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# THE COMPARISON OF PURIFIED WATER SYSTEMS FROM THE ASPECT OF IMPORTANT PHARMACOPEIAS AND LITERATURES*

# ARITILMIŞ SU SİSTEMLERİNİN ÖNEMLİ FARMAKOPELER VE LİTERATÜRLER AÇISINDAN KARŞILAŞTIRILMASI

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*In the pharmaceutical industries, the purity of process water is critical to product integrity. In recent years regarding popularity of the pharmacopeial studies, purified water and water for injection have became the subjects that are studied more in pharmaceutical industry. This article describes typical treatment systems that incorporate with several purification technologies, system designs and detailed specifications of purified water and water for injection. Furthermore the changes proposed for these subjects were also discussed.*

*Bu yazıda, farmasötik endüstride üzerinde en fazla çalışma yapılan hususlardan biri olan ve son yıllarda yapılan farmakope çalışmalarıylada güncelleşen, endüstriyel beklentiler açısından da çok önemli olan arıtılmış su ve injeksiyonluk suyun ayrıntılı özellikleri ile, bunların elde edilmesinde kullanılan sistemlerin yapıları ve bu konuda önerilen bazı değişikliklere dair bilgi verilmektedir.*

**Keywords**: *Purified water; Water for injection; Water purification Technologies, Pharmacopeial standards for water.*

**Anahtar kelimeler**: *Saf su; İnjeksiyonluk su; Su arıtma teknolojileri, Su için farmakopeler standardı.*

## Introduction

Water which exists in various fields in our daily life, is one of the most examined material due to the extensiveness of its field of use. One of the problems about water obtained from underground and overground supplies is that it is affected by the seasonal, regional, climatic and external conditions which creates some changes in its content and it can easily be contaminated.

Table 1. A comparison of the HPW (High-Purity Water) parameters evaluated by the electronics and pharmaceutical industries.

| Parameter | Measurement Unit | Electronics Industry Limit | Purified Water /Water for İnjection Limits |
|---|---|---|---|
| Resistivity | MΩ-cm | 18 | 1 |
| Sodium | ppb as Na | 0.2 | NLE[a] |
| Silica | ppb as $SiO_2$ | 5 | NLE |
| Total organic carbon | ppb as TOC | 10 | 50/20 |
| Bacteria | CFU/ml | 1 | 100/0.10 |
| Particles[b] | NO./L | 1 | NLE |
| pH | | 6.5-7.5 | 5.0-7.0 |

[a]NLE= No limit established

[b]Particle size may vary

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* Review article

It is known that, before purifying the water obtained from sources, a pretreatment process should be applied. The convenience to the specifications of the water being used is also important with respect to the validity of production, the stability and the purity of the products(1).

*Production and Properties:*

Water is one of the products which is obtained with difficulty in desired quality because, not only the chemical properties, but also the microbiological contaminants are important factors(2).

The specifications and the limit values for the water being used in different fields are also different. The properties of water being used in electronic and the pharmaceutical industries are compared in Table 1(1).

In all of the pharmacopeias in the world, properties of the water being used for pharmaceutical purposes should be placed under the title of "Water" because there are only under small differences. In addition to definition and the limit differences, every country also has to renew their pharmacopeias depending on the continuing studies.

Water is a product that may have various contents depending on the source it is obtained from and the possible pollutants can be listed as; particles, organics, iron, manganese oxides, disinfectants (chlorine, chloramine), colloids (organics and inorganics), acides and bases, pyrogens and the inorganic salts. The underground water springs may contain particles, colloids and organic substances in a low level, whereas calcium and magnesium salts and bicarbonates which give hardness are in a relatively high level. Pesticide, nitrate and phosphate may be found in waters of aggricultural regions, whereas naturally generating organic substances like humic and fulvic acid may be found in surface water springs(3,4).

The "Purified Water" mentioned in the USP XXIII is the water obtained by distillation, ion exchange, reverse osmosis and other proper methods from water which is convenient for "Drinking Water Regulations" determined by The Federal Environmental Agency(5-7). On the other hand, the "Purified Water" in BP 1993 is obtained by distillation, ion exchange or other proper methods and is convenient to the related regulations(8). This definition is also accepted by France, Germany, Holland, China, Egypt, Turkey, Japan, Portugal, Romania, Mexico, Belgium and Europe Pharmacopeias(9).

