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CONTEMPORARY TECHNIQUES FOR THE PRODUCTION OF ULTRA-PURE WATER IN THE PHARMACEUTICAL INDUSTRY

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Abstract

The paper reviews the latest manufacturing techniques for producing ultra-pure water to meet the standards specified for the pharmaceutical industry.

The various water treatment techniques are considered in terms of their effectiveness in removing the multiplicity of contaminants found in raw water supplies. The concept of a water purification system is developed, and particular stress is placed on synergistic combinations of ion-exchange and membrane processes that produce high-purity water cost-effectively. Also highlighted is the importance of good system design and validation procedures.

Water treatment principles are illustrated by reference to case histories of pharmaceutical installations, including a low-cost, membrane-based system for providing apyrogenic water.

1. INTRODUCTION

Water is a vital ingredient in many pharmaceutical preparations. Its remarkable properties as a solvent make water an ideal vehicle for a broad range of medicines. But natural waters contain a host of chemical and microbiological contaminants. Since these contaminants could react with the active ingredients of medicines - or adversely affect patients' health - the water used in the manufacture of pharmaceutical products must be purified. Modern water purification systems must deliver low-cost, ultra-pure water directly to the points of application in the production areas.

2. WATER STANDARDS

The quality of the water used in the pharmaceutical industry is defined by the appropriate pharmacopoeia. The British Pharmacopoeia, for instance, recognises three main grades of water. When the term 'Water' is used in recipes without further qualification, it refers to potable water freshly drawn from the public supply and suitable for drinking, or to freshly boiled and cooled Purified Water. This grade of water is specified for the preparation of orally-administered elixirs, linctuses and mixtures.

The second grade of water - 'Purified Water' - must conform to the criteria laid down by the European Pharmacopoeia. It may be prepared from potable water by distillation, ion-exchange or any other suitable method; its quality is defined in terms of acceptable limits for particular inorganic and organic impurities determined by specific chemical tests. Water of this quality is used to prepare ophthalmic and topical solutions.

'Water for Injections' is the grade of water used in the formulation of parenteral solutions. In addition to complying with the tests for Purified Water, it must also be free from pyrogens and practically free from suspended particles when examined under optimal conditions. An important distinction between the European Pharmacopoeia and the United States Pharmacopoeia is that the EP stipulates that Water for Injections must be prepared by distillation, whereas the USP allows it to be produced either by distillation or by reverse osmosis.

3. WATER AS A RAW MATERIAL

Even after treatment by the water authorities, natural waters still contain mineral salts, trace metals, organic compounds, dissolved gases and colloidal matter, together with particles in suspension and micro-organisms. Unlike other raw materials, however, the water supply varies in quality both from one geographical region to another and from season to season.

Water derived from an upland surface source, for instance, usually has a low level of total dissolved solids (TDS), is relatively soft but rich in organic contamination, much of it colloidal. By contrast, water from an underground source generally has high TDS and hardness levels, but a low organic content.

Seasonal variations in water quality are most apparent in surface waters. During the autumn and winter months, dead leaves and decaying plants release large quantities of organic matter into streams, lakes and reservoirs. As a result, the level of organic contamination in surface waters - as

revealed by the number of parts per million of oxygen absorbed in a standard chemical test - reaches a peak in January and February, and falls to a minimum in July and August.

The nature of the raw water supply has an important bearing on the choice of techniques to be used in purifying it. So a complete analysis of the local water supply should always be carried out before a water purification system is designed for a particular factory site. In some cases, site trials may be necessary to establish the feasibility of using particular water treatment techniques.

Table I shows an analysis of the water supply in various parts of Britain, compared with that in Nigeria and the United Arab Emirates.

4. WATER PURIFICATION TECHNIQUES

The water purification techniques used in the pharmaceutical industry fall into two broad categories: ion-exchange and membrane processes. Ancillary techniques - such as depth filtration and adsorption - are often employed to pre-condition the raw water, and ultra-violet sterilisation is sometimes incorporated in later stages of a water purification system.

