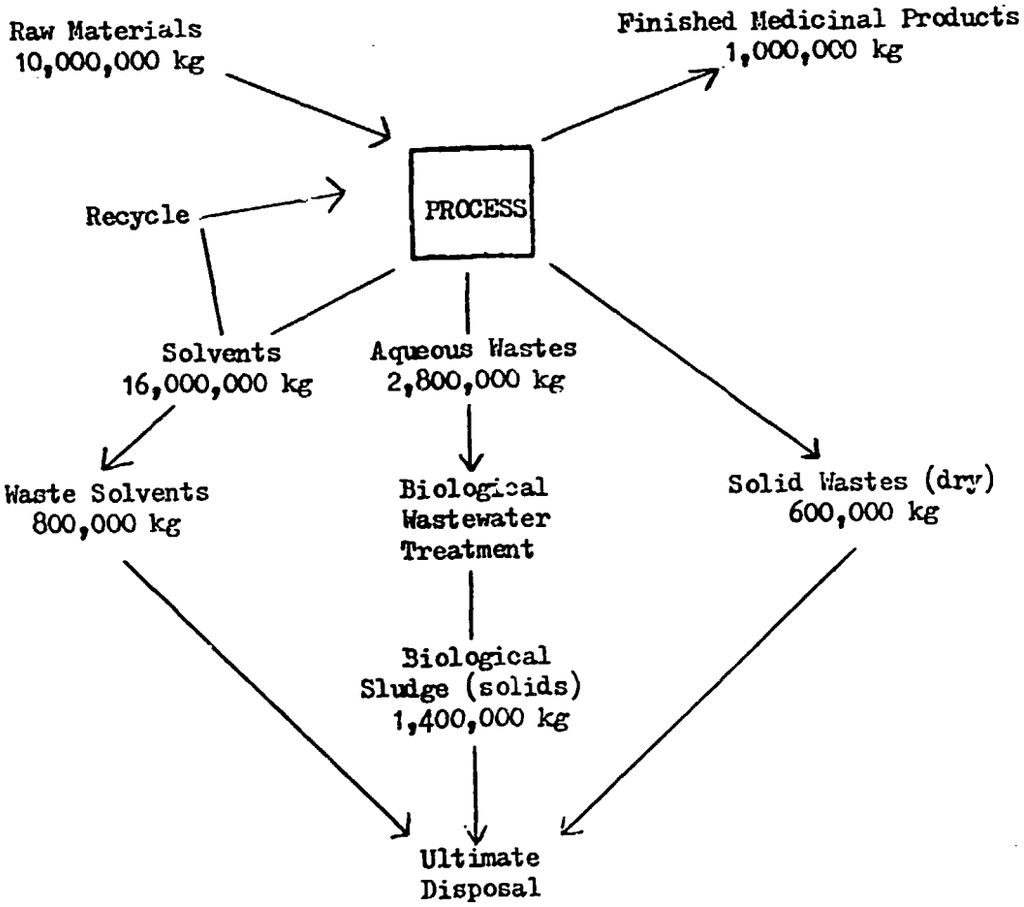
Organic solvents are usually purified and recovered by distillation; in addition to purified solvent, this operation also produces a residuum or "bottoms" product in which impurities are concentrated. Such residua are extremely high-strength pollutants and should not be mixed with wastewaters. Instead, they should be incinerated and the heat thereby produced used to make steam for process heating in the manufacturing operation. Care must be exercised with halogenated solvents which require special corrosion-resistant incinerators to cope with the HCl often produced when such solvents are burned.

Solid wastes are produced in some but not all drug-manufacturing processes. Such solids should be kept out of the wastewaters and disposed of by sale, by incineration or by burying in a landfill. Spent, solid catalysts can often be returned to the manufacturer for a credit reflecting the metal values that can be reclaimed from the catalyst. Among solid wastes that can be sold are the cell mass or mycelium from certain fermentation operations (as an animal feed, a fertilizer or a soil conditioner) and the residual protein (as an animal feed) from extracted animal glands used to make insulin. Unfortunately not all solid waste can be sold in this way; examples include filter cakes which often contain "filter aid" and residual plant material, remaining after the extraction of active botanicals, e.g. the solid mass left behind after reserpine is extracted from the roots of the rauwolfia plant. Whenever possible solid wastes that cannot be sold should be incinerated. Only as a last resort should they be disposed by burial. It should be remembered that rainwater percolates through such burial or landfill grounds and leaches high-strength pollutants from buried wastes. Because such leachate eventually enters surface or ground waters, current good landfill practice requires that the entire burial site be lined with a membrane to catch the aqueous leachate and that such aqueous leachate be pumped to a wastewater treatment plant.

Figure 13 shows schematically the types of wastes and relative amounts of wastes, products and raw materials from a typical synthetic-chemical drug-manufacturing process[48/]. A similar diagram might apply to each drug under consideration in this report, but the relative amounts of each stream will be different depending on the particular drug.

Figure 13.

MATERIALS FLOW FOR A TYPICAL SYNTHETIC ORGANIC MEDICINAL CHEMICAL PROCESS



Source: Arthur D. Little, Inc., estimates

General Waste Management

Certain general rules and manufacturing management procedures can decrease substantially the amount and strength of waste waters, and can therefore lower treatment costs substantially. The first such practices that might be mentioned are some set forth by the U.S.F.D.A:

1. Each significant step in the process, such as the selection, weighing, and measuring of components, the addition of ingredients during the process, weighing and measuring during various stages of processing, and the determination of the finished yield, shall be performed by a competent and responsible individual and checked by a second competent and responsible individual.

2. All containers, lines, and equipment used during the production of a batch of a drug shall be properly identified at all times to indicate accurately and completely their contents and, when necessary, the stage of processing of the batch.

Adherence to such rules will provide a close check on raw materials and products and permit a close watch over inventories, spills and inadvertent discharges.

Special care should be taken to keep antibiotics out of the waste waters and to neutralize acidic wastes before sending them to biological treatment. Excess acidity or high antibiotic concentration can inhibit the organisms responsible for biological treatment processes (e.g. activated sludge or trickling filter units), and thereby upset the treatment process. Table 9 gives the minimum concentrations of various antibiotics necessary to inhibit certain important microorganisms. Pharmaceutical wastes are also generally toxic to higher organisms; in fact, a recent study from a developing country shows how such toxicity to fish and seedlings can be used as a bioassay technique for raw and treated pharmaceutical wastes[49/]. Bioassay using fish is the best indicator of waste water toxicity[50/].

Table 9

Minimum Concentrations of Antibiotics Required
for Complete Inhibition of Organisms

Affected Organisms	Penicillin (mg/l)	Streptomycin (mg/l)	Aureomycin (mg/l)	Chloramphenicol (mg/l)	Ilotycin (mg/l)
Ps. Aeruginosa	Profuse Growth	50-1,000	50-1,000	200-1,000	250
B. Proteus	10-1,200	12.5-1,000	12.5-400	3.1-50	250
Esch. Coli	38-6,000	6.3-1,000	3.1-25	3.1-25	62.5
A. Aerogenus	375-6,000	0.8-1,000	6.3-200	3.1-50	--
K. Pneumoniae	5-600	0.8-1,000	6.3-50	1.6-25	62.5

It is also very important to remove solids from the wastewaters before biological treatment and good practice requires that wastewaters from chemical synthesis and fermentation be filtered before release to biological treatment.

Good practice also requires that "equilization" be an integral part of wastewater management. Equalization is nothing more than a holding and mixing step in a large volume (e.g. a large tank, basin or impoundment) where many different wastewaters are mixed and held for a period of time before passing on to a biological treatment step. During "equalization" very strong wastes get diluted, acid content gets neutralized or diluted (pH increased), antibiotic content gets diluted and suspended solids, (not previously removed by filtration) settle to the bottom of the container where they must be removed periodically. It is usually in the equilization step that high-strength waste waters (from chemical synthesis or from fermentation broths, for example) might be mixed with lower-strength wastewaters (from sanitary sewers or from cooling operations, for example).

A very important general rule is to keep out of the waste waters any component it is possible to keep out. For example, organic solvents should not be allowed to enter wastewaters and mycelia from fermentation should be carefully filtered from the broth. Mycelia should be used as animal food, as fertilizer or as a soil conditioner. Solvents should be recovered and re-used. Any organic solvents that are in aqueous wastes should be stripped out to the greatest extent possible before sending the wastewaters to equalization and biological treatment. Such solvent recovery not only saves raw materials costs but also reduces waste-treatment costs. Organic solvents are such high strength wastes that it is generally considered good practice to install automatic devices for monitoring wastewaters streams for excess solvents that could arise from spills, leaks or other malfunctions. Alarms connected to the monitors can provide warning in sufficient time to intercept and prevent high concentrations of solvent from flowing to equalization or biological treatment steps.

Another frequent practice that is often followed is to evaporate spent fermentation broth rather than mix it with other wastewaters. The syrup which results from the evaporation usually is high in nutrients, minerals and vitamin content (expecially B vitamins) and often can be sold as an animal feed supplement. This practice keeps a high-strength waste from entering the biological treatment process thereby reducing the cost of treatment. Whether it is more economical to evaporate waste fermentation broths, or to treat them biologically, is a decision that must be supported by design and analysis. Evaporation will entail high fuel usage but lower investment cost compared to biological treatment for which the initial investment costs will be higher but operating costs generally lower.

As an example, the following measures were recommended[51/] to Bristol Laboratories at its fermentation plants in Syracuse, NY in 1951:

- o Remove formaldehyde from wastes to prevent bacterial inhibition in the waste treatment
- o Install stripping towers to remove solvents from wastewaters
- o Remove all mycelium
- o Eliminate process leaks
- o Sample and test all wastewaters for the presence of organic solvents
- o Carefully programme and monitor the discharge of fermentation wastes
- o Neutralize acid wastes
- o Provide waste equalization
- o Inform management of the wastewater treatment plant of any changes in process operation that might affect the amount and properties of the wastewaters.

Waste Waters

Pharmaceutical plants (i.e. formulating and compounding operations) usually produce only small amounts of easily treatable wastes, most of it sanitary waste that correlates in amount with the number of employees. Chemical synthesis operations produce the most difficult-to-treat effluents and these are generally combined with other wastewaters, or with domestic sewage, before biological treatment. Spent fermentation broth (beer) generally is a high-strength waste containing residual nutrients. It can sometimes be evaporated to a syrup suitable for use as an animal feed; it can also be treated biologically and is generally diulted with other wastewaters e.g. domestic sewage or waste liquors from a paper mill, before biological treatment. Production of biologicals often entails the use of live animals and the water run-off from such operations is the major wastewater which can be readily treated biologically.

In a survey of plants which manufacture drugs and pharmaceuticals[52/] was found that the wastewaters produced were often discharged as a combined plant effluent to a public collection system for treatment at a central plant. In other cases the manufacturing plant treated its own mixed wastewaters by a settling step, followed by a biological oxidation step that could be either a trickling filter or an activated-sludge operation. The effluent from the biological treatment would often be passed through a sand filter before chlorination and discharge to a stream.

Table 10 is a summary of treatment levels, treatment costs, and BOD and COD levels for the various USA plants surveyed[52/] that practiced self treatment. Table 11 summarizes the wastes produced and removed, on an average basis for a number of different types of drug manufacturing plants which treat their own wastes and have been surveyed[52/]. The averages in Table 11 are based on data for plants which used a wide variety of treatment processes. The three "pharmaceutical" plants all used a type of biological oxidation process. Of the four "chemical/pharmaceutical" plants, two used biological oxidation, one dilution and segregation, and the treatment used by the fourth was not defined. "All other plants" refers to averages for seventeen plants using a wide variety of treatment processes.

Table 10

Costs and Treatment Levels
Plants with Self-Treatment

Plant Category and Company Code	Treatable Effluent Gals/Mo	Treatment Cost $/Year	Treatment Cost $/1000 Gals	BOD in Raw Treatable Effluent #/Mo	BOD in Treated Effluent #/Mo	Percent Reduction in BOD	COD in Raw Treatable Effluent #/Mo	COD in Treated Effluent #/Mo	Percent Reduction in COD	Percent Reduction in Suspended Solids
Pharmaceutical Plants										
1,695	1,777,000	36,750	1.72	1,630	219	87	2,800	310	89	59.0
2,467B	1,413,000	42,100	2.48	3,200	240	92	5,750	790	86	--
8,297B	3,100,000	36,000	0.97	4,500	400	91	13,200	860	91	--
Weighted Average			1.52			91			90	--
Chemical Plants and Pharmaceutical/ Chemical Plants										
1,712A	5,950,000	43,460	0.61	150,000	6,940	95	212,000	--	--	--
3,897B	1,700,000	200,000	9.80	2,870	1,760	39	4,040	3,510	13	--
5,722B	47,350,000	390,000	0.69	520,000	79,000	85	854,000	395,000	54	67
7,794B	3,000,000	41,700	1.12	79,000	7,160	91	124,000	17,150	86	--
Weighted Average			0.97			88			59	--

Cost estimates reflect operating costs and capital amortization. They are probably given in 1973 dollars.

Table 11

Effluent Summary for Self-Treating Plants

Weighted Averages		Pharmaceutical Plants Self-Treating		Chemical Plants and Pharmaceutical/Chemical Plants Self-Treating		All Other Plants Self-Treating	
		In Raw Effluent	In Treated Effluent	In Raw Effluent	In Treated Effluent	In Raw Effluent	In Treated Effluent
BOD_5	Pounds per Month per Employer	3.18	.29	687	85	291	35
	Pounds Per 1000 Pounds Raw Mat'l	5.2	.47	134	16.7	123	15
COD	Pounds per Month per Employee	7.4	.66	1,620	670	882	183
	Pounds per 1000 Pounds Raw Mat'l	53.3	3.8	175	73	276	57
Suspended Solids	Pounds per Month per Employee	←Insufficient Data→				75	8.6
	Pounds per 1000 Pounds Raw Mat'l	←Insufficient Data→				42.7	4.9
Percent BOD Removal		91		88		83	
Percent COD Removal		90		59		79	
Percent SS Removal		--		--		84	

Wastewaters from The 26 Drugs

Table 12 is a summary of the wastes expected from the manufacture of the 26 drugs reviewed in a previous section of the report. It is seen that most drugs will entail the formation of a solid waste and that solvent recovery should be practiced in almost every case. Organic solvents should always be considered hazardous; they can ignite easily, their vapors are explosive and they can be very toxic to man and to the microorganisms which are used in biological waste treatment systems. Aside from organic solvents however, Table 12 indicates that hazardous wastes such as mercury and chromium compounds are generally not expected to arise from the manufacture of these 26 drugs. There is only one possible exception, the possibility that some cyanide ion may enter the waste waters from the manufacture of drug number 25, hydroxycobalamin.

