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

EXECUTIVE SUMMARY

Prepared by the
Division for Industrial Studies

* Presented to the Second Consultation on the Pharmaceutical Industry,

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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.

DEFINITIONS

\textbf{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.

\textbf{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.
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INTRODUCTION

This is a summary of a 125-page study with the same title, document number UNIDO/IS.387, available on request from UNIDO. It is presented to the Second Consultation on the Pharmaceutical Industry as an overview of recommended water use, water supply and effluent-treatment practice associated with the twenty-six drugs on the UNIDO illustrative list for production and/or formulation and packaging in developing countries. In addition to analyzing water requirements, water supply and water use and effluent-treatment practices, the report also explains, using a generic framework, water quality needs that are special for manufacturing pharmaceuticals. Problems of effluent treatment and disposal are examined in generic fashion and specific examples discussed as well. A special section of the report treats the problems of recovering and purifying the various solvents that are widely used in the manufacture of pharmaceuticals.

Section I - The Twenty-six Essential Drugs

Beyond the major topics of water use, effluent treatment and solvent recovery, the report also gives a summary outline for one possible method of manufacture of each of the twenty-six drugs. For some drugs only a brief one-paragraph summary is given, whereas for nine drugs considerably more information is provided including an idealized, schematic, process-flow sheet showing water requirements and where waste generation and solvent use and recovery can arise. The nine drugs treated in such detail are those identified by the UNIDO Consultation on the Pharmaceutical Industry to be considered for production in developing countries starting from raw materials or intermediates. The accompanying table summarizes the special water requirements, waste generation and solvent recovery needs for fourteen drugs among which the nine are included. Each of the drugs in this table requires Drinking Water and Purified Water for its manufacture. Only two or three involve a fermentation waste but more than half involve the production of some solid waste. Each involves the production of wastewater from a filtration operation and each requires the use of a solvent and, therefore, a solvent recovery operation.
<table>
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<th>SOLID WASTE</th>
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<td>PURIF.</td>
<td>WFI</td>
<td></td>
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<tr>
<td>Acetylsalicylic acid</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Ampicillin</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N**</td>
<td>N</td>
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<tr>
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<td>Y</td>
<td>Y</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Diethylcarbamazine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Dapsone</td>
<td>Y</td>
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<tr>
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<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Ethambutol</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Insulin</td>
<td>Y</td>
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<td>Y</td>
<td>N</td>
<td>Y</td>
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<td>Y</td>
<td>N</td>
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<td>Blood Fractions</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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* Water requirements will depend in part on the regulations and standards set by local laws. Water-for-injection (WFI) is required only when a particular drug is to be manufactured in injectable form; PURIF = "purified water"; DRNKG = "drinking water".

* The first nine drugs on this list are those selected by UNIDO as essential and of special economic importance for developing countries.

** It is assumed ampicillin is manufactured from 6-APA. Back integration to include manufacturing 6-APA will generate fermentation wastes.
Section II - Water Supply for Pharmaceutical Manufacture, Formulation and Packaging

The section of the report concerned with water supply and use considers first those general water requirements for drug manufacture and/or formulation and packaging: cooling water, process water, water for steam generation (boiler feed water) and water for sanitary and service use. The report then goes on to discuss the rigorous process water needs specifically required for the manufacture of pharmaceuticals. Of particular interest is the sequence of treatment whereby natural waters can be purified to "drinking water", then to "purified water for drug manufacture", then to "pyrogen-free water" used for preparing injectable drugs. The various criteria for different levels of water purity are discussed. Then the important technologies for purifying water are described. Special attention is given to distillation and other methods of preparing pyrogen-free water. A typical water-purification system for a large drug-manufacturing plant is also discussed with reference to a schematic flow diagram. Detailed costs and economic information are given for water purification by distillation and by ultrafiltration. The economics of drinking water production are also discussed.

Recycling and re-use of cooling water offers great potential for water savings as well as avoiding thermal pollution of streams. Technologies for recycling cooling water include cooling towers with natural or forced-mechanical draft and cooling ponds with spraying units or with large surface area. There are often problems involved in re-using other process water for cooling purposes and extensive treatment of such process effluent water may be required to bring it to the purity required in the cooling systems.