4.1 Ion-exchange Techniques

4.1.1 Anion-exchange

Ionic organic compounds are extracted from raw waters by replacing them with chloride ions released by an anion-exchange resin. The organic impurities - mainly humic and fulvic acids - are taken up by the resin which must be periodically

TABLE I

TYPICAL NATURAL WATERS

	Cambs.	London	Manchester	Scotland	Nigeria	U.A.E.
Cations						
(mg/l $CaCO_3$)						
Hardness	420	270	35	25	10	2000
Sodium	120	30	15	20	10	3000
Total Cations	540	300	50	45	20	5000
Anions						
(mg/l $CaCO_3$)						
Alkalinity	260	250	15	20	10	100
Chloride	100	20	20	20	5	4800
Sulphate/ Nitrate	180	30	15	5	5	100
Total Anions	540	300	50	45	20	5000
Others						
Iron	0.05	0.05	0.2	0.3	1.0	0.05
O.A.	0.5	0.1	0.8	6.5	0.1	0.4
Silica	12	20	5	5	20	40
T.D.S.	800	400	80	60	30	7700
pH	7.1	7.6	8.2	6.7	4.7	7.5
F.I.	2	2	20	85	20	7

regenerated with sodium chloride solution. The anion-exchange resins used in organic scavengers have a macroreticular structure with large pores that allow the bulky organic anions to be eluted out during regeneration.

In some cases a macroreticular de-colloid resin with even larger pores is employed to remove colloid particles from the water supply. The main function of organic scavengers is to protect reverse osmosis membranes and ion-exchange resins from organic poisoning.

4.1.2 Cation-exchange

Base-exchange softeners containing cation-exchange resins in the sodium form are widely used to pre-treat the feedwater for pharmaceutical water purification systems. The resins remove the hardness cations of calcium and magnesium by replacing them with sodium ions.

Once they become exhausted, the resins are restored to the sodium form by regeneration with sodium chloride solution.
Base-exchange softeners are employed mainly to pre-condition reverse osmosis feedwater in order to prevent scaling-up of the membranes. A secondary effect is that the sodium ions stabilise any colloid particles present in the water, making them less likely to settle out on the membrane surface.

4.1.3 Deionisation

Deionisation is the principal ion-exchange technique used in pharmaceutical water purification

systems. It utilises a cation-exchange resin - which releases hydrogen ions in exchange for impurity cations - together with an anion-exchange resin which releases hydroxyl ions in exchange for impurity anions. The hydrogen and hydroxyl ions unite to form water molecules, while the ionic impurities are taken up by the resins. Periodically, the resins must be regenerated by washing the spent cation-exchange resin with acid and the spent anion-exchange resin with alkali.

The two kinds of resin can either be housed in separate pressure vessels (as in a two-bed deioniser) or mixed together in a single pressure vessel (as in a mixed-bed deioniser). The quality of the water produced by a two-bed deioniser is limited by a phenomenon called 'sodium slip' in which sodium ions leak from the cation bed and combine with hydroxyl ions from the anion bed. As a result, two-bed water contains a few parts per million of sodium hydroxide, giving it an alkaline pH and a conductivity of up to 30 μS/cm.

The purity of twin-bed water can be significantly improved by utilising the counter-current mode of regeneration, whereby the purified water leaving the resin bed has its last contact with a layer of highly regenerated resin. Sodium slip is minimised, so that the water has a conductivity of less than 5 μS/cm and a pH in the range of 7.0 to 7.5.

Water of this quality meets the EP specification for Purified Water, but does not

always conform to the USP specification in which the pH must not exceed 7.0. This problem can be resolved either by using a second cation-exchange column after the two-bed unit to remove the sodium hydroxide, or by using a mixed-bed deioniser. Mixed-bed water is, however, expensive to produce and may be unnecessarily pure. The water produced by a three-bed deioniser, for instance, is pure enough to be used as water for irrigation in the manufacture of contact lenses.