Another definition used mostly in pharmaceutical industry is the "Water for Injection". In fact it is not different from the purified

Table 2. The titles of tests for purified water that have taken place in the monographs of current issues of BP 1993 and USP XXII.

| BP | USP |
|---|---|
| Aciditiy or alkalinity | pH |
| Ammonium | Ammonia |
| Calcium and magnesium | Calcium |
| Heavy metals | Heavy metals |
| Chloride | Chloride |
| Nitrate | - |
| Sulfate | Sulfate |
| Oxidizable substances | Oxidizable substances |
| Residue on evaporation | Total solids |
| - | Bacteriological purity |
| - | Carbon dioxide |
| Aluminium (for dialysis sol.) | - |

Table 3. Water Quality Standarts for purified water and water for injection. (Numerical Interpretation of Current USP Standarts)

| Constitutents | Purified Water | Water for Injection |
|---|---|---|
| pH | 5.0-7.0 | 5.0-7.0 |
| Chloride | ≤ 0.5 mg/L | ≤ 0.5 mg/L |
| Sulfate | ≤ 1.0 mg/L | ≤ 1.0 mg/L |
| Ammonia | ≤ 0.1 mg/L | ≤ 0.1 mg/L |
| Calcium | ≤ 1.0 mg/L | ≤ 1.0 mg/L |
| Carbon dioxide | ≤ 5.0 mg/L | ≤ 5.0 mg/L |
| Heavy metals | ≤ 0.1 mg/L | ≤ 0.1/L |
| Oxidizable substances | Passes USP Permanganate test | Passes USP Permanganate test |
| Total solids | ≤ 10 mg/L | ≤ 10 mg/L |
| Total bacterial count | ≤ 50 mg/L | ≤ 10 mg/L |
| Pyrogen | None specified | ≤ 0.25 EU/ml |

In the scientific meeting assembled by Anotel-Atotest, the limits were given as follows:

Table 4. Quantitative interpretation of the USP XXI

| Purified Water Standards | |
|---|---|
| Tests | Required Standard |
| Colour | Colourless |
| Odour | Odourless |
| Appearance | Clear |
| Specific resistance | 100000 ohms-cm minimum |
| pH | 5.0-7.0 |
| Chloride | 0.5 ppm max |
| Sulfate | 0.5 ppm max |
| Ammonia | 0.3 ppm max |
| Calcium | 0.5 ppm max |
| Carbon dioxide | 4.0 ppm max |
| Heavy metals | 0.5 ppm |
| Iron | 0.1 ppm |
| Copper | 0.01 ppm |
| Chromium | 0.01 ppm |
| Cobalt | 0.1 ppm |
| Manganese | 0.1 ppm |
| Nickel | 0.1 ppm |
| Oxidizable substances | Meets Test |
| Total solids | 10 ppm max |
| Microbiology | Not more than one colony forming unit per 100 ml (as a mean of all samples examined per month). Free from lactose fermenting organisms, yeasts, and moulds. |

water physically and chemically. The only difference is that the pyrogen limits of water for injection is determined definetely in many pharmacopeias. Furthermore, according to USP XXII and USP XXIII, the water for injection should not contain particles (5,8)

In Table 2 the titles of the tests that have taken place in the monographs of the current issues of BP 1993 and USP XXII are given for comparison. Although there are some differences, approximately the same physical and chemical properties have been mentioned in both pharmacopeias (5,8).

In USP XXII, the precaution "Do not use the purified water in preparations intended for parenteral administration" also takes place, which was not present in the previous USP (5).

The water quality standarts of "The Purified Water" and "The Water for Injection" are given in Table 3(4), while "The Standarts of Purified Water to be Used in Industry" which are adopted from USP XXI are given in Table 4(2).

The possible total amount of bacteria should be less than 50 colony forming units(CFU)/ml for the purified water and 10 CFU/100 ml for the water for injection(1). It is stated that the water for injection should be pyrogen-free and the total amount of pyrogen determined according to Limulus Amebocyte Lysate(LAL) should be less than 0.25 Endotoxine units(EU)/ml(4).