Process water is used as a solvent, transporter or cleaning medium to remove wastes. In many cases, process water can be conserved by using the water emanating from one process stage in another stage. In some cases process water can be treated and then re-used. In other cases it is discharged after treatment. Such treatment can often recover valuable raw materials, solvents and by-products.
Boiler make-up water is used to replace losses of process steam or condensate not returned to the boiler. High purity requirements must be achieved to prevent corrosion and scale formation which could block the steam system. Recycling of steam and condensate is established industrial practice.

Sanitary water requirements usually depend mostly on the number of employees. There is little recycling of treated sanitary waste waters. Sanitary wastes are usually discharged to a biological waste water treatment plant. Recycled disinfected waters can be used in maintenance, building cleaning, dust control and other non-process related uses.

There are rigorous requirements for process waters which actually come into contact with drugs or drug raw materials. Three levels of quality are usually recognized: Drinking Water, Purified Water and Pyrogen-Free Water. Drinking Water is used in preparation of drug substances but not for the preparation of dosage forms. Purified Water is purified beyond ordinary Drinking Water quality by distillation, ion-exchange, reverse osmosis or other suitable processes. Purified Water is suitable for preparation of dosage forms not intended for injection. Pyrogen-Free Water can be used for injectable dosage forms. It must be free of pyrogenic substances and is almost always prepared by careful distillation, although reverse osmosis can also be used in some instances.

Ion-exchange purification removes salts and minerals including undesirable metallic ions. The ionic impurities are adsorbed on beds of special polymeric resins which must be regenerated periodically.

Reverse osmosis and ultrafiltration are membrane purification processes in which the pure water passes through the membrane but impurities are retained on the high pressure side of the membrane. Fluxes through membranes are usually in the range of about 15-25 gal/ft²-day (0.006-0.01 m³/m²-day). Operating costs for membrane systems usually vary within a range of $0.20 - $5.00 per 1000 gallons.

Distillation is the most widely practiced method for preparing Water for Injection and Purified Water. Special apparatus is required to prevent
microscopic water droplets from contaminating the vapor produced. Some often-used approaches for optimizing energy usage in distillation systems are vapor compression, thermocompression and multi-effect staging. Depending on the costs of energy and cooling water, the operating costs for purifying water by distillation can range from about $60 per 1000 gal of product water for a small (50 gal/hr) single-effect still to about $6 per 1000 gal of product water for a large (3000 gal/hr) multiple-effect still. Some approximate comparative operating costs for a low capacity system are $40-60 per 1000 gal for ordinary distillation, $4-8 per 1000 gal for thermocompression distillation or for reverse osmosis. Some comparative capital costs for a 200 gal/hr system are $60,000 for ordinary distillation, $140,000 for thermocompression distillation and $20,000 for reverse osmosis. Approximate costs for production of Drinking Water in plants of 1 million gal/day capacity are:

<table>
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<tr>
<th></th>
<th>Construction Costs</th>
<th>Annual Operating and Maintenance Cost</th>
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<td>Conventional Municipal Plant</td>
<td>$1.1 Million</td>
<td>$62,600</td>
</tr>
<tr>
<td>Packaged Plant</td>
<td>$0.5 Million</td>
<td>$40,400</td>
</tr>
</tbody>
</table>

Under reasonable assumptions as to interest rates and plant lifetime this suggests Drinking-Water costs ranging up to about $0.50 per thousand gallons. All figures are in 1979 U.S. dollars.

Section III - Solvent Recovery

The section of the report or solvent recovery is concerned primarily with the purification of used solvents so they can be used again. The following major methods of purification are examined: fractional distillation, liquid-liquid extraction and decantation. The stripping and enriching sections of a continuous fractional distillation column are explained and means of dealing with the special problem of azeotrope formation are discussed. Azeotropes are those compositions for which the liquid and its equilibrium vapor have the same composition; simple distillation, therefore, cannot separate such mixtures. In a continuous, multistage,
distillation column, the upper rectification section is where heavier components are condensed into a descending liquid phase from an ascending vapor phase. In the lower stripping section the descending liquid gives up lighter components to rising vapors.