Deionised water of the highest quality is produced by a mixed-bed deioniser. The juxta-position of cation - and anion - exchangers in a single column ensures that highly efficient ion-exchange takes place with minimal leakage of ions. Thus mixed-bed water is ultra-pure, with a conductivity of less than 0.5 μS/cm (usually less than 0.1 μS/cm) and a pH of 7.0. Table II compares the quality of mixed-bed water with that of purified water obtained from a standard two-bed plant and a counter-current plant.

4.2 Multi-media Filtration

This technique is used to pre-condition the feedwater for the main water purification system. Multi-media filters incorporate several graded layers of sand - to provide depth filtration - together with other media which can remove either organic impurities or iron compounds from the feedwater. Instead of using an organic scavenger, for example, a layer of activated carbon can be included in a multi-media filter to adsorb organic

TABLE II

Comparison of Water Quality from Mixed-bed and Two-bed Deionisers

	Mixed-bed	Two-bed (counter-current)	Two-bed (co-current)
Conductivity	<0.5 μS/cm	<5.0 μS/cm	<30.0 μS/cm
Resistivity	>2.0 MΩ-cm	>0.2 MΩ-cm	>0.03 MΩ-cm
Sodium	<0.01 ppm	<0.1 ppm	2-10 (avg)
Silica	<0.05 ppm	<0.1 ppm	<1.0 ppm
Residual solids	<0.5 ppm	<3.0 ppm	<15 ppm
Average pH	7.0	7.5	8-9

compounds. If the raw water is rich in iron, a bed of catalysed manganese dioxide in the filter will promote the conversion of ferrous iron compounds to ferric salts. These form insoluble precipitates which can be removed from the filter media by backwashing.

4.3 Membrane Processes

4.3.1 Reverse Osmosis

The most important membrane process for purifying water for pharmaceutical production is reverse osmosis (RO). In this technique, feed-

water under pressure is pumped into a module containing a semi-permeable membrane. A proportion of the influent water passes through the membrane - and is stripped of its contaminants in doing so - to form the 'permeate'. The contaminants accumulate in the residual water - called the 'concentrate' - which is bled continuously to drain.

The higher the proportion of feedwater recovered as permeate, the greater the build-up of impurities in the concentrate stream. There is therefore a risk that the membrane might become fouled by the formation of scale, the precipitation of ferric salts or the deposition of particulate or colloidal matter. To prevent membrane fouling, the feedwater for industrial RO plants must pass through a sequence of pre-treatment units that may include ultrafilters, multi-media filters, organic scavengers and base-exchange softeners.

The key component of a reverse osmosis plant is the semi-permeable membrane. Cellulose-based membranes are susceptible to both chemical and biological degradation and can only be used within a limited pH range.
Most of the membranes used in the pharmaceutical industry are made of polyamide materials that are non-biodegradable and able to tolerate a wide range of pH.

Asymmetric polyamide membranes are fabricated with a hollow fibre configuration, and have a thin, dense active skin on their outer surface.

They have a very large surface area per unit volume, and are operated at high pressures (normally about 28 bar). Hollow fibre RO membranes are prone to fouling, especially by organic-laden surface waters.

Thin-film composite polyamide membranes are manufactured with a spiral-wrap configuration. They have a smaller surface area per unit volume than hollow fibres, but are less susceptible to fouling by surface waters. Moreover, they can be operated at lower pressures (4-15 bar) than hollow fibre membranes.

4.3.1.1 Membrane Performance

Reverse osmosis is an all-embracing water purification technique capable of removing the complete spectrum of impurities found in raw water supplies. Figure I shows that RO membranes are able to take out not only particulates, colloids, micro-organisms and macromolecules from the feed-water, but small molecules and ions as well.

The performance of the asymmetric and thin-film composite polyamide membranes - together with that of cellulosic membranes - is shown in Table III.
Both kinds of polyamide membrane have a better performance than the cellulosic membrane, but the thin-film composite membrane has a lower molecular weight cut-off than the asymmetric one, as well as a higher removal efficiency for inorganic ions and silica.