It is further evident from Table 12 that a fermentation process, and therefore fermentation wastes (i.e. broth and mycelia), is associated with only about one third of the 26 drugs on the list.

It is impossible to predict here a product mix for a typical future manufacturing plant which would produce some of the 26 drugs in a developing nation. For this reason only typical examples of waste production can be given; one such is shown in Figure 13 for the production of 500,000 kg of synthetic organic medicinal chemical products. An other example is shown in Table 13 for production of penicillin G, Table 14 for production of botanical medicinals (e.g., reserpine), and Table 15 for production of insulin and Figure 15 already given in the previous section for manufacture of blood fractions.

Waste Water Treatment Technology

Biological waste treatment is the most commonly used method of purifying wastewaters from modern, drug-manufacturing plants. In these treatment technologies a mixture of microorganisms converts a waste of complex organic molecules into simple products (such as CO_2 and H_2O) and into additional

Table 12

Drug	Solid Waste	Hazardous Waste*	Fermentation Waste	Solvent Recovery	Pyrogen-free Process Water
1	Yes	No	No	No	No
2	Yes	No	No	Yes	No
3	No	No	No	Yes	No
4	Yes	No	Yes	Yes	Yes
5	Yes	No	Yes	Yes	Yes
6	Yes	No	Yes	Yes	Yes
7	Yes	No	Yes	Yes	Yes
8	No	No	No	No	Yes
9	Yes	No	Yes	Yes	No
10	No	No	No	Yes	No
11	Yes	No	No	Yes	No
12	No	No	No	Yes	No
13	Yes	No	No	Yes	No
14	Yes	No	No	No	No
15	No	No	No	Yes	No
16	Yes	No	Yes	Some	Yes
17	No	No	No	Perhaps	No
18	Perhaps	No	No	Yes	Yes
19	Yes	No	No	Yes	Yes
20	No	No	No	Perhaps	Yes
21	Yes	No	No	Yes	Yes
22	No	No	No	Yes	No
23	Yes	No	No	Yes	Yes
24	Perhaps	No	Depends on process	Yes	No
25	Yes	Perhaps CN^-	Yes	Yes	Yes
26	Perhaps	No	No	Yes	No

*Other than organic solvents

Table 13

Typical Antibiotic Production Plant
(Procaine Penicillin G)

A.	Annual Production	950,000 kg		
B.	Waste Characterization			
			Weight per 1000 kg Product	
	Non-Hazardous Waste	Stream No.	Dry	Wet
	Mycelium	1	2,300 kg	10,000 kg
	Biological sludge	9	3,500 kg	35,000 kg
	Non-Hazardous Waste to Biological Treatment			
			Liters per 1000 kg Product	
	Waste fermentation broth	3	56,000	
	Crystallization water	4	100	
	Phosphate buffer solution	5	3,000	
	Crystallization water	7	100	
	Potassium chloride solution	8	4,000	
	Hazardous Waste			
			Liters per 1000 kg Product	
	Solvent Waste Concentrate	2	1,200	
	Solvent (butyl acetate)		600	
	Dissolved organics (fats, protein)		600	

Table 14

Typical Plant for Producing Botanical Medicinals
(Plant Alkaloids)

A. Annual Production 680 kg

B. Waste Characterization

	Stream No.	Weight per kg Product		
Non-Hazardous Waste		Dry	Wet	
Wet botanical material	1	330 kg	660 kg	
		kg per kg Botanical Material	Quantity per kg Product	
			Liters	kg
Hazardous Waste				
Halogenated solvent	2	0.03	7	9
Methanol--water concentrate	4	0.36	130	120
Non-halogenated solvent	3	0.06	30	20

Table 15

Typical Plant for Producing Medicinals from Animal Glands
(Insulin)

A. Annual Production 284 kg

B. Waste Characterization	Stream No.	kg per kg Animal Glands (Dry Wt.)	kg per kg Product Dry	kg per kg Product Wet
Non-Hazardous Waste				
Rendered pancreas	1	0.94	3000	--
Protein and filter aid	2	0.025	80	160
Recovered fats	3	0.04	140	--
Protein and filter aid	4	0.006	20	40
Ammonium sulfate/ sodium chloride	5	0.125	400	--
Insulin precipitation wastewater	7	0.022	--	70

			Quantity per kg Product	
			Liters	kg
Hazardous Waste				
Waste solvent concentrate (ethanol, methanol, water, fats, oils)	6	0.10	350	320
Precipitation wastewater (may contain traces of zinc)	8	0.025	80 (1-5 gm Zn per kg product)	80

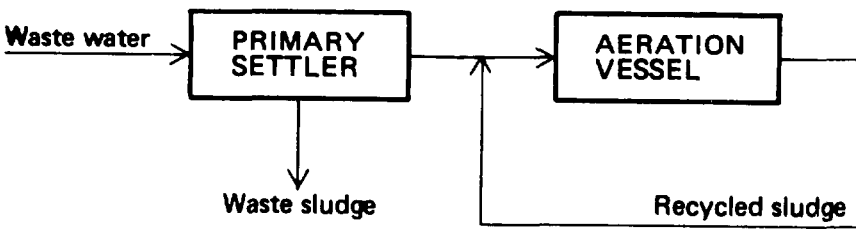
biological cell mass. There are two major biological treatment processes used to oxidatively purify wastewaters from drug manufacture: the activated sludge process and the trickling-filter process, each of which are described below.

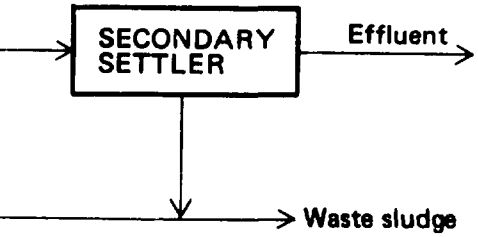
1. Activated Sludge Treatment

The treated wastewater from this process is separated from the active microorganisms (usually by gravity settling) and a portion of the separated biological solid mass (sludge) is recycled to the beginning of the process where it is mixed with incoming wastewater and oxygen. The recycled biomass sludge oxidizes a portion of the organic compounds in the wastewater feed to CO_2 and H_2 and incorporates another portion into newly grown cell mass. Both soluble and suspended organic matter can be removed from the water by such reactions.

Conventional activated-sludge treatment systems make use of an aeration vessel followed by a settling vessel where the sludge is separated. These vessels are connected by a pipe through which a portion of the settled sludge is recycled to the aeration vessel. Referring to Figure 14, wastewater from the primary settler (which may also serve as an equalization basin) is mixed with recycled sludge and the mixture enters one end of the aeration vessel which is usually rectangular. As the mixture flows through the aeration vessel it is charged with air bubbles. During passage of the mixture through the aeration vessel the organisms in the activated sludge convert the organic wastes to gases, to additional cell mass and to other oxidized compounds. The excess biological sludge formed during this process is removed as a waste. The recycled sludge is returned to the front of the process at a rate about equal to 25 - 35% of the inlet wastewater flowrate. The microorganisms consume oxygen at a more rapid rate near the front end of the aeration vessel where the concentration of organic wastes (BOD, COD, TOC) is greatest. In many installations the aeration rate can be gradually reduced along the length of the aeration vessel provided the oxygen concentration in the liquid is kept at least as great as 2 mg/l throughout the vessel.

Figure 14. Activated Sludge Process Flowsheet




SECONDARY
SETTLER
Effluent
Waste sludge

Some important typical design parameters[53] of conventional activated sludge processes are as follows:

Loading = 0.02 - 0.04 lb BOD/ft^3-day
Sludge age = 3 - 14 days
Residence time = 4 - 8 hours
Removal Efficiency = 85 - 95% of the BOD
Solids Concentration = 1100 - 3000 mg MLSS/litre
Sludge Volume Index (SVI) = 35 - 100 ml/g
Recycle Ratio = 0.15-0.75

The residence time is approximately the average time the wastewater spends in the aeration vessel. Likewise the sludge age is approximately the mean residence time of the solids in the system. If sludge is not recycled its age is the same as the residence time of the feedwater; increasing the fraction of sludge recycled increases its mean age or residence time.

It is important that sludge age be between 3 - 14 days to insure that its handling and settling characteristics be in the proper range. Sludges younger than about three days usually contain biological flocs insufficiently derse to settle at a conveniently rapid rate, and a "bulking sludge" is said to be produced. In sludges older than about 14 days the floc particles are usually too small to settle rapidly and the fraction of living cells in the sludge is low. Good sludge settling characteristics are essential for the proper separation of sludge from the wastewater in the secondary settler; rapid, reliable settling is necessary for overall stability of the steady-state operation of the process. The sludge age is set by proper choice of sludge recycle rate and rate of rejection of waste sludge from the process. The nature and properties of the sludge are also strongly influenced by the nature and composition of the wastewaters. So setting the proper sludge age must be based on empirical measurements and experience with the particular wastewaters being treated. A commonly used empirical measure of sludge settleability is the sludge volume index - volume (ml) of sludge (after 30 minutes of settling) per gram of dried solids.

The loading factor is sometimes called the food-to-microorganism ratio nd falls in the range 0.2 to 0.6 mass BOD/mass MLSS-day. This range is closely and quantitatively related to the desired range of sludge age of 3 - 14 days. These ranges are typical of many processes but it is not unexpected that desirable operating parameters for a particular wastewater from pharmaceutical manufacture might fall outside these ranges.

Production yields of waste sludge usually fall in the range of 0.3 - 0.9 mass of dry solids per mass of BOD removed. Often a significant fraction of the total volatile solids in a sludge is biologically inactive, as much as 25 - 50% for a typical municipal waste.

There are a number of variations of the basic activated sludge process. For example, the conventional long, rectangular aeration tank ordinarily provides that the sludge-wastewater mixture pass through it in an approximation to plug flow. It is possible to substitute a cylindrical, mechanically-stirred aeration vessel for the rectangular tank, thereby providing a well mixed volume and a situation approximating perfectly back-mixed flow. The well mixed tank is more resistant to "shock loads" (i.e. sudden increases) of BOD or toxic compounds in the feed wastewaters because it very rapidly dilutes abrupt concentration fluctuations. "Step aeration" is another variation in the flow pattern in which the retangular aeration tank is retained but the wastewater is fed into the tank at various points along its length while the recycled sludge traverses the entire length of the tank. This flow arrangement keeps the ratio of applied BOD/sludge more uniform throughout the tank and provides for a more uniform consumption rate of oxygen throughout the tank. Often the arrangement allows higher throughputs of wastewater because of more uniform and higher average oxidation rates throughout the aeration tank. "Contact stabilization" is a process arrangement which separates the two separate steps of (1) absorption of organic waste components from the water into the sludge (i.e. the contact) and (2) the slower oxidation step within the sludge (i.e. the stabilization). In this variation the sludge and waste water are mixed and remain in the "Contact tank" for about one hour, the time required for absorption; then the sludge is separated from the wastewater

and the portion of the sludge to be recycled is aerated in the "stabilization tank" for an additional 3 - 6 hours required for the oxidation step. Because only a concentrated sludge, and not the wastewater, is aerated, aeration tank volumes can be reduced considerably (up to about 50%) by this arrangement.

Another relatively recent variation of the activated sludge process is to use pure oxygen rather than air to achieve higher rates of oxygen transfer and help maintain dissolved oxygen concentration above the critical value of 2 ppm, even under conditions of shock loads. A typical system is Union Carbide Corporation's UNOX process in which oxygen, wastewater and recycled sludge flow concurrently through several well mixed stages consisting of covered agitated tanks. Pure oxygen systems can usually be designed based on a higher loading parameter than for air systems, in some cases up to about 1.0 mass BOD/ mass MLVSS - day. This permits more treatment capacity to be installed in the same volume and can be viewed as a useful approach where there are space limitations, or as a method of expanding the capacity of an existing, conventional activated sludge system without having to make substantial increases in aeration-tank capacity. On the other hand, this kind of process requires more highly trained operators and more maintenance than the more conventional biological oxidation processes. For these reasons, as well as because of the need for a supply of pure oxygen, pure-oxygen treatment processes may not be appropriate for use in developing countries. To give one example, Lederle Laboratories installed a UNOX pure-oxygen process at its Pearl River N.Y. plant which produces fermentation products and biologicals[51].

2. Trickling Filters

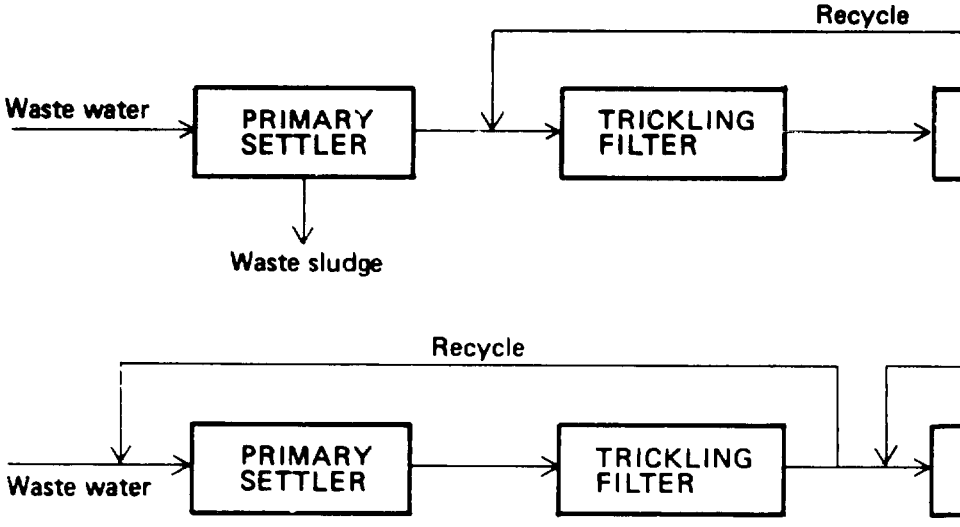
Although their BOD removal efficiency is less and they require more land area, trickling filters are generally regarded as costing less to operate and having a simplicity that demands less skill of the operators who run them. For treating pharmaceutical wastes trickling filters are more common in England than in the U.S. When they are designed with large recycle ratios which provide large dilution rates, trickling filters are often able to withstand shock loads.