The simple separation of binary mixtures is considered from the standpoints of two-phase formation and azeotrope formation. Decantation and combined decantation and stripping are discussed for two-phase systems. The application of batch and continuous distillation as well as steam stripping is examined for single-phase systems which do not form azeotropes. For two-component systems which form azeotropes the following methods are explained: distillation at different pressures, adding an "entrainer" for "azeotropic distillation", adding a "solvent" for "extractive distillation", adding a salt or other chemical agent to destroy the azeotrope, or extraction of one of the components into an immiscible solvent which does not form an azeotrope.

When a binary mixture does not involve azeotropes, or when azeotropic compositions are acceptable as products, a continuous fractionating column can be used. A batch still could also be used and would often be preferred for small-scale, low-volume or intermittent operation, or when the feed mixture contains solids. When a binary mixture forms two phases that are relatively pure, it may be sufficient merely to decant one phase from the other to get a satisfactory separation. Binary mixtures which form two phases with significant mutual solubility usually have an azeotropic composition within the two-phase composition range; such mixtures can be purified using two stripping columns and a decanter.

There are several approaches to purifying single-phase, binary systems which form azeotropes: (1) Change the pressure to modify azeotropic behavior, (2) Add a third component to form a ternary azeotrope that separates into two layers, one of which is enriched in the third component (called an entrainer). This kind of process is called azeotropic distillation and an example is the use of benzene as an entrainer for ethanol-water mixtures, (3) Add a third component or "solvent" which does not form an azeotrope with either component of the
feed. The solvent's role is to alter the relative volatility of the original pair. An example of this "extractive distillation" technique is the use of dimethylformamide as solvent for separating mixtures of tetrahydrofuran and water. (4) Add a salt to reduce the vapor pressure of the component in which the salt is more soluble, (5) Extract one of the components into an immiscible solvent.

Solvent systems containing more than two components are also discussed. For multi-component systems which do not form azeotropes two approaches are explained: a series of continuous fractionation columns and the use of batch distillation when the number of components is large. Such a series of continuous fractionation columns would ordinarily require a number of columns equal to one less than the number of individual solvent components in the system. When azeotropes form in multi-component systems the separation problem can be quite complex and a research project may be required to develop a purification scheme in such cases unless already-worked-out technology is available. Systems for separating multicomponent mixtures which form azeotropes can entail combinations of continuous and batch distillation, decanting, multistage extraction and chemical treatment. For example the system ethanol-ethylacetate-water involves three binary azeotropes and its separation requires a combination of multistage fractional extraction, binary distillation and azeotropic distillation.

Capital and operating costs of fractional distillation plants for purifying solvent mixtures are presented. The major portion of operating costs for distillation plants is the cost of steam. The installed cost of fractionating equipment varies from about $400,000 for a single column with a solvent rate of about 1000 gal/hr to about $20,000 for a single column with a solvent rate of about 10 gal/hr. These figures are in December 1975 U.S. dollars and cover the fractionating column, heat exchangers, pumps, piping and instruments. If more than one column is required then these costs should be multiplied by the number of columns.
Section IV - Wastes and Waste Water Treatment

This section of the report begins with a general discussion of the various types of waste which arise during drug manufacture. Careful waste management and good general manufacturing practices can reduce the generation of wastes and conserve raw materials. Careful attention to spent organic solvents, fermentation mycelia and fermentation broths can often find alternative uses or recycling uses for such materials thereby preventing them from becoming wastes which require costly treatment.

Wastewaters from pharmaceutical manufacturing will be different for different types of operations: organic synthesis, fermentation operations, formulating, compounding and packaging. A survey of various such manufacturing plants is reviewed including treatment methods, treatment levels and wastewater pollution concentrations. In a similar context the wastes expected from the manufacture of the UNIDO twenty-six drugs are discussed in summary form, based on the schematic manufacturing information given in Section I of the report.

The amount and strength of wastewaters can be reduced substantially by good manufacturing practices such as: careful supervision of each step of the process including a system of checking supervision; proper identification and control of all containers, pipes, equipment and chemicals; special care to keep antibiotics out of wastewaters; removal of solids from wastewaters before biological treatment; practicing "equalization" as an integral part of wastewater management; keeping out of wastewaters any component it is possible to keep out, especially organic solvents; extracting byproduct values from fermentation wastes or finding alternative uses for these high-strength wastes rather than releasing them to a biological waste-treatment system.