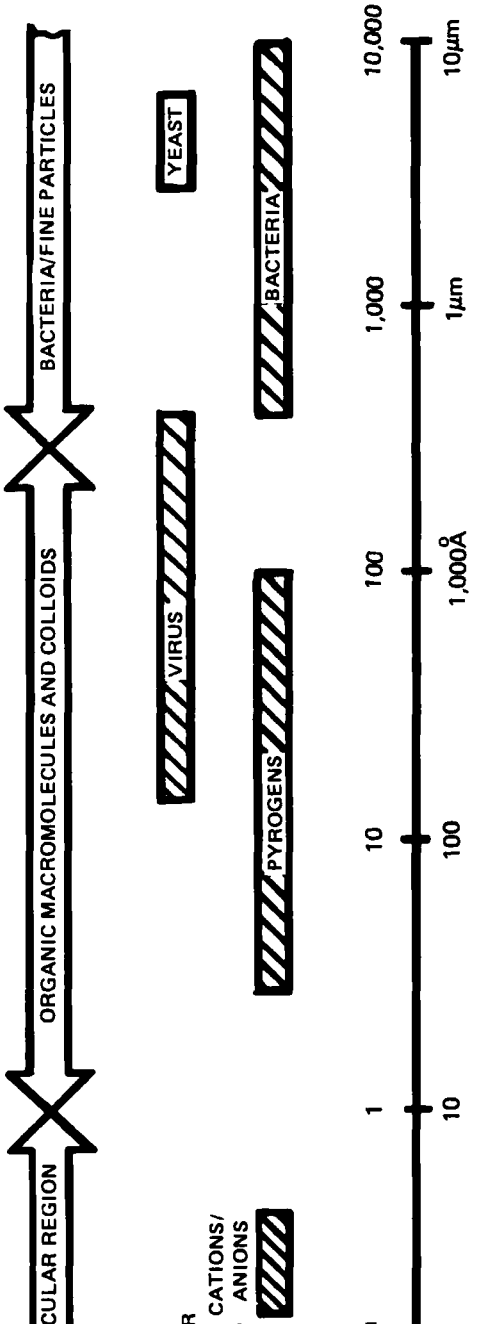

FIGURE I

Effectiveness of Membrane Processes in Removing Contaminants from Water

TABLE III

Comparison of Performance of RO Membranes

Substance	Removal Efficiency %		
	Spiral-wrap Cellulosic	Hollow Fibre Asymmetric	Spiral-wrap Composite
Suspended solids	100	100	100
Colloids) Bacteria) --- Viruses) Pyrogens)	99.5	>99.5	>99.5
Molecular Weight Cut-off	500	250	100
TDS Rejection Rate (inorganic ions)	85-95	90-95	96-98
	Notes (i) Polyvalent ions rejected more efficiently than monovalent ions. (ii) Bicarbonate and fluoride rejected more efficiently at high pH.		
Silica Rejection Rate	82-90	88-90	95-98

4.3.2 Ultrafiltration

Ultrafiltration (UF) is a low-pressure membrane process in which the rejection of impurities is governed by the size of the impurity molecules or particles in relation to the pore size in the membrane structure. Ultrafiltration membranes can therefore be fabricated to have a specific molecular weight cut-off - usually between 6,000 and 80,000 daltons in the UF membranes used in water treatment.

The membranes normally have a hollow fibre configuration, and are non-biodegradable with a high degree of physical and chemical stability. They have a larger diameter than RO hollow fibres, and the active skin of the membrane is on the inner surface of the fibre. Unlike RO membranes UF hollow fibres can be cleaned by regular backflushing, together with periodic chemical treatment to remove the gross contamination.

4.3.2.1 Membrane Performance and UF Applications

Figure I reveals that ultrafilters are able to remove three broad categories of contaminants from feedwater: particulates and micro-organisms; colloids; and organic macromolecules, including pyrogens. They can be used either for pre-treatment or 'polishing' applications in pharmaceutical water purification systems. Ultrafilters are particularly effective, for instance, in removing colloids from heavily contaminated raw waters.

The principal polishing applications for UF are in ring-main distribution loops and at points of use.