A committee of the Pharmaceutical Manufacturers Association (PMA) working with United States Pharmacopeial Convention cooparation, in order to establish water quality parameters, have proposed the needs of purity levels taking place in USP XXII and the testing methods. On the other hand, Water Quality Committee, has been studying for making necessary changes on the water monographs in USP XXII, the general notices stimuli articles, general information chapters and the general test chapters, depending on the conditions of the present time. The members of PMA made some suggestions to USP XXII in their studies. The most important ones of these were the necessity of conductivity measurement and the measurement of total organic carbon (TOC) instead of oxidizable substances. In addition to these two subjects, the necessity to bring a certainity in the microbiological levels for purified water has also been proposed. The proposed changes are shown in Table 5(1,10). The term "TOC" mentioned here is used for low molecular weight fulvic acid and high molecular weight humic acid, which are accepted to be originating from the ground. The structure of humic acid, which is not completely defined, can contain some anions which are bonded to its molecules. Furthermore, some silica and iron also might be in complex with the colloids. The organic colloidal complexes creates a weak negative current which is indicated as increased conductivity. On the other hand, the chlorine tends to react with this humic acid and as a result trihalomethane generates which is cancerogen and should be in a level below 100 ppb(3).

In USP XXII, TOC limits are stated as 1 mg/100 ml (10 ppm), while in the USP XXIII the conductivity specification is 1.25 microsiemens/cm which is nearly equal to 0.8 ppm of TOC(11).

The ionized contaminants such as NaCl and $CaCO_3$ may be found in water and as a result of this the conductivity can vary. So the resistance and the conductivity are used as the indicator of the contaminants. (The resistancy is determined by ohm-cm, while the conductivity is determined by Mohm-cm or siemens- cm). The existence of carbondioxide results in a lower value of resistance(12).

Table 5. Changes proposed by PMA for the USP XXII water monograh.

| Current USP Tests | Proposed changes |
|---|---|
| pH | Keep |
| BET | Keep |
| Calcium | Substitute conductivity |
| Sulfate | Substitute conductivity |
| Chloride | Substitute conductuvity |
| Ammonia | Substitute conductivity |
| Carbon dioxide | Substitute conductivity |
| Oxidizable substances | Substitute TOC Test |
| Heavy metals | Delete |
| Total solids | Delete |
| Coliforms | Delete |

In the scientific meeting assembled by Anotel-Atotest, the limits were given as follows:

Proposed limits for pharmaceutical water (10);

| | |
|---|---|
| pH | 5.0-7.0 |
| Total organic carbon | Maximum 500 ppb |
| Coductivity | Limits of 4.7 to 5.8 µS/cm (depending upon pH) |
| Bacterial count | Purified Water 100 CFU/ml<br>Water for injection 10 CFU/100 ml |
| Endotoxin | 0.25 EU per LAL test |

As discussed at the beginning of the text, there may be many pollutants in the water obtained from the springs. In order to adapt the specifications of water to the determined limits and to have a reasonable production expense, a pretreatment process is necessary. This pretreatment process should consist of sand filter, activated carbon bed, softener, organic scavenger, cartridge prefilter and chemical substance addition(4). Particle filtration has the priority and cartridge prefilters and sand filters should be used for this purpose. Polypropylene cartridge prefilters have a porous, graded, density structure, which traps particles throughout its tortuous network of the flow channels. Depth filters are numerated depending on the size of particles they can remove. The sand and the granular filters from the secondary particle separation system. For the filtration of surface water loaded with particles, sand filters are inserted over the cartridge prefilter, in order to extend the lifetime of the cartridge prefilter.

There are three types of sand filters(4);

1) Singlemedia filters

2) Dualmedia filters (layer of anthracite over the layer of sand)

3) Multimedia filters (three layers with garnet over sand and anthracite)

It is also suggested to remove the $CO_2$ with a degasification process during filtration(4). After the removal of particles, the activated carbon filtres are used in the purification of the system. These filters are used for the removal of TOC and chlorine. The organic substances that can be found in surface waters can be listed as; humic and fulvic acids, oils, phenols, pesticides, surfectants, tannins, chlorinated methanes (also called halomethanes and tri-halomethanes)(3,4). The removal of organic substances is made by absoption method where weak Van der Walls forces exist. Different organic substances have different absorption coefficients and their binding forces are also different. The substances with high molecular weight and large dimensions and low molecular weight but high polarity can not be absorbed easily(4). The granular activated carbon also removes the free chlorine in feedwater. The free chlorine should be removed before the process, since it affects the reverse osmosis membranes and the resins. Activated carbon can remove active chlorine by the formation of surface oxides. These activated carbon beds should be placed before the softeners because, it is easier to remove the organic material in the presence of calcium and magnesium.