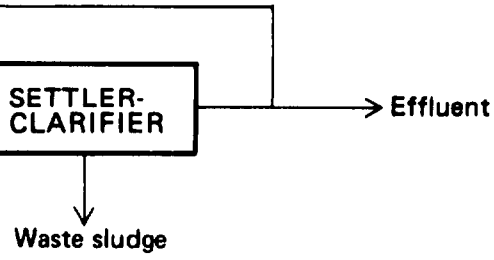
A trickling filter is made up of a deep cylindrical bed of gravel, stone, stag, clinker, plastic forms or similar material usually in the size range of about one to 2.5 inches. In use, a layer of microbial growth forms on the surface of the packing material in depths ranging up to about two millimeters. It is this layer that absorbs the organic waste components from the water and oxidizes them under aerobic conditions. Both oxygen and waste molecules must diffuse into this film in order for biological oxidation to be accomplished. If the COD of the wastewater is less than about 400 - 500 mg/liter the rate of oxidation is controlled by the rate of diffusion of organic material in the biological film[53]. For larger COD values the rate of the process is limited and controlled by the rate of oxygen transport into the film. It is for this reason that when such trickling filters are used to treat high-strength industrial waste the interior of the microbial films can get depleted in oxygen and generate unpleasant oders usually associated with anaerobic microbial processes in such biomass.

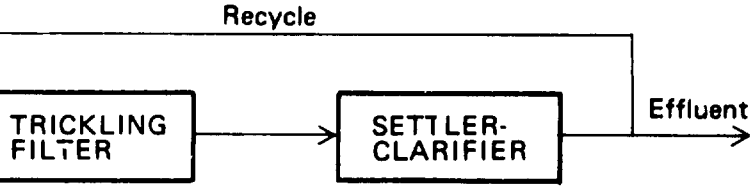
The flow scheme for using trickling filters is similar to activated sludge arrangements in that the process is preceded by a primary settler upstream and a secondary settler downstream. An important difference is that liquid effluent, rather than concentrated sludge, is recycled back to the front end of the trickling filter and mixed with wastewater feed. Figure 15 shows this type of flow scheme for a single trickling filter with recycle of clarified effluent as well as a two-stage trickling-filter flow scheme in which the recycle pattern is more complex. Recycle ratios ranging from one to three are normal in order to insure sufficient flow through the filters to keep all portions of the packing wet. Such recycle also dilutes the feed thereby damping out "shock load" fluctuations in wastewater concentration.

Design of trickling filters are usually classified according to liquid "loading": low rate (1-10 million gal/acre-day (MG/AD)), high rate (10-30 MG/AD) or super rate (30-150 MG/AD). Corresponding waste loadings (lb BOD/cu ft - day) are 5-30, 30-60 and 50-100. Removal efficiencies for all three types range from about 70 - 90% removal of BOD.

Figure 13. Trickling Filter Effluent Treatment Flow Sheet




SETTLER-
CLARIFIER
Effluent
Waste sludge


Recycle
TRICKLING
FILTER
SETTLER-
CLARIFIER
Effluent

3. Other Methods of Biological Treatement

Those worthy of mention here are lagoons and ponds, anaerobic digestion and rotating biological contactors. Lagoons or ponds generally require considerable land area and can generate odors. Where land is cheap, however, this kind of approach may provide practical intermediate solutions for some developing countries where simplicity of operation and ease of maintenance might be very important. Such treatment basins open to the air can simultaneously accomplish settling and some biological oxidation by diffusion of oxygen into suspended or settled microorganisms.

Anaerobic digestion is generally used to decompose and thus lower the volume of waste biological sludge. The complex process of anaerobic breakdown of organic matter is usually viewed as occurring by two consecutive steps; (1) conversion to volatile organic acids and (2) conversions of the acids to products such as methane and CO_2. The slowest step is methane formation and it can be impeded by too rapid a build up of acids to give pH's that are too low (< 6.2). The methane generated by anaerobic digestion can be burned to provide process heat or space heating. Rotating biological contactors are large plastic disks upon which an active biological film is kept in growth. While half submerged in the wastewater the disks are rotated so that the surface film is alternately exposed to waste water and to air. The biological growth on the disks assimilates and oxidizes organic molecules from the wastewater solution in a manner similar to the film on the packing of trickling filters ; they are also similar to trickling filters regarding low energy requirements and simplicity of operation and maintenance.

4. Tertiary Treatment Methods

The initial operations to remove suspended solids from wastewater are often called "primary treatment" (e.g. primary settling). Biological oxidation with associated "secondary" settling of solids is usually called "secondary treatment". "Tertiary treatment" is sometimes used to remove pollutants not removed from the wastewater by primary and secondary treatment. The most important tertiary processes are absorption on activated carbon and denitrification. For example, tertiary treatment at the Beerse, Belgium, plant of Janssen Pharmaceuticals consists of sand filtration, followed by

contact with activated carbon and finally disinfection using ultraviolet light. A portion of this tertiary-treated water is used for cleaning and maintenance instead of being discharged.

Adsorption on activated carbon provides efficient removal of dissolved organic compounds and should be considered for removal of those organic compounds not susceptible to biological oxidation. Wastewaters from chemical/pharmaceutical manufacturing are likely to contain significant quantities of such "biologically refractory" organic compounds. In such cases both BOD (biochemical oxygen demand) and COD (chemical oxygen demand) should be used as measures of wastewater pollution and of removal efficienty of a wastewater treatment process. Activated carbon absorption should be considered for lowering wastewater COD if secondary biological treatment does not do this sufficiently. BOD is a measure of concentration of pollutants that can be oxidized by biological processes whereas COD is measured in terms of the amount of pollutants that can be oxidized by a strong chemical oxidizing agent. Because of the measurement methods and definitions, COD generally includes BOD and the COD value of a waste water is generally considerably larger than the BOD value. The major reason is that COD includes the effects of to the biologically refractory pollutant compounds.

Nitrogen in sanitary waste waters is generally present in a reduced chemical state, e.g. as amino groups of organic compounds. The oxidation state of nitrogen in industrial wastes will vary greatly, of course, depending on the chemical nature of the wastes.

During biological treatment the organic amino nitrogen is usually converted into dissolved ammonia or, if biological oxidation is sufficiently extensive, the ammonia can be oxidized further to nitrate (nitrification). Depending on the nature of the wastes, the receiving wasters and the relative volumes of each, nitrification may be desirable or not. In some instances release of ammonia containing wastes should be avoided and this can be accomplished by extensive secondary biological oxidation to remove ammonia by nitrification.

In some instances nitrate can be a serious pollutant and in such cases it may become necessary to introduce a separate denitrification process to convert the nitrate in the wastewaters to harmless nitrogen. Such processes employ a separate biological sludge-based redox process in which an organic reducing agent such as methanol may be added purposely to reduce nitrate to nitrogen.

5. Other Methods

Some other methods which have been used for treating wastewaters are land disposal (spray irrigation), anaerobic fitration, oxidation ponds and deep-well injection (soil injection).

Land disposal has been successful in many instances but its applicability is very strongly dependent on climate, terrain, the nature of the crop and the nature of the wastewater. In particular, a season of freezing temperatures can make the entire system ineffective and inoperable. In any event, frequent testing of surface waters and groundwaters in the locale must be performed to monitor the extent of removal of contaminants and determine their possible migration into water supplies. Reference 54 gives extensive discussions of the limitations of the various methods of land disposal.

Anaerobic filtration is an effective treatment method but the deep filters gradually become saturated and plugged by solids. At some stage they must be dug out, cleaned and new filtration media installed, or they can be abandoned altogether. Sometimes underdrained volumes of porous ground or earth can be employed and the capacities of such arrangements are difficult to design or predict. In any event removal of nitrogen and heavy metals can be less effective then desirable and continual monitoring of effluents is usually necessary.

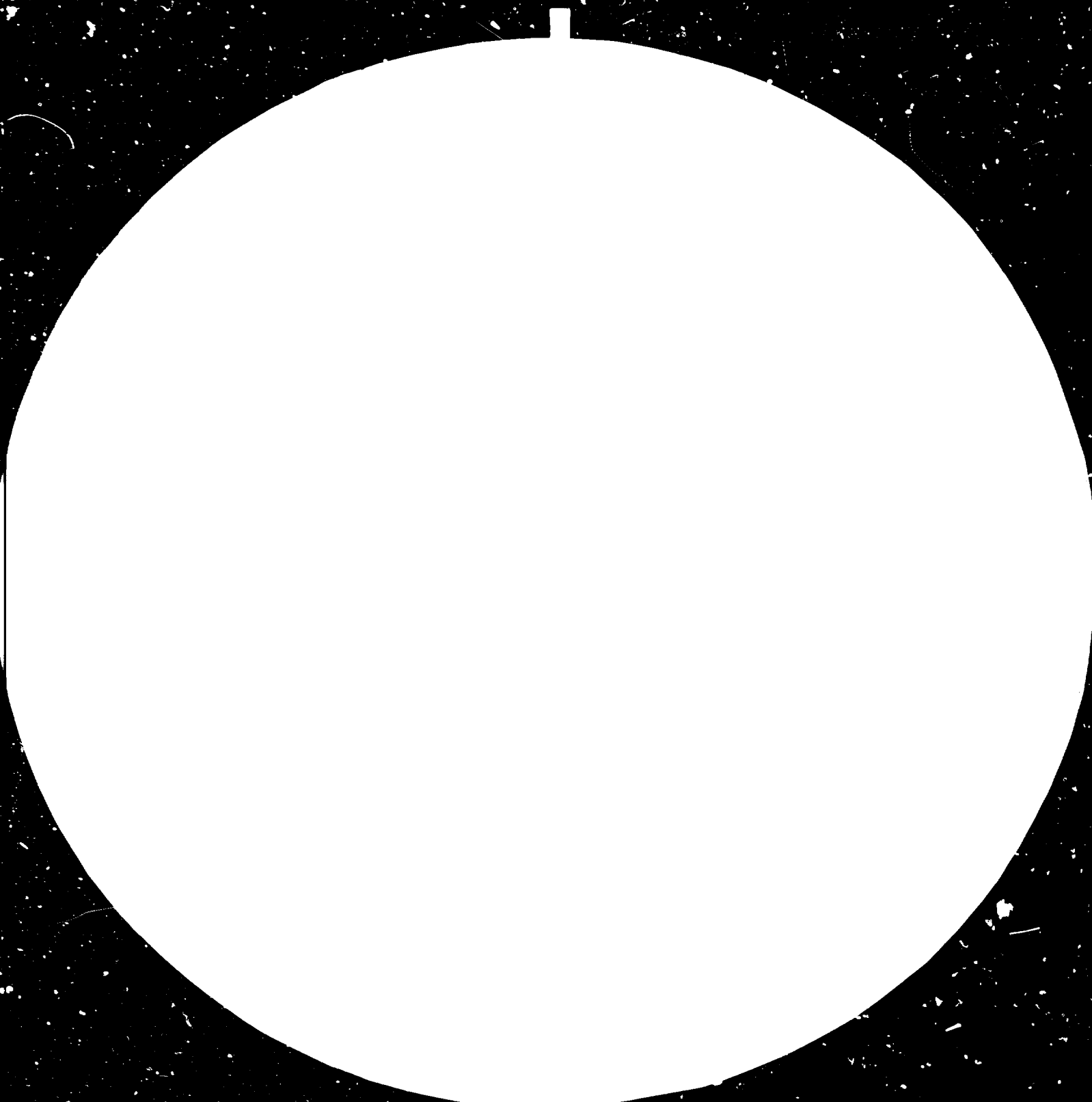
Anaerobic treatment of industrial waste has seldom been applied to industrial waste treatment. This is due to the long residence time needed, the inherently slow reaction rates and the usual situations of high flow rates of dilute waste. The long residence time implies large treatment-vessel volumes and associated high investment costs. Recent developments[55/], however, now promise reduced residence times for anaerobic processes. High investment

costs can also be offset by recovery of the methane that is produced in the anaerobic process, thereby make anaerobic treatment more competitive and attractive as an industrial waste treatment process. In this reference (55) Pipyn et al. report a situation where anaerobic digestion became a suitable alternative where aerobic treatment proved difficult. At a distillery in Belgium aerobic treatment was not satisfactory due to high COD levels and abundant sludge production. In addition, the intensive aeration of the waste water caused a serious odour problem and the aerobic sludge tended to float, leading to only a 40% COD reduction (80% reduction with centrifuging). A two-stage anaerobic process designed[55/] to overcome this problem provided 80% reduction of COD and 90% BOD reduction. Furthermore, it produced more than 1.8 million Nm^3 biogas per year and withstood stress conditions. This shift from aerobic to anaerobic treatment resulted in an annual saving of 640,000 DM in electricity costs and the excess gas was valued at 500,000 DM per year for a net savings of 1.1 million DM per year. The odour problem was also removed. Oxidation ponds are seldom used alone because of the adverse influence of freezing weather, the large land requirements and the possibilities of odor generation if conditions become anaerobic.

Deep-well injection is under suspicion because it appears to cause geological disturbance such as earth tremors and also because the ultimate destination and effect of the wastes remain unknown or uncertain at best.

6. Sludge Disposal

Typical sludge-treatment practices include aerobic oxidation, anaerobic digestion, centrifugation, and vacuum filtration. Typical disposal methods are landfilling, land application, incineration, composting and dumping in the deep ocean. All have their composting limitations and ocean dumping is in disrepute because of its potential adverse effects on fish and the marine food chains.