Of particular interest to the pharmaceutical industry is a new generation of high-temperature UF membranes that can be incorporated in hot-water loops. Reverse osmosis membranes are normally operated at temperatures up to 35°C and require chemical disinfection from time to time. The latest generation of UF membranes can be operated at temperatures up to 80°C - continuously if necessary - and withstand steam-sterilisation at 121°C. Units utilising these membranes must be specially designed to conform to all the requirements of good manufacturing practice.

A test rig has been assembled in the Elga laboratories to demonstrate that hot-water loops incorporating steam-sterilisable UF membranes can produce purified water that meets the EP specification for Water for Injections. Moreover, test data have shown that, in some cases, steam-sterilisation is unnecessary and that an acceptable level of sterility is obtained by using traditional hot-water membrane systems.

5. The Systems Approach

The modern approach to water purification for pharmaceutical production is to integrate synergistic combinations of water treatment techniques into systems that produce ultra-pure water in the most cost-effective manner. Reverse osmosis and deionisation, for example, are complementary processes: when a reverse osmosis plant is placed upstream of a deioniser, the RO membranes remove the non-ionic contaminants and most of the ionic compounds from the feedwater, leaving the ion-exchange resins to take out the remaining ions.

As a result, the resins are protected from organic poisoning and have a greatly extended inter-regeneration lifespan, with a corresponding reduction in running costs. Such systems are installed in many pharmaceutical manufacturing facilities to produce large quantities of low-cost ultra-pure water.

When reverse osmosis and deionisation are combined in the opposite configuration - with the RO unit downstream from the deioniser - the RO membranes act as a final barrier for the removal of bacteria, viruses and pyrogens from the deionised feedwater. Although apyrogenic water produced in this way cannot be used to prepare parenteral solutions in Europe, several pharmaceutical companies have installed membrane-based systems to provide apyrogenic water for washing ampoules and vials and for other non-critical applications.

5.1 System Design

The distribution pipework is a vital component of any water purification system; it must be designed to ensure that the water leaving the purification plant maintains its purity and meets the required specification at the points of application.

The normal arrangement is to feed the purified water into a recirculation tank, from which it is pumped continuously around a ring-main distribution system. Ideally, it should be recirculated at a velocity of approximately 1.5 m/s to discourage bacterial growth. The ring-main may incorporate polishing units and should be constructed without 'dead legs' in which bacteria could proliferate.

The pipework material is another key factor in minimising the level of impurities present in the

recirculating water. In some pharmaceutical water purification systems, the pipework is made entirely of ABS (acrylonitrile-butadiene-styrene) or polypropylene. In other cases, plastic pipework is used in the early stages of the system, but polishing loops that require steam-sterilisation are made from internally-polished 316-grade stainless steel. Plastic pipework can be disinfected with hydrogen peroxide (1-3% solution), sodium hypochlorite (solution containing 1% free chlorine) or, in cases of extreme contamination, peracetic acid.

5.2 Validation Procedures

Pharmaceutical water purification systems must be validated to make sure that the purified water meets the required specifications. The usual procedure is for microbiologists from the pharmaceutical company to liaise with the water purification specialists and agree on a system for monitoring bacterial counts and pyrogen levels in the ultra-pure water.

A bacterial sampling port has been specially developed for this purpose. The sampling ports are incorporated in the distribution pipework and allow water samples to be obtained by injecting a hypodermic needle through a self-sealing silicon rubber septum. It is often convenient to link the monitoring system to the disinfection programme; once the bacterial count approaches an alarm level - say 5 colony-forming units per millilitre - the disinfection procedure is initiated.

Chemical validation of the water purification system is provided by on-line conductivity meters that indicate the ionic quality of the water. Where necessary, on-line

TOC (total organic carbon) meters can be fitted to monitor organic levels.

6. Case Histories

The following case histories illustrate how water purification systems incorporating the latest techniques can be used to produce ultra-pure water for the pharmaceutical industry.