The removal of iron and magnesium in water is also one of the main problems. The underground water usually contains reduced substance like ferrous bicarbonate whereas the surface water contains ferric ions(4). The water softeners separate the basic valuable cations from the feed water and decreases the possibility of formation of precipitates which do not dissolve in reverse osmosis systems. The softener ion exchange process removes magnesium and calcium ions which form a significant percentage of total available cations and a small amount of the undesired ions like barium and aluminium. (The softeners ensure the hardness of water to be less than 3 ppm) (13).

Another stage is the removal of colloids. The colloids (submicron particles in charged and suspended state) were found in a large amount in surface waters. Almost all the colloids in natural conditions are negatively charged. A reverse electric charged substance is added in order to remove the colloids by means of agglomerations. The colloids can also be removed by the ultrafiltration method. The membranes used for this purpose are capable to remove colloids with a particle size 1-20 nm and organics with high molecular weight (4).

After all these pretreatment processes, purification methods are selected according to the properties of the water to be purified. One or more methods can be selected for the purification process.

*Deionization processes:*

The ion-exchange system is an important unit operation that has been used in many purified water systems. For example, most of the water purification systems which use single or double pass reverse osmosis (RO) unit still use ion exchange systems in the softening of feedwater(4,13). The deionization process can generally purify total dissolved solids at a level of less than 150-200 ppm, the high concentrations of colloids and silica and trace amounts of barium and manganese (14).

The ion-exchanging is made by the resins. The cation and anion exchanging resins and the geluler and macroreticular resins (with fine and porous surface) are divided into groups as strong acid cation exchange resin, weak acid cation exchange resin, strong base anion exchange resin and weak base anion exchange resin. Some physical factors that affect the resins and the ion-exchange systems are as follows:

-- The ion-exchange resins should not be subjected to a temperature neither over 49°C nor below 0°C because freezing can cause physical fracture which occurs particularly in macroreticular resins.

-- The continual wetting and drying of resins causes expansion and contruction and so the resin beads fracture. For this reason, storing the resins in a moist condition is necessary.

-- The resins should not be subjected to high concentrations of abrasive materials which cause chemical shocks.

-- The cation resins can be polluted by iron.

-- The anion resins can be polluted by organic substances.

-- As a result of excessive backwash of resins, the resin beads strike to the top and the walls of the column and the resin starts fracturing physically and mechanically.

-- It is necessary to adjust the length of piping in order to make the backwash treatment.

-- The flow of the resins to purified water is controlled by means of sight glass part between the interface of resin and water in columns.

-- The filter should be placed before the softeners if the water purification system contains carbon filter for the removal of organic substances. The absorption of organic substance is increased by the activated carbon filter.

-- The most important disadvantage of this system is the need for regeneration which is time consuming and increases the use of energy and finance.

-- The cation resin is a substance with carbon and for this reason and by introduction of bacteria to the system by regenerating with salty water, microbial growth can be seen.

-- If the feedwater contains disinfectant residues, the cation resin oxidates and the fertility decreases.

-- The pollution of the resin by iron is also a factor that decreases the fertility(13).

*Distillation method:*

This technique is one of the most preffered systems for the purification of water and is realized by two methods:

1)*Boiling method*: The method works by the condensation of water vapour obtained by boiling water in a closed pot, and passing through coolers. Since water is used for cooling in such systems, a great loss of water occurs unless a closed cycling is provided. Another problem in this system is that it requires too much energy(4,12). The advantage is boiling water at a high temperature, damages some organic substances, pyrogens and microorganizms.