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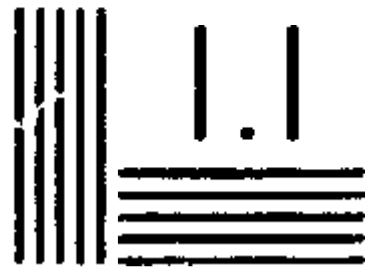
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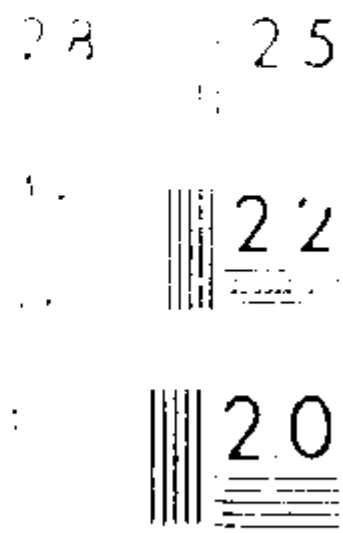
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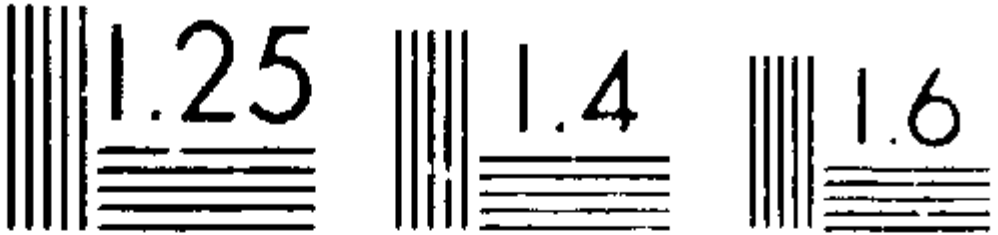
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A major problem is that sludge can contain heavy metals that can enter the food chain when certain methods of disposal are practiced. Also sludge can cause odor problems unless good practices are followed in landfilling or composting operations. Incineration can circumvent odor problems and heavy-metal problems but it is often expensive. As Carmichael[56] reports, in an American Cyanide plant manufacturing fermentation products and synthesized organic chemicals, sludges were dewatered by vacuum filtration an disposed of by landfilling. Carmichael[56] also reports on a sludge composting operation by Lederle Laboratories on 4 ha of open land which was eventually discontinued.

Examples of Waste Treatment Installations

Hoffman-Laroche, Belvidere, NJ, U.S.A.

Information taken from ref. (51) indicates that during the period of interest here this plant was using at least 80 different raw materials to manufacture sulfa drugs, vitamin C, riboflavin and various dry-powder drugs. The average waste water flow after start-up was 1,020 m^3/day (0.27 mgd) with a raw wasteload of 5,400 kg BOD/day (1,200 lb. BOD/day), projected to reach 13,600 kg BOD/day during the second half of 1972. By September 1973 the flow estimate was about 8,000 m^3/day (2.1 mgd). The investment in the wastewater treatment system was estimated at $2.6 million as of June 1972. Waste streams included industrial and sanitary waters and various blowdowns, water treatment plant sludges and regenerants.

In the treatment installation the wastewater passed first through a comminuter and bar screens into a preclarifier (284 m^3 or 75,000 gal) followed by an equalization basin (2,780 m^2 or 1 million gal). The equalization basin is equipped with two turbine-type surface aerators, each of which operate at 25 hp. The equalized wastewaters are pH - adjusted and are then treated in a deep (10 ft) floculator - clarifier (673 m^3 or 178,000 gal). Next the waters pass to an aeration basin (6m x 36.6m x 12m). From the aeration basin the waters are routed to a secondary clarifier (673m^3 or 178,000 gal), and then to two shallow oxidation ponds (each 3,780 m^3 or 1 million gal).

Finally the water is chlorinated and discharged to the Delaware River. The treatment plant also has a basin 6m x 36.6 m x 12m used as an aerobic sludge digestion tank. Another tank ($134m^3$) can be used as a sludge thickener. After drying, waste sludge is buried in a landfill.

It was estimated (ref. 51) that this plant removes about 97.5% of BOD and about 90% of TSS (total suspended solids). The range of several ratios was as follows (where TOC = total organic carbon)·

	BOD/TOC	COD/TOC	COD/BOD
influent wastewater	0.64-0.88	2.32-2.83	3.13 - 4.35
treated effluent	0.03-0.05	2.00-2.83	33.30 -142.43

The high ratios of COD/BOD and TOC/BOD for the treated water indicates the treatment process did not remove a significant proportion of the total soluble pollution.

Abbott Laboratories, North Chicago, IL, U.S.A.

An activated sludge plant was constructed in 1953 and it consisted of twin primary settling tanks (each $76m^3$ or 20,000 gal), twin aeration tanks (each 1,140 m^3 or 300,000 gal), secondary settling tanks (each $150m^3$ or 40,000 gal), a chlorination unit, a sludge filter and a land disposal operation. Design capacity of this plant was 2,720 kg (6000 lb.) BOD/day, average flow rate of $1,890m^3$/day (0.5 mgd) and 90% BOD removal.

The plant was subsequently expanded and redesigned so that in 1972 it consisted of the following·

1. Raw waste handling for chemical and fermentation wastewaters· bar screens and neutralization.

2. Equalization: two basins (each 1,890 m^3 or 500,000 gal) giving 1 to 1.5 days detention. Each basin is equipped with three 25 hp mixers.

3. Activated sludge aeration tanks consisting of six compartments (each 378m^3 or 100,000 gal). Four compartments are aerated by two 50-hp turbines and the remaining two have a single 50-hp turbine. Waste retention time is about 24hr and operating temperatures are closely controlled at 38°C ±2°C. The F/M ratio is about 0.25 (units not given in original reference - probably kg BOD/kg MLSS-day) and the optimum range for MLVSS is 8,000 - 12,000 mg/litre.

4. Degassing chamber (625m^3 or 165,000 gal) with mean residence time about 8 hr.

5. Final settling: two 18-m (60-ft) diameter secondary clarifiers ; flow rate of 1.3m^3/m^2-day (180 gsfd).

6. Sludge recycle rates of 15,100 liters/min (4,000 gpm).

7. Sludge centrifuges processing 570 liters/min (150 gpm).

8. Pasteurization (rather than chlorination) at 66°C (150° F) for 20 min.

Hydraulic capacity was about 3,780m^3/day (1 mgd), waste loading of 13,600 kg (30,000 lb) BOD/day and BOD removal was greater than 90%. Multiple-effect evaporators were also used to concentrate spent fermentation beers to make an animal feed additive, thereby helping reduce the amount of wastewater sent to the treatment plant.

Further information about this plant can be found in references[51, 57, 58, 59].

Merck, Sharpe and Dohme, West Point, PA, U.S.A.

This was a trickling filter plant completed in 1951 for treating wastewaters from drug formulation, some fermentation wastes, and sanitary and research-laboratory waste. The plant consisted of a comminutor, primary settling, two-stages of high-rate trickling filters, followed by a secondary

settler, intermittent sand filtration and final chlorination. A portion of the effluent from the first trickling filter is recycled around the first stage and a portion of the effluent from the second trickling filter is recycled back to the feed of the second filter.

This biological treatment plant was designed as follows: flow - 380m^3/day (113,000 gpd) ; BOD concentration - 1,450 mg/liter ; BOD loading - 620kg/day; TSS (total suspended solids) - 220 mg/liter ; first filter recycle ratio - 3/1; second stage recycle ration - 2/1. The cost of the plant was about $600,000 (probably 1950 dollars) and the cost of operation and maintenance in 1952 was $40,500.

Further details about this trickling filter plant can be found in references[60, 61].

Economics of Waste Water Treatment

Treatment costs ranging from $0.20 to $9.80 per 1,000 gallons have already been given in Table 10 taken from ref. 52. It is stated that these costs were furnished by Pharmaceutical Manufacturing Association member companies and reflect both capital amortization and operating costs. No further information is given in the reference however and it must be assumed that capital costs are amortized over a period reasonable for such facilities, say from 25 to 40 years. Furthermore, there is no indication in the reference as to the dates corresponding to the economic estimates. In the absence of more substantive information it is probably safe to assume the costs are in 1973 dollars because the date of the report is July 1974.

More informative cost estimates can be obtained by using ref. 54 which gives two-page capsule summaries of 113 different operations or processes used in treating wastewaters. These data sheets usually contain graphical information giving construction costs and costs for operation and maintenance as a function of process size. Examples of these capsule summaries are shown in Figures 16-18 and Tables 16-18 for flow equalization, the activated sludge process and secondary settling, respectively. Most of the costs given are in 1976 dollars but this manual[54] also gives the EPA Sewage Treatment Plant

Table 16. Fact Sheet for Flow Equalization

Description - Wastewater flows into treatment facilities are subjected to diurnal and seasonal fluctuation in quality and in quantity. Most waste treatment processes are sensitive to such changes. An equalization basin serves to balance the extreme quality and quantity of these fluctuations to allow normal contact time in the treatment facility. This Fact Sheet addresses equalization basins that are used only to equalize flow; however, it should be noted that the quality of the wastewater will also equalize to some degree.

Equalization basins may be designed as either in-line or side-line units. In the in-line design, the basin receives the wastewater directly from the collection system, and the discharge from the basin through the treatment plant is kept essentially at a constant rate. In the side-line design, flows in excess of the average are diverted to the equalization basin and, when the plant flow falls below the average, wastewater from the basin is discharged to the plant to bring up the flow to the average level. The basins are sufficiently sized to hold the peak flows and to discharge at a constant rate.

Pump stations may or may not be required to discharge into or out of the equalization basin, depending upon the available head. Where pumping is found necessary, the energy requirements will be based on total flow for in-line basins and on excess flow for side-line basins.

Aeration of the wastewater in the equalization basin is normally required for mixing and maintaining aerobic conditions.

Common Modifications - There are various methods of aeration, pumping and flow control. Tanks or basins can be manufactured out of steel or concrete, or can be excavated and be of the lined or unlined earthen variety.

Technology Status - Has been used in the municipal and industrial sectors for many years. Over 200 municipal installations in the United States.

Typical Equipment/No. of Mfrs. (23) - Lift pumps/34; air compressors/8; basin liners/6, flow controllers/29; aerators/30.

Applications - Can be used to equalize the extremes of diurnal and wet weather flow fluctuations. The secondary benefits are equalization of quality and the potential for the protection from toxic upsets.

Limitations - Its application to equalize diurnal fluctuation is rather limited because the cost may be high when compared to the benefits. It may require substantial land area.

Performance - Flow equalization basins are easily designed to achieve the objective. Use of aeration, in combination with the relatively long detention times afforded can produce BOD_5 reductions of 10 to 20 percent.

Residuals Generated - Due to the settling characteristics of influent wastewater solids, some materials will collect at the bottom of the basin, and will need to be periodically discarded. Provisions must be made to accommodate this need.

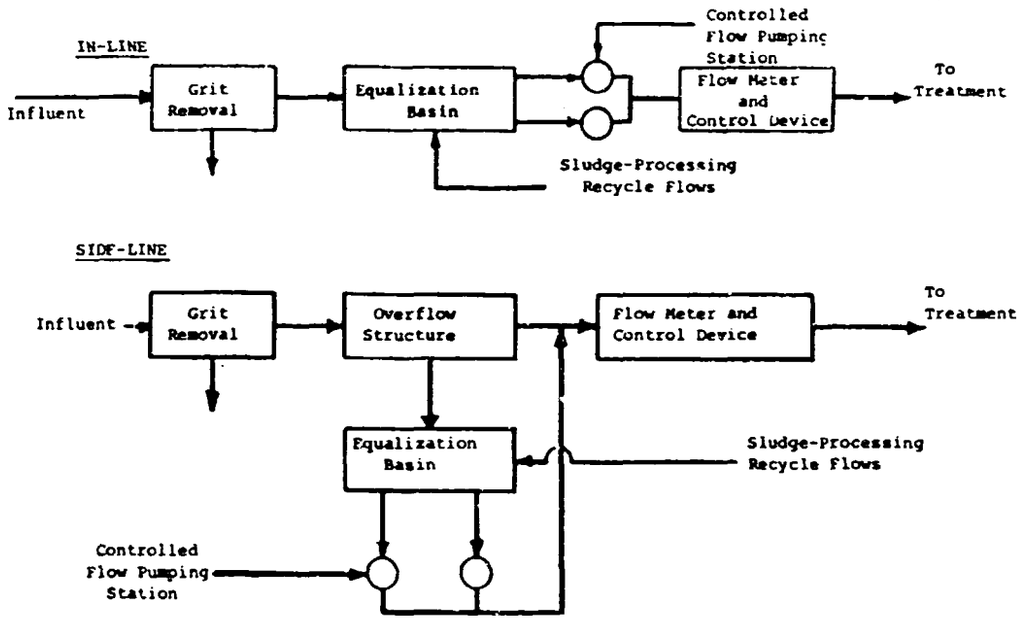
Design Criteria (122) - Design of an equalization basin is highly site specific and dependent upon the type and magnitude of the input flow variations and facility configuration. The pumping/flow control mode, aeration, mixing and flushing methods are dependent upon the size and site conditions. Grit removal should be provided upstream of the basin. Mechanical mixing at 20 to 40 hp/Mgal of storage. Aeration at 1.25 to 2 ft^3/min/1,000 gal of storage.

Process Reliability - These units have been found to be reliable from both a unit and process standpoint and are used to increase the reliability of the flow-sensitive treatment processes that follow.

Environmental Impact - Can consume large land areas. Impact upon air quality and noise levels are minimal. There may be some sludge generated that will require disposal.