6.1 Increasing the Capacity and Cost-effectiveness of a System

A pharmaceutical company in the south of England had a traditional water treatment plant consisting simply of a manually-operated mixed-bed deioniser with downstream sub-micron filters. Difficulties had arisen because an increase in the total dissolved solids content of the raw water supply had coincided with an increase in production needs for pure water.

The deioniser was having to be regenerated every day - with high costs for labour and chemicals - and the filter elements were being replaced every week. The company wanted to increase the capacity of the water purification system and had asked for a larger deioniser and bigger bacterial filters to be installed.

Instead, the problem was resolved by installing a system in which the raw water was pre-conditioned by passing it through an iron-removal filter followed by base-exchange softeners. The pre-treated water was then fed into a reverse osmosis plant from which the permeate was pumped, via a holding tank,

around a ring-main recirculation system incorporating the original deioniser and sub-micron filters (Figure II).

By removing 90-95% of the dissolved solids from the raw water, the RO plant increased the inter-regeneration capacity of the deioniser 10-20 times, with a corresponding reduction in running costs. Moreover, the exclusion of bacteria from the recirculating water considerably extended the lifespan of the sub-micron filters in the ring-main. The overall running costs of the system were reduced to approximately one-fifth of the original figure, and the quality of the water at the points of use was significantly improved.

Nevertheless, one puzzle remained unsolved. Although the filters in the ring-main were lasting for several months, point-of-use filters were still having to be changed weekly. Careful investigation showed that bacteria were growing in static water in the pipes connecting the ring-main to the terminal filters. The problem was overcome - and normal filter life obtained - when the pipework was modified to provide a continuous bleed of water through the filters.

6.2 A Low-cost System for Apyrogenic Water

Producing apyrogenic water by distillation is an expensive process. Not only do stills consume large quantities of electrical power and cooling water, but in many cases the feedwater has to be pre-treated to avoid scale formation in the boiling

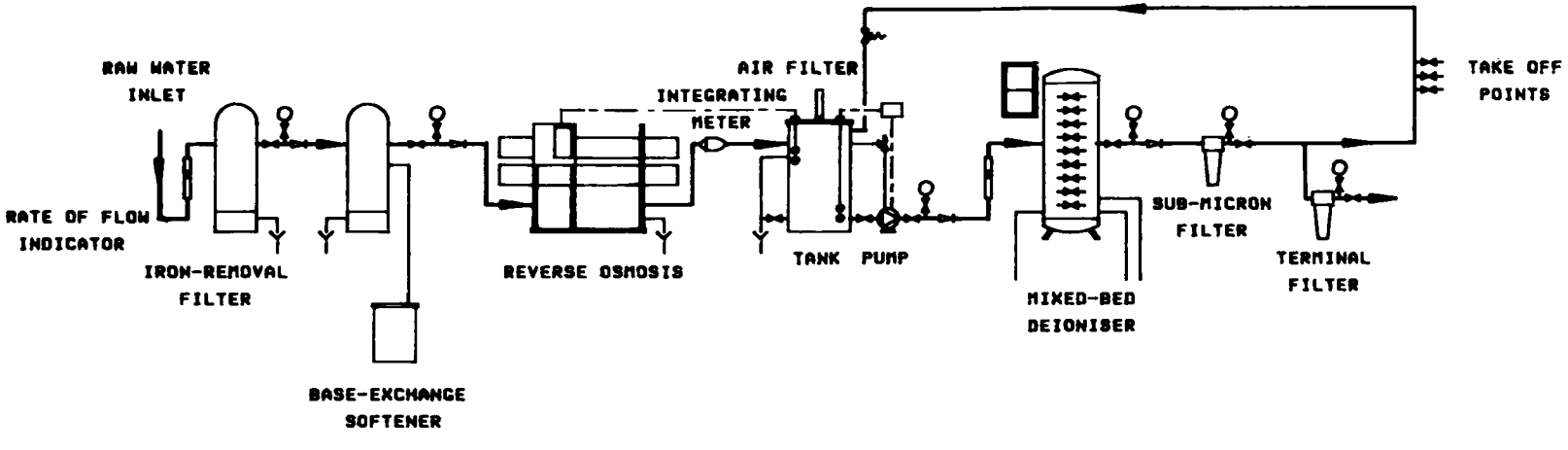

FIGURE II

A Water Treatment System for the Production of Ultra-pure Water

chamber. One way of minimising production costs is to use a membrane-based system to produce the large quantities of apyrogenic water required for rinsing purposes. High-purity water from this system can then form the feedstock for a small still producing apyrogenic water for parenteral solutions.