Table 6. Comparison of the different membranes used for RO.

| | Cellulose acetate | Polyamide | Thin Film Membrane |
|---|---|---|---|
| pH | 4-8 | 1-11 | 1-11 |
| Langlier saturation index | Negative | Negative | Negative |
| Free chlorine | 0.2-1.0 ppm of free chlorine | 0.0 | 0.0 |
| Bacteria | Requires chlorine affected by bacteria | Not affected | Not affected |
| Temperature | 4-30°C (40-86°F) | 4-30°C (40-86°F) | 4-30°C (40-86°F) |
| S.D.I.* | <%5 | <%5 | <%5 |
| Turbidity | | <1 NTU | <1 NTU |

S.D.I.:" Silt Density Index", a value indicating the content of humic and fulvic acid generating from the ground (12).

2) *Thermocompressor method*: There are equipments which can provide water boiling at 50°C by applying vacuum, so the usage of cooling water is eliminated.

*Reverse osmosis (RO):*

This method of purification removes the contaminants present in water by reversing the direction of osmosis by means of pressure. In order to make a reverse osmosis in water, a pressure which is 5-6 times stronger than feed water osmotic pressure is created by a pump. This method removes the impurities, particles, colloids, organic substances, microorganisms and pyrogenic substances from the water(4,12,14). There is a 24 hours long flow in an ideal RO system which also minimizes the storage time for water. If the system does not work for 48 hours bacterial growth may occur(14).

*Reverse Osmosis Membranes*: Cellulose acetate, polystren, celophan, PVC, and ethyl cellulose membranes are used. Cellulose acetate membranes are uniform and very dense chemically and are composed of cellulose acetate, cellulose triacetate or combination of both. The hardness and the relatively cheapness of cellulosic composite membranes is a big advantage but they are relatively sensitive to chlorine.

The noncellulosic membranes are prepared in order to produce membranes which have a higher flux and are less sensitive to pH and oxidizing agents. Moreover they have a fertility similar to cellulosic membranes. The thin film composite membranes contain both cellulosic and noncellulosic membranes and provide a good permeability in a low pressure(4).

The specifications of the different membranes are compared in Table 6.

*The Reverse Osmosis Equipment*: The reverse osmosis membranes are placed in modules which control the turbulance, pressure and the feedstream velocity for reducing the polarisation concentrations. There are four types of modules depending on the membrane types used; spiral-wound, plate-and-frame, tubular and hollow-fiber modules(4,6).

The capacity of reverse osmosis system decreases by the reduction of temperature of feedwater so preheaters are used in some systems(14). One of the most undesired factor in reverse osmosis systems is the growth of algae and the membranes are affected due to pH changes.

Pretreatment is proposed for this reason. In reverse osmosis system only 90-95% of pyrogen removal is achieved so another method should be preferred for eliminating pyrogens completely. An interval of 5% is very risky from the aspect of the level of acceptance of human body for pyrogen.

*Electrodialysis Method:*

This method is based on the elimination of ions. Negative and positive electric forces are applied and anions and cations in water move towards opposite poles and in the mean time pass through ion selective membranes(4,15,16).

Besides all these purification processes, the water provided is subjected to posttreatments as well and ultrafiltration and UV lights are used for this purpose. The purification of water by UV is a rapid and the unique technique (except membrane filtration) for the elimination of bacteria without using heat and chemicals. The germicidal portion of UV spectrum is approximately 200-300 nm. As a result of the absorption of UV light by the microorganism, some irreversable changes which prevent reproduction occurs in their genetic structure. The most convenient wavelength is 260 nm, although the equipments spread light at 254 nm wavelength.

Table 7. The comparison of effectiveness of water purification systems.

| | Distilation | Deionization | Screen Filtration | Depth Filtration | Reverse Osmosis | Adsorption | Ultrafiltration | UV Oxidation |
|---|---|---|---|---|---|---|---|---|
| Dissolved Ionized Solids | E/ G | E | P | P | G | P | P | P |
| Dissolved Organics | G | P | P | P | G | E | G | G |
| Dissolved Ionized Gases | P | E | P | P | P | P | P | P |
| Particulates | E | P | E | E | E | P | E | P |
| Bacteria | E | P | E | P | E | P | E | G |
| Pyrogens | E | P | P | P | E | P | E | P |

E = Excellent G = Good P = Poor

The effect of UV units in the decrease of TOC amount has also been stated(4).

*Ultrafiltration (UF):*

The ultrafiltration method can be used for both pre and post-treatment purposes. The use of UF together with a purification method like deionization is also a very effective process. The production of water with bacterial level of 1-10 CFU/100 ml can be achieved by the use of UF besides ion-exchange method. (In other words, the water for injection can be provided by this method)(4,10).