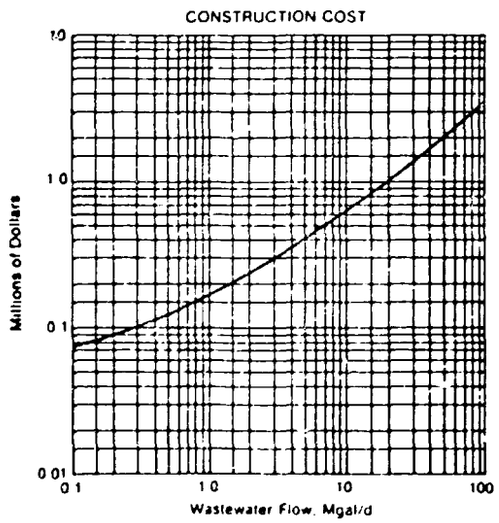
Figure 16. Flow Diagramme and Costs for Flow Equalization

FLOW DIAGRAM -



ENERGY NOTES - Pumping energy requirements may be approximated by using the following equation:
kWh/yr = 1900 X Mgal/d* X discharge head ft, assuming 60% wire to water efficiency -
For the typical head requirements of 10 ft for this process, an energy requirement of 19,000 kWh/yr/Mgal/d can be expected. *In the case of in-flow basins, the flow through the plant and in the case of side-line basins, the excess flow.

COSTS - Assumptions: Construction costs are based on concrete basin for design flows less than 1 Mgal/d and 6-inch concrete lined earthen basin for design flows greater than 1 Mgal/d. Detention time = 1.0 d. Mixing requirements = 20 to 40 hp/Mgal of storage volume. Costs include basin and mechanical mixing equipment. Pumping is not included. ENR Index = 2475.



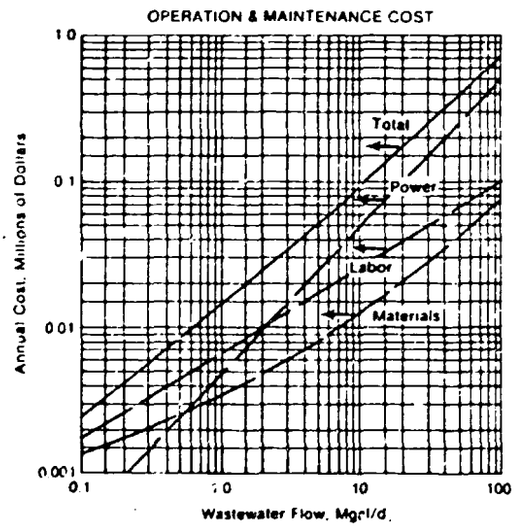


Table 17. Fact Sheet for Activated Sludge, Conventional, Diffused Aeration

Description - Activated sludge is a continuous flow, biological treatment process characterized by a suspension of aerobic microorganisms, maintained in a relatively homogeneous state by the mixing and turbulence induced by aeration. The microorganisms are used to oxidize soluble and colloidal organics to CO_2 and H_2O in the presence of molecular oxygen. The process is generally, but not always, preceded by primary sedimentation. The mixture of microorganisms and wastewater formed in the aeration basins, called mixed liquor, is transferred to gravity clarifiers for liquid-solids separation. The major portion of the microorganisms settling out in the clarifiers is recycled to the aeration basins to be mixed with incoming wastewater, while the excess, which constitutes the waste sludge, is sent to the sludge handling facilities. The rate and concentration of activated sludge returned to the aeration basins determines the mixed liquor suspended solids (MLSS) level developed and maintained in the basins. During the oxidation process, a certain amount of the organic material is synthesized into new cells, some of which then undergoes auto-oxidation (self-oxidation, or endogenous respiration) in the aeration basins, the remainder forming net growth or excess sludge. Oxygen is required in the process to support the oxidation and synthesis reactions. Volatile compounds are driven off to a certain extent in the aeration process. Metals will also be partially removed, with accumulation in the sludge. Activated sludge systems are classified as high rate, conventional, or extended aeration (low rate) based on the organic loading. In the conventional activated sludge plant, the wastewater is commonly aerated for a period of four to eight hours (based on average daily flow) in a plug flow hydraulic mode. Either surface or submerged aeration systems can be employed to transfer oxygen from air to wastewater. Compressors are used to supply air to the submerged systems, normally through a network of diffusers, although newer submerged devices which don't come under the general category of diffusers (e.g., static aerators and jet aerators) are being developed and applied. Diffused air systems may be classified as fine bubble or coarse bubble. Diffusers commonly used in activated sludge service include the following: porous ceramic plates laid in the basin bottom (fine bubble), porous ceramic domes or ceramic or plastic tubes connected to a pipe header and lateral system (fine bubble), tubes covered with synthetic fabric or wound filaments (fine or coarse bubble), and specially designed spargers with multiple openings (coarse bubble).

Common Modifications - Step aeration; contact stabilization; and complete mix flow regimes. Alum or ferric chloride is sometimes added to the aeration tank for phosphorus removal.

Technology Status- Activated sludge is the most versatile and widely used biological process in wastewater treatment.

Typical Equipment/No. of Mfrs. (23, 97) - Equipment normally associated with diffused air, activated sludge systems include the following: air diffusers/19; compressors/44.

Applications - Domestic wastewater and biodegradable industrial wastewater. The main advantage of the conventional activated sludge system is the lower initial cost of the system, particularly where a high quality effluent is required. Industrial wastewater (including some "priority pollutants") which is amenable to biological treatment and degradation may be jointly treated with domestic wastewater in a conventional activated sludge system.

Limitations - Limited BOD_5 loading capacity; poor organic load distribution; required aeration time of four to eight hours; plant upset with extreme variations in hydraulic, organic, and toxic loadings; operational complexity; operating costs; energy consuming mechanical compressors; and diffuser maintenance.

Performance (26, 39) -

BOD_5 Removal (conventional activated sludge)	85-95 percent
NH_4^+-N removal (non-nitrified systems)	10-20 percent

Residuals Generated - The following table illustrates the anticipated increase in excess sludge, volatile suspended solids (VSS) production from the conventional activated sludge process as settled wastewater food-to-microorganism (F/M) loadings increase:

F/M (lb BOD_5/d/lb MLVSS)	Excess VSS (secondary effluent plus waste sludge)
0.3	0.5 lb/lb BOD_5 removed
0.5	0.7 " "

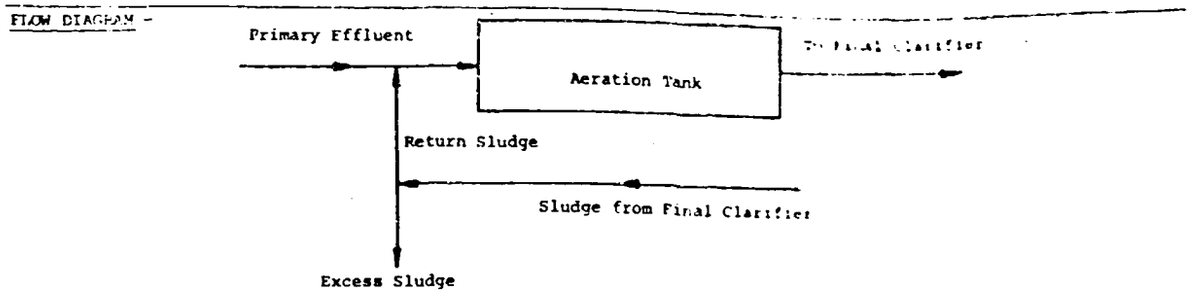
Design Criteria (26, 31, 30) - A partial listing of design criteria for the conventional activated sludge process is summarized as follows:

Volumetric loading, lb BOD_5/d/1000 ft^3	25-50
Aeration detention time, h (based on avg. daily flow)	4-8
MLSS, mg/l	1500-3000
F/M, lb BOD_5/d/lb MLVSS	0.25-0.5
Air required, std. ft^3/lb BOD_5 removed	800-1500
Sludge retention time, days	5-10

Unit Process Reliability (31) - Good.

Environmental Impact - Sludge disposal; odor potential; and energy consumption.

Figure 17. Flow Diagramme and Costs for Activated Sludge, Conventional, Diffused Aeration

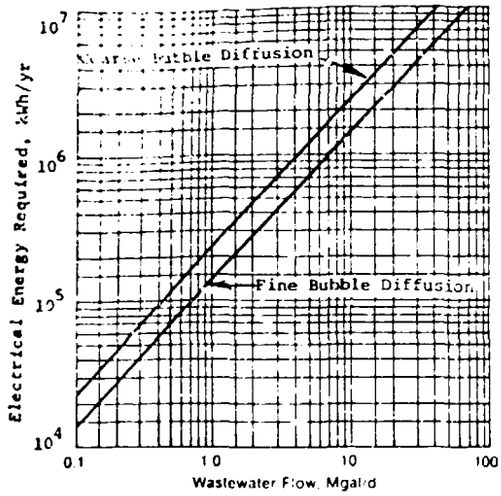


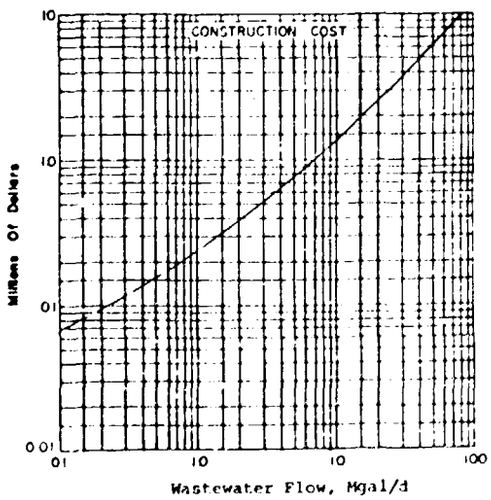
ENERGY NOTES - Assumptions:
The hydraulic head loss through the aeration tank is negligible. Sludge recycle and sludge wasting pumping energy are a part of clarifier operation.

Water Quality:	Influent (mg/l)	Clarifier Effluent (mg/l)
BOD_5	130	20
Suspended Solids	100	20

Oxygen Transfer Rate (wire to water) in wastewater for:
Fine Bubble Diffusion = 2.5 lb O_2/hph
Coarse Bubble Diffusion = 1.5 lb O_2/hph
Average oxygen requirement = 1300 lb/d/Mgal/d

COSTS* - Assumptions:
Service life = 40 years. ENR Index = 2475
Construction cost includes aeration basins, air supply and dissolution equipment and piping, and blower building. Clarifier and recycle pumps are not included. 1.1 lb O_2 supplied/lb BOD_5 removed. MLVSS = 2100 mg/l. F/M = 0.25 lb BOD_5/d/lb MLVSS. Detention time = 6 hours (based on average daily flow). Volumetric loading = 32 lb BOD_5/d/1,000 ft^3. Power costs are for an average energy requirement of 2.0 lb O_2/hph @$.02/kWh.





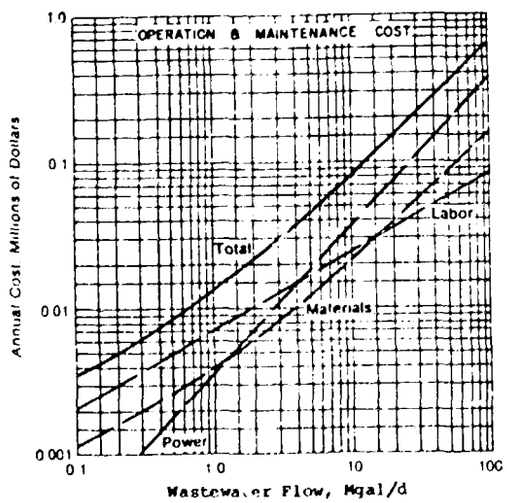


Table 18. Fact Sheet for Clarifier, Secondary, Rectangular

Description - The design of secondary clarifiers is similar to primary clarifiers except that the large volume of flocculant solids in the mixed liquor must be considered during the design of activated-sludge clarifiers and in sizing of sludge pumps. Further, the mixed liquor, on entering the tank, has a tendency to flow as a density current interfering with the separation of the solids and the thickening of the sludge. To cope successfully with these characteristics, factors that must be considered in the design of these tanks include: (1) type of tank to be used, (2) surface loading rate, (3) solids loading rate, (4) flow-through velocities, (5) weir placement and loading rates, and (6) scum removal.

Flow through rectangular tanks enters at one end, passes a baffle arrangement, and traverses the length of the tank to effluent weirs. The maximum length of rectangular tanks has been approximately 300 ft with depths of 12 to 15 ft. Where widths of greater than 20 ft are required, multiple bays with individual cleaning equipment may be employed, thus permitting tank widths up to 80 ft or more.

Sludge removal equipment usually consists of a pair of endless conveyor chains. Attached to the chains at 10 ft intervals are 2-in thick wooden crosspieces or flights, 6 to 8 in deep, extending the full width of the tank or bay. Linear conveyor speeds of 2 to 4 ft/min are common. The settled solids are scraped to sludge hoppers in small tanks and to transverse troughs in large tanks. The troughs, in turn, are equipped with cross collectors, usually of the same type as the longitudinal collectors, which convey solids to one or more sludge hoppers. Screw conveyors have also been used for the cross collectors. Tanks may also be cleaned by a bridge-type mechanism which travels up and down the tank on rails supported on the sidewalls. Scraper blades are suspended from the bridge and are lifted clear of the sludge on the return travel. For very long tanks, it is desirable to use two sets of chains and flights in tandem with a central hopper to receive the sludge. Tanks in which mechanisms that move the sludge toward the effluent end in the same direction as the density current have shown superior performance in some instances.

Scum is usually collected at the effluent end of rectangular tanks by the flights returning at the liquid surface. The scum is moved by the flights to a point where it is trapped by baffles before removal, or it can also be moved along the surface by water sprays. The scum is then scraped manually up an inclined apron, or it can be removed hydraulically or mechanically, and for this process a number of means have been developed (rotating transverse rotating helical wiper, chain and flight collectors, scum rakes).

Common Modifications - Multiple inlets with balanced flow at various spacings and with target baffles to reduce velocity of streams; hydraulic balancing between parallel clarifier units; Control of wind effects on water surface; Sludge hopper collection systems; Flocculation inlet structures; Use of traveling bridge sludge collectors and skimmers, as an alternate to chain and flight systems; Use of steeply inclined tube settlers to enhance SS removal in either new or rehabilitated clarifiers; Use of wedge wire settler panels at peak hydraulic loading of less than 800 gal/d/ft^2 for improved SS removal.