Figure III shows a typical membrane system - installed in a pharmaceutical factory in Britain - in which ultrafiltration is used in tandem with reverse osmosis to form a double membrane barrier.

The flow-path of the water is as follows. After passing through a 10 micron prefilter, the raw water flows through a multi-media filter followed by a two-bed deioniser. The deionised water is then fed into an ultrafilter and sterilised by ultra-violet light before passing through a heat-exchanger into a reverse osmosis unit.

Permeate from the RO plant feeds into a stainless steel tank and is pumped constantly around a stainless steel ring-main. A heat-exchanger in the system enables the ring-main to be pasteurised at 80°C every day; it is also steam-sterilised on a regular basis.

The system has been operating for several years, and produces high-quality apyrogenic water. The purity of the water is monitored by testing samples obtained at frequent intervals from septum sampling ports located throughout the distribution system.

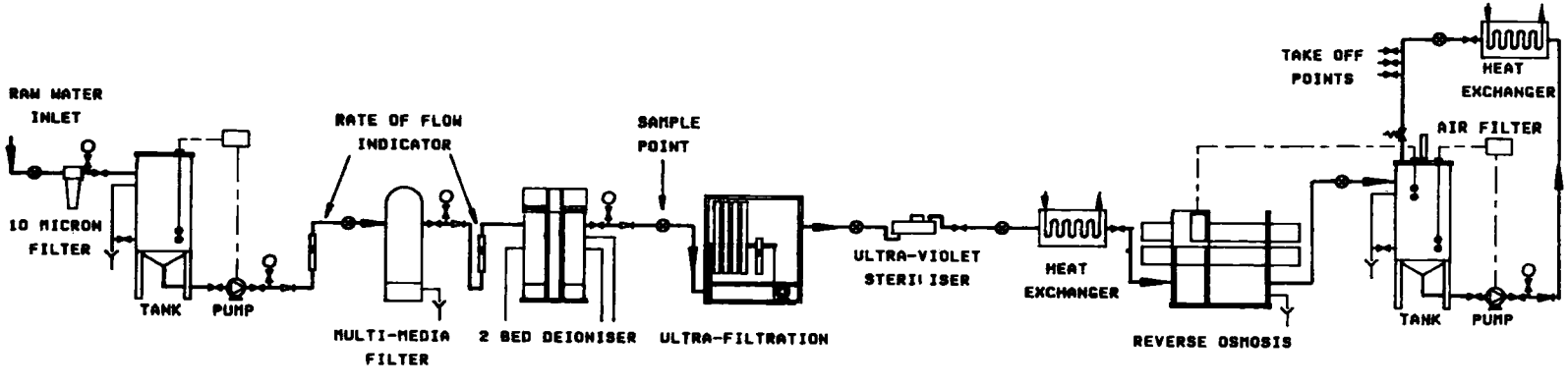

FIGURE III

A Low-cost Water Treatment System for the Production of Apyrogenic Water

7. Conclusion

Recent developments in water treatment technology have produced significant advances in the design of ultra-pure water systems for the pharmaceutical industry. State-of-the-art systems incorporating membrane processes now produce water that meets the exacting standards defined by the pharmacopoeias, while keeping production costs to a minimum.

Yet research continues apace; currently under investigation is a technique for destroying pyrogens with free radicals produced by irradiating molecules with high-energy photons. Water purification specialists must not only keep pace with advancing technology, but maintain a dialogue with pharmaceutical companies to ensure that the industry's demands for ultra-pure water will continue to be satisfied in the best possible way.

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