Pharmaceutical plants which are merely formulating, compounding and packing operations usually produce only small amounts of waste that is easily treatable, most of it sanitary waste from employees. Chemical synthesis operations generally produce the most difficult-to-treat wastewaters and these are often diluted with other wastewaters, or with domestic sewage before treatment. Spent fermentation broth is a very strong wastewater;
often its treatment costs can be reduced by converting the broth into a byproduct such as animal feed. In a survey of waste treatment at three pharmaceutical plants, treatment costs ranged from about $1.00 to $2.50 per 1000 US gallon, with BOD reduction ranging from 87 to 92% and COD reductions ranging from 86 to 91%. In a similar survey for four chemical synthesis plants (some of which also performed pharmaceutical formulation) the treatment cost range was about $0.40 to $9.50 per 1000 gallon, the BOD reduction range was 39 to 95% and the COD reduction range 13 to 86%.

Of the 26 drugs on the UNIDO list most entail the formation of a solid waste during manufacture and solvent recovery is required in essentially every case. Fermentation, and therefore fermentation wastes, is associated with the manufacture of about one third of these drugs.

Various types of wastewater treatment technology are discussed in detail, including primary and secondary treatment, biological treatment, tertiary treatment methods and other methods such as land disposal, anaerobic filtration and oxidation ponds. Treatment and disposal of biological sludges are also considered. Activated sludge treatment processes receive particularly detailed discussion and ranges for important design parameters are given for such processes. Trickling filters, lagoons, ponds and rotating biological contactors are included in the presentation. Two important tertiary treatment processes discussed are adsorption on active carbon and denitrification.

Conventional activated-sludge treatment systems make use of an aeration vessel followed by a settling vessel where the biological sludge (i.e., the mass of active microorganisms) is separated from the treated wastewater. A portion of the separated biological sludge is recycled to the beginning of the process where it is mixed with incoming wastewater and oxygen (usually as air). The recycled biomass sludge and the air oxidizes a portion of the organic compounds in the wastewater feed to form CO₂ and H₂O and incorporates another portion into newly grown cell mass. Both soluble and suspended organic matter can be removed from the water by this process. The aeration vessel and settling vessel are
connected by a pipe through which a portion of the settled sludge is recycled to the aeration vessel. Settled but unrecycled sludge is removed as a waste. The yield of such waste sludge is usually in the range of 0.3 - 0.9 mass of dry solids per mass of BOD removed from the wastewater. Often as much as 25-50% of the total volatile solids in such a sludge can be biologically inactive. There are several variations of the activated sludge process, such as substituting a cylindrical mechanically agitated tank for the more usual long rectangular aeration tank. Such a well mixed tank is more resistant to shock loads because of the dilution effect. Other variations of the activated sludge process are "contact stabilization", "step aeration" and processes which use pure oxygen instead of air. Design loadings for activated sludge processes can range from 0.02 to 0.04 lb BOD/ft$^3$-day. Removal efficiencies range from about 85 to 95% of the BOD.

The trickling filter is a biological treatment process in which the active microbial growth forms as a layer on solid material such as gravel, stone, slag or plastic forms within a deep cylindrical bed. The layer of biological growth absorbs organic waste components from the wastewater that passes through the filter under aerobic conditions. Continual sloughing off of the biological film produces a settleable sludge, at least a part of which is withdrawn as a waste. The flow scheme for using trickling filters is similar to activated sludge systems in that the biological-treatment stage is preceded by a primary settler upstream and followed by a secondary settler downstream. Loading rates of trickling filters can range from about 10 to 150 million gal/acre-day and about 5-100 lb BOD/cu ft-day. Removal efficiencies range from 70-90% of the BOD.

Lagoons and ponds open to the air can sometimes provide adequate treatment in the form of simultaneous settling and some biological oxidation. They should be considered for use where land is cheap and plentiful, simple operation is required, freezing weather does not occur and new ponds can be created to replace old ones filled up by accumulated solids. Anaerobic wastewater treatment processes such as deep filtration are not often used but in certain instances they may offer solutions
to odor problems and provide by-product heating values in the form of methane gas generated during treatment. Disposal by application of wastewaters to agricultural land can be successful but is limited by climate, terrain, the nature of the crop and the composition and toxicity of the wastewaters. Tertiary treatment refers to add-on processes used to remove pollutants from wastewater not removed by the primary settling process and the secondary biological-oxidation processes. The two most widely practiced tertiary processes are adsorption of dissolved components from the wastewater onto beds of activated carbon and denitrification which converts nitrate in the waste-waters to harmless nitrogen by means of an organic reducing agent.