Technology Status - Rectangular clarifiers are in widespread use.

Applications - Secondary clarifiers are used for solids separation and for the production of a concentrated return sludge flow to sustain biological treatment. Multiple rectangular tanks require less area than multiple circular tanks and for this reason are used where ground area is at a premium. Rectangular tanks also lend themselves more readily to nesting with primary tanks and aeration tanks in activated sludge plants. They are also used generally where tank roofs or covers are required.

Limitations - Must operate at relatively low hydraulic loadings (large space requirements). The maximum length of tank has been about 300 ft. Horizontal velocities in the clarifier must be limited to prevent "scouring" of settled solids from the sludge bed and their eventual escape with the effluent.

Typical Equipment/No. of Mfrs. (10) - Clarifiers/35; Sludge Pumps/20.

Performance - Maximum practical solids concentrations of sludge from secondary clarifiers in activated sludge systems range from 0.5 to 2.0 percent depending on settling and compaction characteristics of the sludge (99). Effluent TSS = 20 to 30 mg/l (7).

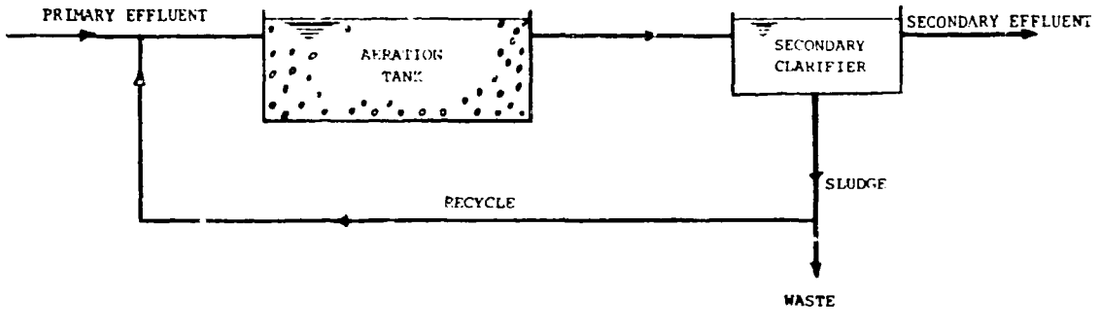
Design Criteria - Average hydraulic loading in activated sludge systems varies from 400 to 800 gal/d/ft^2 and peak loadings range from 700 to 1200 gal/d/ft^2 depending on mixed liquor suspended solids concentration and percent sludge recycle. Average solids loadings of 0.6 to 1.2 lb/h/ft^2 and peak loadings of 1.25 to 2.0 lb/h/ft^2 have been suggested for activated sludge plants. Weir loading = 10,000 to 30,000 gal/d/lin ft. Maximum inflow velocity in vicinity of weir = 12 to 24 ft/h. Depths are normally 12 to 15 ft.

Unit Process Reliability - Mechanical reliability can be considered high provided suitable preventive maintenance and inspection procedures are observed. Plugging of sludge hoppers has been a problem when cross collectors are not provided. Process reliability is highly dependent upon the upstream performance of the aerator for the production of good settling sludge with acceptable compactability. Rising sludge caused by denitrification of the sludge is a problem in certain cases.

Environmental Impact - Although it requires large land areas, it offers a higher space efficiency than circular clarifiers.

Figure 18. Flow Diagramme and Costs for Clarifier, Secondary, Rectangular

FLOW DIAGRAM -



ENERGY NOTES - Cost design assumptions applicable. Energy usage shown on energy curve is for sludge return and waste pumps, sludge scrapers and skimmers.

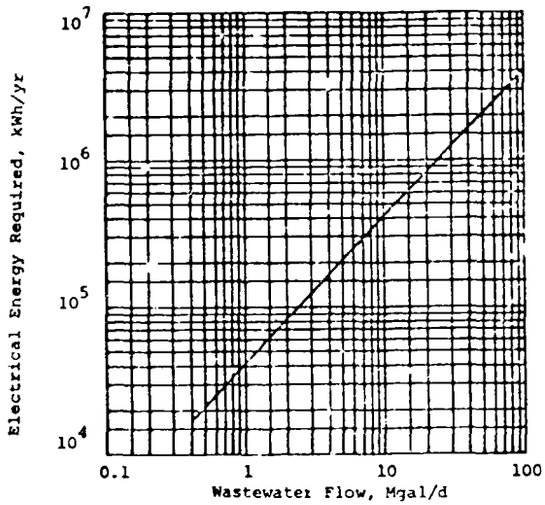
Energy required for providing the head loss for 2-3 ft through the clarifier can be approximated by the following equation: kWh/yr = 1625 (Mgal/d plant flow + Mgal/d return sludge flow)(TDH)at a wire to water efficiency of 70 percent.

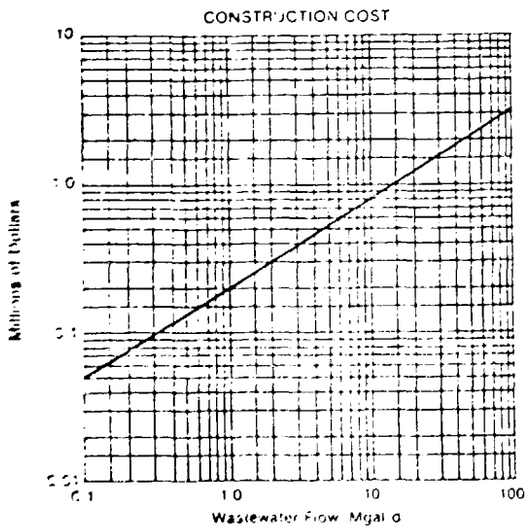
COSTS - Assumptions:

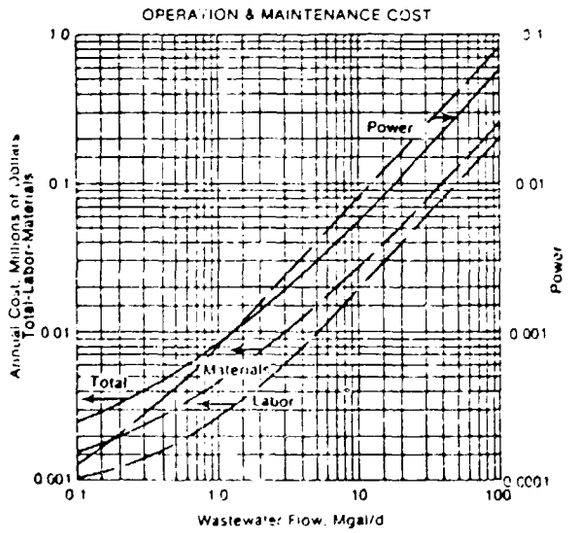
Service Life: 40 years, ENR = 2475 (Sept. 1976), Power Cost: $0.02/kWh.

Design Basis:

1. Flocculator-type clarifier: 600 gal/d/ft^2
2. Costs include sludge return and waste pumps. Sludge concentration of 1 percent solids. Pump TDH at 10 ft. Spare pumps included as necessary. (non-clog centrifugal pumps).
3. To adjust construction cost for alternative flow rates, enter the curve at effective flow (Q_E) = Q_{DESIGN} x 600 gal/d/ft^2 x (1/New Design Overflow Rate).







Construction Cost Index from 1957 through 1979 and the EPA Municipal Wastewater Treatment operation and Maintenance Cost Index for 1967 - 1979. The indexes can be used to convert costs from any given year to any other. More recent values of the index are available from EPA.

It must be emphasized that these cost data entail many inherent assumptions. Some of the more important assumptions pertain to labour rates, energy costs, chemical costs, land costs and location. As might be expected the costs have been developed for locations in the U.S.A. and probably will be different for locations in developing nations.

Here we apply the cost information (all figures 1976 dollars unless otherwise shown) in this manual to Abbott Laboratories waste water treatment plant (capacity 1 mgd) described above as follows with all costs in 1976 U.S. dollars unless otherwise stated:

Flow Equalization

construction cost	-	$170,000
annual O&M cost	-	$ 15,000

Activated Sludge

construction cost	-	$200,000
annual O&M cost	-	$ 12,000

Secondary Clarification

construction cost	-	$200,000
annual O&M cost	-	$ 85,000

Chlorination (assumed equiv. to pasteurization)

construction cost	-	$ 50,000
annual O&M cost	-	$ 12,000

Centrifugal Sludge Dewatering

construction cost	-	$150,000
annual O&M cost	-	$ 16,000

Sludge Digestion

construction cost - $210,000

annual O&M cost - $ 13,000

Sludge Disposal by Landfill (1st Q, 1978 dollars)

site & equipment - ($7.50/wet ton) × (250 wet ton/day) = $1,125/day

O&M - ($4.00/wet ton) × (150 wet ton/day) = $ 600/day

(here 150 tons wet sludge/day is an approximate estimate)

Development of Capital Costs (thousands of dollars)

(Abbott Laboratories Plant - 1976 dollars)

Installed Component Costs of Unit Processes

Flow Equalization	$170	
Activated Sludge	200	
Secondary Clarification	200	
Chlorination	50	
Centrifugal Dewatering	150	
Sludge Digestion	210	
Misc. structures (office, labs, etc)	196	
(assumed 20% of others)	Subtotal -	$1,176.00

Non Component Costs

Piping (10%)	117.60	
Electrical (8%)	94.10	
Instrumentation (5%)	58.80	
Site Preparation (5%)	58.80	
	Subtotal - $	329.30

Non-Construction Costs

Engineering & Supervision, 15%	225.80	
Contingencies, 15%	225.80	
	Subtotal - $	451.60
	Total Capital Cost -	$1,956.90

Convert Capital Costs from 1976 to 1979 dollars (thousands)

$$\frac{357.8}{262.5} \times 1{,}956.9 = \$2{,}518$$

Assume plant life is 40 years and total principle is borrowed at 8% per annum simple interest; then monthly capital cost is $6.96/thousand.

Capital Cost of Treatment

$$\frac{6.96 \times 2518 \times 12}{1000 \times 365} = \$0.58/\text{thousand gallons}$$

Annual Operating and Maintenance Costs (thousands of 1976 dollars)

flow equalization	- 15
activated sludge	- 12
second clarification	- 8.50
chlorination	- 12
centrif. dewatering	- 16
sludge digestion	- 13
	76.50

Convert to 1979 dollars (thousands):

$$\frac{2.62}{2.09} \times 76.5 = \$95.9/\text{thousand}$$

Convert O&M costs to cost of treatment basis:

$$\frac{95,900}{365 \times 1000} = \$0.26/\text{thousand gallons}$$

Convert Sludge Disposal Costs to 1979 dollars:

($1,125/day)	x	(337.8/290.1)	=	$1,310
($600/day)	x	(2.62/230)	=	$ 683.5
				$1,993.5/day

Convert sludge costs to cost of treatment basis:

($1,993.50/day)/(1000 gal/day) = $1.99 per thousand gallons.

Summary of Estimated Treatment Costs for Abbott Plant

Capital Cost	-	$0.58/thousand gal
O&M Cost	-	$0.26/thousand gal
Sludge Disp. Cost	-	$1.99/thousand gal
Total		$2.83/thousand gallons (1979 dollars)

Considering the many assumptions and approximations made in the foregoing calculations, the value of $2.83 per thousand gallons (in 1979 dollars) is not totally discordant with the cost of $4.50 per thousand gallons (1978 dollars) reported informally by Abbott Laboratories to Carmichael[56]. It should be stressed that the capital costs are very sensitive to the assumed interest rate and lifetime (amortization period) of the plant. Similarly O&M costs are very sensitive to the cost of labor and sludge disposal costs are very sensitive to land costs and labor costs. The cost structure assumed above for plants in the USA may not hold for plants in developing nations.

CASE STUDY - The Gedeon Richter Pharmaceutical Company, Hungary

The Gedeon Richter company produces pharmaceutical products from three routes:

(1) through synthetic organic chemical means
(2) through fermentation processes
(3) biologically based products.

Tablets, ointments and injectables are among the forms in which the various pharmaceutical products are prepared.

Gedeon Richter prepares many drugs which appear on the UNIDO illustrative list, including 3. Mebendazole (trade name Vermon), 19. Reserpine, 22. Ethinylostradiol and levonorgestrel, and 25. Hydroxocobalamin. The drug 15. Isoniazid was formerly manufactured by Gedeon Richter and the technology is available.

A. Water use and treatment practices at the Dorog plant

At the Dorog plant, Gedeon Richter produces pharmaceuticals through the synthesis of fine organic chemicals and through fermentation (25. Hydroxo-cobalamin, Vitamin B-12).

1. Water use practices within the plant

The plant has two sources of water for use within the plant. One of these is potable and used for drug production. The other is partially treated Danube water for applications which do not involve contact with the pharmaceutical product.

a. The potable water comes from the municipal water supply. It is used for drug production without further pretreatment. Microbiological quality control is carried out by the Ministry of Public Health and, if necessary, by the Central Laboratory of the Pharmaceutical Industry. This water is also used for cleaning equipment.

b. The Danube River water is received at the plant after partial treatment at the municipal power plant. There the water is first filtered through a vacuum cylinder with a fabric liner. Following coagulation with $FeCl_3$ the water passes through a sand filter. Finally the water is softened with CaO. This water is used in the plant as (1) non-contact cooling water in a closed system with a cooling tower, and (2) technical water for gas absorption in the treatment of process residues. This water is only used when it will not come into direct contact with the pharmaceutical product.

General observations· This plant has a direct economic incentive to minimize the amount of water used. According to law the plant must supply capital for investment in government facilities for production of drinking water according to the amount of this water used at the plant. As a consequence therefore, this government regulation should also reduce the quantity of waste water discharged.

2. Solvent recovery operations

The Dorog plant operates a distillation unit for solvent recovery operations. This unit allows the recovery of costly solvents and simultaneously reduces the pollution that would otherwise be caused from discarding these waste solvents.

3. Fermentation waste recovery

The fermentation sludge from Vitamin B-12 production is recovered and sold as Vitamin B-12 additive for animal food.