The UF equipment was developed currently for the elimination of particles from deionized water and is made of UF membranes in polyvinylidene fluoride (PVDF) structure which is bounded to the PVDF support plates thermostaticaly(4,15). UF membranes are compatible with ozone, which is an advantage of UF usage together with ozonation in deionization systems(4). It is also suggested as an effective system for providing the required TOC level. These membranes are also effective in obtaining the desired conductivity levels. One of the most important difference of this system from reverse osmosis system is that, there is no need for continious feeding. The system can be kept without working for a period of 48 hours. The UF membranes also have a chemical and thermal resistance.

By UF systems the pyrogens can completely be removed from the water. For this reason, purification of pyrogen is done after the RO and distillation methods. It is an effective system, because membranes that can hold particles with a molecular weight higher than 10 000 are used(4). The statement of "progen level for the water for injection should not be more than 5 EU/kg "takes place in pharmacopeias. The level of 0.5 EU/ml is equivalent to the lev el of 7 EU/kg for a human weighting 70 kg. On the other hand the limit that human can resist is 4 EU/kg. There fore, it is clear that the water we obtain may contain pyrogen at a level lower than 0.5 EU/ml. (The production of water that is completely free of pyrogen is a very expensive procedure)(17).

The advantages and the disadvantages of purification systems are shown in Table 7(12).

The most effective systems observed in the table are RO and UF (D>RO>UF). However the most suitable system should be selected depending on the targeted aims, the systems defined, considering the properties of spring water, the properties of water obtained and the financial limits. For instance, although the water with almost the same properties is provided by RO and distillation systems, 26.5 dollars were spent in RO system while 94 dollars were spent in distillation method for 1000 galons of water(4,12).

As stated at the introduction, many researches have been done on water and its purification systems and are still being studied. The innovations and changes discussed migth be valid for a short period of time and it is possible for us to face with completely new standards and methods in the future.

## References

1. Gagnon, R.S., Rodriguez, J.: Microcontamination, January, 43-50 (1994)
2. Cole, G., "Pharmaceutical Process Utility Systems", Mc Kee, D., (Ed), In: "Pharmaceutical Production Facilities Design and Applications", Ellis Horwood Lim., London, 47-54, 1990
3. Collentro, W.V.: Pharmaceutical Technology, May, 40-56 (1994)
4. Parekh, B.J.: Chemical Engineering, January, 70-85, (1991)
5. The United States Pharmacopeia, The National Formulary, (USP XXII, NF XVII), Rockville, United States Pharmacopeial Convention, inc., 1990
6. Remington's Pharmaceutical Science, 18 th Edition, Easton, Pensiylcania, Mack Publishing Company 1990
7. The United States Pharmacopeia, The National Formulary (USP XXIII, NF XVII XVIII) Rockville, United States Pharmacopeial Convention, inc, 1995
8. British Pharmacopeia 1993, Volume II, Office of the British Pharmacopoeia Commission, London. HMSO, 1993
9. Martindale The Extra Pharmacopeia, Twenty-ninth Edition, London, The Pharmaceutical Press, 1989
10. Scientific meeting at İstanbul-Hilton, 17 March 1995, by Anatel-Atotest
11. Collentro, W.V.: Pharmaceutical Technology, April, 38-46 (1994)
12. Barnsted, The Water Book 1993-1994, USA, Barnsted/Thermolyn Corp.
13. Collentro, W.V.: Pharmaceutical Technology, September, 100-116 (1994)
14. Collentro, W.V.: Pharmaceutical Technology, September, 54-70 (1986)
15. Applegate, L.E.: Chemical Engineering, June, 64-89 (1984)
16. Ganzi, C.G., Parise, P.L.: Journal of Parenteral Science and Technology, 44, No:4, (July-Aug), 231-241 (1990)
17. Mettzer, T.H., "Pharmaceutical Water: Generation, Storage, Distribution and Quality Testing", Graves, M.J., Olson, M.P., Anisfeld, M:H., (Ed), In: "Steril Pharmaceutical Manufacturing Applications for the 1990's Volume I", Interpharm Press Inc., II., USA, 109-221, 1991

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