The waste sludge from biological treatment processes represents a major disposal problem. Typical alternatives are disposal in a secure land fill, land application if no solvents or other hazardous materials are present, composting or incineration. Before disposal it is common practice to reduce the sludge volume by aerobic or anaerobic digestion, centrifugation or vacuum filtration.

Several actual waste treatment installations for pharmaceutical manufacturing are discussed in the report. These include facilities at the Hoffman-LaRoche Company, Belvidere, NJ, U.S.A., Abbott Laboratories, Chicago, IL, U.S.A. and the Merck Sharpe and Dohme Company, West Point, PA, U.S.A. Various operations, treatment units, flow rates, equipment sizes and types are presented for each of these installations. Examples of such equipment are screens, pre-clarifiers, equalization basins, agitators, aeration basins, flocculator-clarifiers, secondary clarifiers, oxidation ponds, chlorinators, sludge thickeners, neutralizers, degassing chambers, sludge centrifuges, pasteurization units, evaporators, comminuters and sand filters.

A subsection on wastewater treatment economics discusses general treatment costs for the pharmaceutical manufacturing industry and the assumptions inherent in such cost estimates are also considered. Tables and graphs are given for capital costs and operating costs for various unit operations used in wastewater treatment. This information is then
applied, as a hypothetical example, to the Abbott Laboratories wastewater treatment plant discussed above. The overall estimated treatment costs are shown to agree approximately and within the assumptions made with those actually reported for that plant. The total treatment cost estimated was capital cost ($0.58/thousand gal), operating and maintenance cost ($0.26/thousand gal) and sludge disposal cost ($1.99/thousand gal) for a total cost of $2.83/thousand gal in 1979 U.S. dollars. The treatment cost reported by the pharmaceutical company was $4.50/thousand gal (1978 U.S. dollars).
CASE STUDY - The Gedeon Richter Pharmaceutical Company, Hungary

The Gedeon Richter company produces pharmaceuticals through synthetic organic chemical means, through fermentation processes and produces 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 Vermox), 19. Reserpine, 22. Ethinyloestradiol and levonorgestrel, and 25. Hydroxocobalamin.

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

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.

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

The plant has three separate sewer systems for waste water: sanitary sewer, rain water run-off, and process effluents. There are government regulations for the control of effluent discharges:

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.
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. About 90% removal of organic pollutants and about 99% removal of suspended solids from the effluent are achieved by the waste water treatment plant.

A laboratory at the plant site carries out daily analyses of untreated and treated effluents. A chemical coagulation unit is planned for further polishing the secondary treated effluent. Sludges are land filled.

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. Distillation columns are used to further purify the water that is used to prepare injectables and solutions to be taken orally. 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.

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. Microbiological testing of final pharmaceutical products is also carried out by the Central Control Laboratory.

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.
CASE STUDY: Janssen Pharmaceuticals, Beerse, Belgium

The Janssen Pharmaceutical plant at Beerse, Belgium, is a large complex carrying out research and manufacturing a broad range of pharmaceutical products based on organic chemicals synthesis. 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 manufactured.

Water meeting the drinking water quality standards of WHO is used for all production requirements of pharmaceuticals synthesis. Ground water 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. 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.

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 is first passed through ion exchange columns to remove the hardness. 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 Janssen to ensure the water and the final injectable products are pyrogen-free.

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. Waste solvents which cannot be recovered are discharged to a sewage system separate from the one which receives waste waters. The waste solvents are collected and disposed by incineration.
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.

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 primary-treated waste waters next enter a high rate trickling filter. The filter contains a corrugated polyvinyl chloride medium. About 60-70% of the remaining organic pollution are removed by the trickling filter. The effluent then receives activated sludge treatment with extended aeration and final clarification. Forced aeration occurs utilizing compressed air. The activated sludge plant removes about 90% of the 30-40% of organic pollution 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.

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. Janssen has the capability of re-using all of the tertiary treated effluent. 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.

The final effluent is analysed twice daily by Janssen personnel. 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 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.

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.
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.)