4. Waste water treatment

The plant has three separate sewer systems for waste water· Sanitary sewage, rain water run-off, and process effluents.

There are government regulations for the control of effluent discharges. These are divided into two categories·

a. Effluent discharge limits for discharges into municipal sewers, in which two general categories of pollutants are recognized (i) general pollutants, and (ii) toxic pollutants.

b. Effluent discharge limits for discharges into natural waters. Here the allowable discharge varies according to the category of water quality into which the body of water has been classified (categories I - IV).

In each case above the effluent discharge limits are presented in mg/l. The tables describing the effluent limitations in force are shown in Tables 19 and 20.

The process effluent from the Gedeon Richter Dorog plant receives primary and secondary (biological) treatment to enable the discharged treatment effluent to meet the Hungarian discharge limits.

First the process waste waters enter a primary treatment plant where sludge is mechanically removed following sedimentation. The pH of the waste waters is adjusted. Presently there is no equalization basin, but one is planned.

The primary treated effluent enters a two-stage biological treatment process: an activated sludge plant followed by an extended aeration basin.

The handling of primary and secondary sludges is presently the greatest problem at the waste water treatment plant. A sludge dewatering unit is under construction and will solve the sludge handling problems. Sludges are land filled.

A chemical coagulation unit is planned for further polishing the secondary treated effluent. $Al_2(SO_4)_3$ and $Ca(OH)_2$ will be utilized as coagulants.

A laboratory at the plant site carries out daily analyses of untreated and treated effluents. BOD_5, COD, and suspended solids are measured by conventional means. The possible presence of solvents is monitored using dual column gas chromatography.

The untreated process waste waters of the plant have a BOD_5 in the range of 2,000 - 3,000 mg/l and a COD in the range of 5,000 - 10,000 mg/l. Following treatment the BOD_5 is reduced to 200 - 300 mg/l and the COD is reduced to around 500 mg/l. About 99% removal of suspended solids from the effluent is achieved by the waste water treatment plant.

B. Process water use and treatment practices at the Gedeon Richter main plant

Water from the municipal water supply serves as the source of process waters at the Gedeon Richter main plant in Budapest. This water receives a preliminary treatment consisting of sand filtration followed by ion exchange. Cation and anion columns packed with ion exchange resin are arranged in series. The columns have a capacity of treating 120 m^3 of water before resin regeneration is required. The treated water passes to a storage tank where the conductivity is monitored. A maximum conductivity of 5 micro Siemens is permitted. The normal range is 1 - 5 micro Siemens. The filters and ion exchange columns are disinfected with a 0.5% formaldehyde solution when not in use.

1. Distillation of water for injectables and oral solutions

a. Distillation columns are used to further purify the water that is used to prepare injectables and solutions to be taken orally. The distillation unit used to purify water for oral solutions is described here. The other unit is similar. The distillation unit is of Finnish manufacture and has an output of 500 litres/hour. The conductivity of input water is monitored continuously. Samples of the output water are sent to the central Hygiene Laboratory for bacteriological analyses. Following distillation the water goes to a reserve tank where it is stored at 95°C. The maximum residence time is one day. There is a heat exchanger following the reserve tank to reduce the water temperature to 30°C.

b. Careful quality control procedures ensure the absence of pyrogens in injectable products. Tests for the presence of pyrogens in pharmaceutical products are carried out by the Central Control Laboratory of the Union of the

Hungarian Pharmaceutical Industry. Other analyses may be carried out on products of raw materials at the request of a particular pharmaceutical company. About 6,000 samples of raw materials, infusions, intermediates and final products are analysed annually for pyrogens. The methodology used is specified in the Hungarian Pharmacopoeia, 6th edition. About twenty of the samples analyzed annually are found to contain pyrogens. However, no pyrogens have been detected in the water used for preparation of injectables of infusions during the last ten years.

Microbiological testing of final pharmaceutical products is also carried out by the Central Control Laboratory. This department also tests the water used in various pharmaceutical products upon request of the particular pharmaceutical company.

C. Design of plants for process water treatment and effluent treatment for the pharmaceutical industry in Hungary

The Hungarian Chemical Industries Engineering Centre, Vegyterv, designs the water treatment and effluent treatment plants for the Hungarian pharmaceutical industry.

Chemokomplex, a Hungarian trade company, is responsible for the export of the design and application for complete pharmaceutical plants (as well as those covering other branches of industry), including water treatment and effluent treatment.

Table 1. Type of pollutants discharged to the sewage system, maximum pollution loads and penalty for infringement

Number	Type of pollutant	Maximum pollution load (mg/l)	Penalty (Forint/kg)
I. Pollutants			
1.	Oils, aromatic oils, grease (extracts of organic solvents)	60	20.-
2.	pH	6,5 - 10,0	15.-
3.	Sulphate	400	0.50
4.	Phenol	80	50.-
5.	Settleable solids (after 10 min. settling time)	75	0.50
6.	Tars	20	120.-
7.	Detergents	100	60.-
8.	Sulfide (S^{--})	1	100.-
9.	Chlorine (free)	50	50.-
10.	Fluoride	100	50.-
II. Toxic pollutants			
11.	Free cyanide	0.2	5000.-
12.	Total cyanide	1	500.-
13.	Copper	25	50.-
14.	Lead	10	100.-
15.	Hexavalent chromium	10	100.-
16.	Trivalent chromium	50	5.-
17.	Arsenic	5	200.-
18.	Cadmium	10	100.-
19.	Mercury	2	500.-
20.	Nickel	2	500.-
21.	Silver	0.1	1000.-
22.	Zinc	5	100.-
23.	Tin	1	1000.-
24.	Benzol	1	500.-
25.	Carbon disulfide	2	50.-
26.	Organic solvents insoluble in water	2	50.-
27.	Radioactive matter	individually decided	

Table 2. Discharge limits for pollutants in effluents discharged into natural waters

Number	Type of pollutants	Maximum pollution load (mg/l) Categories I.	II.	III.	IV.	V.	VI.	Penalty (Forint/kg)
	Pollutants							
1.	Dichromate oxygen consumption	50	75	100	100	150	75	1
2.	Oil and grease	2	5	10	10	10	10	20
3.	pH	6,5-8,5	6,5-9	5 - 9	6 - 9	5 - 10	6 - 9	5
4.	Total salt							
	- natural origin	1000	1000	2000	1000	-	2000	0.1
	- industrial origin	1000	1000	2000	1000	-	2000	1
5.	Sodium—equivalent %	-	-	45	45	-	45	2
6.	Phenol	0.1	0.1	3	3	3	3	50
7.	Total suspended solids	100	100	200	200	500	200	1
8.	Tar	0.1	0.1	2	2	2	1	120
9.	Ammonia-ammonium ion	2	5	30	10	30	10	5
10.	Total iron	5	5	20	20	20	10	2
11.	Total manganese	2	2	5	5	5	5	20
12.	Detergents	2	2	5	5	5	5	60
13.	Sulfide	0.01	0.01	2	2	5	2	100
14.	Free chlorine	2	2	2	2	2	2	50
15.	Fluoride	2	2	10	5	10	10	50
16.	Total phosphorous	2	2	2	2	-	2	20
17.	Nitrate	20	20	50	50	-	50	1
18.	Coliform bacteria/ml				10			
	Toxic pollutants							
19.	Free cyanide	0.1	0.2	0.2	0.2	0.2	0.2	5000
20.	Total cyanide	2	10	10	10	10	10	50
21.	Total copper	2	5	5	2	5	5	50
22.	Total lead	0.2	1	1	1	1	1	200
23.	Total chromium	2	2	5	5	5	5	50
24.	Hexavalent chromium	0.5	0.5	1	1	1	1	200
25.	Total arsenic	0.1	0.5	1	1	1	0.5	200
26.	Total cadmium	0.02	0.05	0.2	0.1	0.2	0.1	500
27.	Total mercury	0.002	0.01	0.02	0.02	0.02	0.02	10000
28.	Total nickel	2	5	5	5	5	5	300
29.	Total zinc	5	5	20	20	10	10	50
30.	Total silver	0.05	0.05	0.1	0.1	0.1	0.1	1000
31.	Toxicity	1 Ft/m^3 is charged for effluents exceeding allowable toxicity limits (determined by bioassay)						

CASE STUDY - Janssen Pharmceuticals, Beerse, Belgium

The Janssen Pharmaceuticals plant at Beerse, Belgium, is a large complex carrying out research and manufacturing of a broad range of pharmaceutical products based on organic chemicals synthesis. The plant employs about 2,000 people. The anti-infective drug Mebendazole, item 3 on the UNIDO illustrative list of 26 drugs, is manufactured there. Various injectable drugs requiring pyrogen-free water are also manfactured there.

I. Water treatment practices for water used in pharmaceutical manufacturing operations

A. Synthesis of pharmaceuticals

Water meeting the drinking water quality standards of WHO is used for all production requirements of pharmaceutical synthesis. Ground water obtained from 80 metre deep wells on Janssen property is the source of all water used in the plant. Prior to use in synthesis operations the water undergoes treatment to raise the pH and remove the iron. The raw water typically has a pH of 6.9 to 7.0 and an iron content of 0.2 to 0.3 ppm. The treatment utilized is filtration through a bed of calcium carbonate (limestone) pellets. During this process, the pH is raised to about 8. The iron precipitates as $Fe(OH)_3$ due its insolubility at higher pH and the precipitate is filtered out and retained in the bed. The filters must be back-washed from time to time to remove the precipitated $Fe(OH)_3$. No disinfection is necessary because the bacterial content of the ground water is very low.

Analyses of the water before and after treatment are carried out weekly at Janssen. Furthermore, a monthly analysis of the treated water is carried out by a government laboratory and reported to the provincial government. This analysis is not required under Belgian law. Janssen submits the water samples, however, because of the company's desire to ensure the highest standard of quality since that water is used in synthesis operations and is the source of drinking water at the plant. The results of the analysis by the Antwerp Provincial Institute for Hygiene of the water sample taken on 1 June 1982 are shown in Table 21.

B. Preparation of injectables, formulation plant

Within the formulation plant the operations of encapsulation, granulation, tabletting, and preparation of injectables are performed. The preparation of injectables requires the use of pyrogen-free water. A special treatment procedure is followed to produce this pyrogen-free water.

The drinking-water quality water described in Section A is first passed through Wanson ion exchange columns to reduce the hardness to less than 2 mg/l as $CaCO_3$. No disinfectant is used but the columns can be steam-sterilized any time the subsequent quality control of the final products indicate the presence of pyrogens. The softened water is then distilled in a 500 l/hour capacity still manufactured by the Borzini Company, Italy. The conductivity of the distilled water is measured continuously as a quality control check. Following distillation the water is stored at 90°C with continuous circulation. Ordinarily the water is used as it is produced but it could remain in storage for a period of up to 7 days.

Tests are carried out by the Quality Control Department of the Pharmaceuticals Plant Janssen to be sure the water and the final injectable products are pyrogen-free. Laboratory instrumental analysis tests are carried out daily and tests using rabbits are carried out weekly.

II. Waste water treatment practice

A. In-plant practice to reduce the pollution load produced by the plant

1. Solvent recovery

Janssen Pharmaceuticals employs a variety of organic solvents in many syntheses. Many of these solvents are costly. Furthermore they may impart a shock load to the operation of the waste water treatment plant. Therefore whenever a solvent is used alone in a chemical synthesis, it is recovered and recycled, if possible. An estimated 60% of the solvents used at Janssen are recycled in this manner.

2. Separate collection system for waste solvents

At some point, the continued recycling of a particular solvent may not be economically attractive. Or mixed solvents may be required for a particular synthesis and their subsequent separation for re-use prohibitively expensive. Then the waste solvents are discharged to a sewage system separate from the one which receives waste waters. The waste solvents are collected and disposed by incineration.

3. Re-use of tertiary treated, disinfected effluent

Janssen has the capability of re-using up to 75 m^3/hour of effluent from the waste water treatment plant (whose operations are to be described in the following section) after a tertiary treatment operation and disinfection. This water is available for cleaning and maintenance operations, especially for cleaning the animal housing facilities in the veterinary research department. The water could also, in principle, be used for non-contact cooling operations. But right now ground water is cheaper to use for this purpose. In the future, if Janssen expands operations at this site, the sources of ground water on site may prove to be insufficient to meet all water needs of the plant. Then the alternative of using the tertiary-treated, disinfected effluent for non-contact cooling and other uses may be economically attractive. Presently, if the tertiary treated effluent is not used in full, it is mixed with the secondary-effluent and discharged.

B. Waste water treatment plant

All waste waters from the Janssen plant site are discharged to a waste water treatment plant which is one of the most modern and effective plants in Europe. Waste waters from the different departments, e.g. research, chemical production and pharmaceutical production, are treated together with the sanitary wastes and the rain water run off. Relative amounts of each source of waste water are as follows: chemical plant - 16%, pilot plant - 22%, pharmaceutical plant - 4%, veterinary department - 32%, laboratories - 8%, utilities - 8%, others - 10%. The average composition of the plant effluent is: pH - 8,5, BOD - 400 mg/l, COD - 940 mg/l, Kjeldahl N 50 mg/l, chloride - 134 mg/l, sulfate - 160 mg/l.

1. Primary treatment

The waste waters enter an equalization basin where mechanical aeration is supplied to begin the aerobic decomposition process. Following neutralization, the waste waters enter a primary sedimentation basin. The sludge is removed from this basin for subsequent thickening and conditioning in combination with the sludges collected at further stages of the waste water treatment plant.

2. Secondary treatment

a. High-rate trickling filter with intermediate clarifier

The primary-treated waste waters next enter a high rate trickling filter. The filter contains a corregated polyvinyl chloride medium. About 60-70% of the BOD_5 from the primary-treated effluent are removed by the trickling filter. The higher removal efficiencies are obtained during warm weather operations. The effluent leaving the filter passes through an intermediate clarifier, from which another source of sludge is obtained, prior to further biological treatment by activated sludge. If an unexpected shock load of toxic material reaches the effluent treatment plant, the trickling filter can be temporarily bypassed.

b. Activated sludge treatment with extended aeration and final clarification

The activated sludge plant consists of two identical units which operate in parallel. This design feature was incorporated to provide flexibility of operation in the case of arrival of a shock load of toxic material in the waste waters. Forced aeration occurs utilizing compressed air. The parameters of the activated sludge process are: volume - 3455 m^3, total suspended solids - 2-3 g/l (volatile - 85%, fixed - 15%), influent - 150 m^3/h, return sludge - 105 m^3/h, waste sludge - 100-200 m^3/day. The activatedsludge plant removes about 90% of the 30-40% BOD_5 which remain in the effluent after the trickling filter. The effluent leaving the activated sludge plant undergoes a final sedimentation. This effluent is then suitable for discharge. The receiving water is a small ditch called Oude Dijkloop.

c. Tertiary treatment and disinfection

As mentioned earlier in section II.A.3, a tertiary treatment facility also is present. This system has the capacity of accepting a maximum of 75 m^3/hour treated effluent from the activated sludge plant (about one third of the average dry weather flow). The tertiary treatment process consists of sand filtration, filtration through activated carbon, and disinfection using ultraviolet light. That portion of the tertiary-treated effluent not re-used by the company is mixed with the effluent from the activated sludge plant and discharged, thereby improving the quality characteristics of the discharged effluent.

d. Effluent quality

The final effluent is analyzed twice daily by Janssen personnel. The Company reports the following average composition of the treated effluent: pH - 7, BOD - 32 mg/l, COD - 180 mg/l, Kjeldahl N - 37 mg/l, chloride - 150 mg/l, sulfate - 240 mg/l. Once a month an analysis is performed by a provincial government laboratory. This analysis is legally required under the royal decree for pharmaceutical waste water treatment standards. The authorities arrive without prior notice and take a random grab sample of the treated effluent. The analytical results obtained on the effluent sample of 3 July 1982 are shown in Table 22.

e. Sludge handling

The sludge from all three treatment phases is combined and collected in two sludge thickeners. After conditioning with lime and ferric chloride, the sludge is filtered in a filter press. The resultant sludge cakes are dumped in a sanitary land fill.

f. Overall operating characteristics of the waste water treatment plant

The treatment plant has a design capacity for treating 468 m^3/hour of waste waters. The normal dry weather discharge of treated effluent is 200 m^3/hour.

The excess capacity allows for modifications in treatment operations in the case of arrival of a shock load of toxic materials in the waste waters. The average waste load arriving at the treatment plant is 2,300 kg BOD_5/day, a population equivalent of 42,700 inhabitants. The average residence time of the effluent is 24 hours. The treatment efficiency, expressed as % removal of BOD_5, averages 97%.

About 180 tons of chemicals/year are required by the waste water treatment plant. A total of 1,000 tons/year of waste sludge are produced.

The total costs of the plant (depreciated capital costs and all operating costs) are 10.8 BF/m^3 of effluent treatment, or about \$ 0.20/m^3 (1982 US \$).

A sophisticated plant such as this one requires well trained personnel. Three full-time technicians operate the plant and carry out analyses during the normal 8 hour working day. All have completed a six-month waste water treatment course. After normal working hours the plant is checked every hour by an inspector. In case of any irregularity, the plant supervisor is contacted.

Table 1. Analytical results reported by the Antwerp Provincial Institute for Quality of the Treated Water Supply for Janssen Pharmaceutical Company

Temperature	22°C
Conductivity	0,33 $mScm^{-1}$
pH (glass electrode)	8,63

Chemical Analysis:

Na^+	17	ppm	Cl^-	30	ppm
K^+	5	ppm	NO_2^-	< 0,02	ppm
NH_4^+	< 0,02	ppm	NO_3^-	1,0	ppm
Ca^{++}	34	ppm	HCO_3^-	71	ppm
Mg^{++}	8	ppm	OH^-	0	ppm
Fe^{++}	0,04	ppm	CO_3^-	2,4	ppm
Pb^{++}	< 0,005	ppm	SO_4^{--}	71	ppm
Cu^{++}	< 0,002	ppm	PO_4^{--}	< 0,05	ppm
Zn^{++}	0,02	ppm			
Cd^{++}	< 0,001	ppm			

Total hardness	120 mg (as $CaCO_3$)
Total alkalinity, phenolphthalein end point	2 mg/l as $CaCO_3$
Total alkalinity, methylorange end point	62 mg/l as $CaCO_3$
Dissolved O_2	7,2 ppm
Free O_2	0 ppm
$KMnO_4$ required to oxidize organic materials	7 ppm

Chemical judgement: Good

Bacteriolcgical Analysis:

Total number of coliform bacteria per 20 ml	0
Number of Faecal coli per 100 ml	0
Number of Faecal streptococci per 100 ml	0

Bacteriological judgement: Good

GENERAL JUDGEMENT: FALLS WITHIN ACCEPTABLE LIMITS

Table 2. Analysis of treated effluents, 8 July 1982

Temperatur	22°C	
pH	7,15	
Dissolved O_2 in the sample as measured on site	3,3	mg/l
COD	164	mg/l
Settleable solids	0,1	ml/l
Dissolved solids	30	mg/l
- evaporated at 105°C	26	mg/l
- residue remaining at 600°C	4	mg/l
Kjeldahl - N	26,5	mg/l
Chloride	347	mg/l
BOD_5 at 20°C	14	mg/l

REFERENCES

1. Selection of Essential Drugs, WHO Technical Report Series 641, 1979

2. Second Panel Meeting or Industrial Experts on the Pharmaceutical Industry, UNIDO, ID/WG. 267/4/Rev.1, 1978

3. Background Paper on Availability Pricing and Technology of Essential Drugs, UNIDO/PC.14, 1981

4. First Consultation on the Pharmaceutical Industry, Lisbon, Portugal, UNIDO Report ID/259, December 1-5, 1980

5. Meeting on Cooperation among Developing Countries, organized by the National Council of Pharmacists, Morocco, December 4-5, 1981

6. Remingtons' Pharmaceutical Sciences, 16th edition, Mack Publishing Co., Pennsylvania, 1980

7. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 17, pp. 723-743, 3rd edition, Wiley, 1970
U. S. Patents, 2,731,492 (January 1956); 2,890,240 (June 1959); 3,235,583 (February 1966)

8. U. S. Patent 2,998,450 (August 1961)

9. U. S. Patent 3,657,267 (April 1972)

10. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 14, pp. 652-707; Vol. 15, pp. 213-224, 3rd edition, Wiley, 1970

11. U. S. Patents 2,985,648 (May 1961); 3,079,307 (February 1963); 3,140,282 (July 1964 ; 3,144,445 (August 1964); 3,157,640 (November 1964)
F. P. Doyle, G. R. Fosker, J. H. Naylor, H. Smith, J. Chem. Soc., p. 1440 (1962)
UNIDO Regional Seminar on Ind. Applic. of Microbiology in the Pharmaceutical Industry, Havana, 1979, ID/WG. 300/6

12. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 14, pp. 652-707; Vol. 15, pp. 213-224, 3rd edition, Wiley, 1970

13. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 12, pp. 632-661, 3rd edition, Wiley, 1970

14. U. S. Patents 2,407,966 (September 1946); 3,119,818 (January 1964)
W. T. Caldwell, E. C. Kornfeld, C. K. Donneil, J. Amer. Chem. Soc. 63, 2188 (1941)
K. C. Roblin, P. S. Winnek, J. P. English, J. Amer. Chem. Soc. 64, 567 (1942)

15. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 20, pp. 1-33, 3rd edition, Wiley, 1970
UNIDO Regional Seminar, Havana, 1979, ID/WG. 300/3
Anonymous, Chem. Engin. pp. 228-231, March 1957

16. U. S. Patents 2,487,893 and 2,487,895 (April 1949)

17. U. S. Patent 2,385,899 (October 1945)
R. E. Buckles, J. Chem. Ed. 36 (1954)

18. A. R. Surrey and H. F. Hammer, J. Amer. Chem. Soc. 68, 113-116 (1946)
U. S. Patent 2,233,970 (March 1941)

19. R. C. Elderfield, H. E. Mertel, R. T. Mitch, I. M. Wempen, E. Werble, J. Amer. Chem. Soc. 77, 4816-4819 (1955)

20. R. G. Wilkinson, R. G. Shepherd, J. P. Thomas, C. Baughn, J. Amer. Chem. Soc. 83, 2212-2213 (1961)
F. H. Radke, R. B. Fearing, S. W. Fox, J. Amer. Chem. Soc. 76, 2801-2803 (1954)

21. Kirk-Othmer Encyclopedia of Chemical Technology, 21, 528-541, 3rd edition, Wiley, 1970
U. S. Patents 2,830,994 (April 1958); 2,596,069 (May 1952)

22. Kirk-Othmer Encyclopedia of Chemical Technology, 19, 33-48, 3rd edition, Wiley, 1970
H. Irhoffen, W. Logemann, W. Hohlweg, A. Serini, Berichte 71, 1024-1029 (1938)
H. Smith et al., J. Chem. Soc., 4472-4492 (1964); G. H. Douglas et al., S. Chem. Soc., 5072-9411 (1963)

23. U. S. Patents 2,484,029 (October 1949) and 3,058,882 (October 1962)

24. U. S. Patent 3,337,628 (August 1967)

25. U. S. Patent 2,833,771 (May 1958); L. Dorfman, A. Forlenmeier, C. Huebner, R. Lucas, H. MacPhillamy, J. Mueller, E. Schlittler, R. Schwyzer, A. St. Andre', Helv. Chim. Acta 37, I. No. 7, 59-75 (1954)

26. Kirk-Othmer Encyclopedia of Chemical Technology, 19, 255-261, 3rd edition, Wiley, 1970

27. Kirk-Othmer Encyclopedia of Chemical Technology 11, 838-846, 3rd edition, Wiley, 1970

28. U. S. Patents 2,243,887 (June 1941); 2,251,934 (August 1941); 2,265,976 (December 1941), 2,267,257 (December 1941)

29. Kirk-Othmer Encyclopedia of Chemical Technology, 4, 25-61, 4th edition, Wiley (1978)

30. Kirk-Othmer Encyclopedia of Chemical Technology, 2, 747-762, 3rd edition, Wiley, 1970

31. U. S. Patents 2,738,301 and 2,738,302 (March 1956);
Kirk-Othmer Encyclopedia of Chemical Technology 21, 542-549, 3rd edition, Wiley, 1970

32. U. S. Patents 2,972,634 (February 1961) and 3,060,229 (October 1962)
O. Isler, W. Huber, A. Ronco, M. Kofler, Helv. Chim. Acta 30, VI, 1911-1927 (1947)
A. F. Wagner and K. Folkers, Vitamins and Coenzymes, 280-307, New York 1964

33. C. R. Kunin "Ion Exchange Resins," 2nd edition, Wiley, New York, 1958

34. K. Doerfner, "Ion Exchangers-Properties and Applications" Ann Arbor Science, 1972

35. T. V. Arden, "Water Purification by Ion Exchange," Butterworths, London, 1968

36. J. A. Marinsky, "Ion Exchange," Vol. 1, Marcell Dekker, 1966

37. V. Marten, "Desalination by Reverse Osmosis," MIT Press, Massachusetts, 1966

38. E. Sourirajan, "Reverse Osmosis," Academic Press, New York, 1970

39. M. C. Porter, I & E C Prod. Res. & Dev. 11(3), 234-248, 1972

40. R. L. Goldsmith, I & E C Fundamentals 10(1), 113-120, 1972

41. P.A. Disessa, Pharmaceut. Technol. 4(11), 103-112, 1980

42. R. Saari et al., Bull Parenteral Drug Assn. 31(5), 248-253, 1977

43. R. G. Stevie and R. M. Clark, "Package Water Treatment Plants," EPA-600/2-80-8008b (July 1980)

44. R. C. Gumerman, R. L. Culp and S. P. Hansen, "Estimating Water Treatment Costs," EPA-600/2-79-162a (August 1979)

45. J. R. Drew, Chem. Eng. Progr. 71(2), 92-99 (February 1975)

46. J. R. Drew in Handbook of Separation Techniques for Chemical Engineers; P.A. Schweitzer, ed.; 1-201 to 1-219, McGraw Hill, New York, 1979

47. W. F. Furter, Chem. Eng., CE173, June 1968

48. Anonymous, Pharmaceutical Industry Hazardous Waste Generation, Treatment, and Disposal U. S. EPA 1.17:508 (1976)

49. S. G. Saad and M. I. Zaki, paper presented at First Intern. Symposium on Environmental Technology for Developing Countries, Bogazici University, Istanbul, July 1982

50. Development Document for Pharmaceutical Manufacturing Point Source Category, p. 169, EPA 440/1-75/060, December 1976

51. E. J. Struzeski, Jr., Waste Treatment and Disposal Methods for the Pharmaceutical Industry EPA/330/1-75/001 (PB 255-582), March 1975

52. J. H. Mayes, Characterization of Wastewaters from the Ethical Pharmaceutical Industry, USEPA 670/2-74-057 (July 194) [PB-233 116]

53. D. W. Sundstrom and H. E. Klei, Wastewater Treatment, Prentice Hall, 1979

54. Innovative and Alternative Technology Assessment Manual, EPA-430/9-78-009, February 1980

55. P. Pipyn, W. Verstraete and J. P. Ombregt, Biotechnology Letters 1, 495-500 (1979)

56. J. B. Carmichael, Environmental Pollution Control in the Pharmaceutical Industry, paper prepared for UNIDO world-wide study on the pharmaceutical industry, UNIDO, Vienna, February 1978

57. R. H. L. Howe, Wastes Engineering 31,728-731, 752-753 (1960)

58. W. G. Barker et al., Proceedings of the 15th Purdue Industrial Waste Conference, Indiana, pp. 58-67, May 1960

59. W. G. Barker et al., Proceedings of the 28th Purdue Industrial Waste Conference, Indiana, May 1973

60. R. E. McKinney, Biotechnology & Bioengineering IV, 181-195, 1962

61. R. W. Herion & H. O. Loughhead, Proceedings of the 18th Purdue Industrial Waste Conference, pp. 218-232, May 1963

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