

Summary of 510 (k) Submission and Statement of Equivalence for 95°C/1.5% Citric Acid Dialyzer Reprocessing

Hemodialyzer reuse has been practiced throughout the world by the renal community since the introduction of dialysis as a recognized replacement therapy for chronic renal disease. In the United States many forms of hemodialyzer reuse have been practiced (formaldehyde, glutaraldehyde, peracetic acid to name a few) and medical devices and procedures have been reviewed by the FDA and have been found to be substantially equivalent to medical products and practices in use prior to 1976. Fresenius Medical Care is requesting by submission of this application that the Commissioner find that the procedure and components used in the reprocessing of Fresenius polysulfone hemodialyzers with 95°C/1.5% citric acid be found substantially equivalent to other forms of hemodialyzer reuse that have been in medical practice in the US prior to 1976.

Radiant heat (moist or dry) has been used for over 100 years as a means to sterilize or disinfect utensils, solutions and containers. Scientists since the time of Pasteur noted that exposure to a specific temperature for a specific amount of time would allow for preservation of the compound or component tested. This observation of specific time/temperature exposure is the basis of current thermal sterilization of medical products and pharmaceuticals. Figure 1 in Attachment 1 shows, in graphic form, the amount of exposure time (hours) required to attain sterilization of a medical product at various temperatures (°C). In this case sterilization is defined as the amount of time at the specified temperature to attain a 6 log reduction in bacterial concentration. Table 1 shows that exposure at 121°C for 15 minutes is comparable to 105°C for 10 hours.

Also enclosed in Attachment 1 is a copy of a chapter from Principles and Methods of Sterilization titled "Thermal Destruction of Microorganisms". In this attachment relationships are presented for the relative resistance to heat for various microorganisms. As an example, vegetative microorganisms, such as *Escherichia coli*, are as much as 3,000,000 times more sensitive to heat than bacterial spore formers. Likewise, bacterial spore formers have different heat resistance. *Bacillus stearothermophilus*, the recognized indicator organism for moist heat sterilization processes, is 50-100 times more resistant to moist heat than *Bacillus subtilis*.

Citric acid is a natural forming, non-toxic compound that when diluted to 1.5%, weight per volume, results in a solution of approximately pH 2.1 that has no chemical effect on components used in the manufacture of Fresenius polysulfone hemodialyzers. Citric acid is commonly used as a stabilizer in food and cosmetic products as well as a bacteriostatic compound. However citric acid alone is not considered a bacteriostat or bactericide. Enclosed in Attachment 2 is a copy of test results where 1.5% citric acid solution was challenged according the USP antimicrobial effectiveness test as a bactericide. The test results indicate that a 1.5% citric acid solution does not meet the requirements of the antimicrobial effective test in that the test organisms did not exhibit an accelerated death rate different than the control, but no organisms proliferated in the solution.

Citric acid was selected as a non-toxic additive to enhance the effectiveness of low temperature disinfection procedures. The plastic components used in the manufacture of Fresenius polysulfone dialyzers are heat-labile and malleable at temperatures of 121°C so lower temperatures were required for longer periods of exposure time. The addition of

citric acid to the dialyzer reprocessing solution (water) increased the effective kill of the indicator organism during the disinfection process.

The validation process used to qualify the 95°C heat disinfection procedure is based on the standard monograph developed by the Parenteral Drug Manufacturing Association for steam sterilization. Test dialyzers were selected after exposure to blood at least 10 reprocessing procedures. Thermocouples were positioned in dialyzers to demonstrate heat penetration variability within the dialyzer. Heat penetration studies were carried out in standard convection ovens completely filled with dialyzers to determine the "coldest" position in the oven. Various dialyzer sizes (F60 and F80) were evaluated for differences in heat penetration profiles. Studies were carried out multiple times to demonstrate reproducibility. The data collected from these studies are enclosed in **Attachment 3**. In summary, the temperature penetration studies demonstrated that the lower right shelf position was the coldest position within the oven, there was no difference in heat penetration studies of F60 or F80 dialyzers and that there was no "cold" position within the dialyzer (all thermocoupled positions heated at the same rate).

Based on the thermal penetration studies, 10X blood contacted reprocessed F80 dialyzers biologically seeded on the blood side with approximately 1,000,000 *B. stearothermophilus* spores were positioned in the "cold spot" of the oven for determination of kill effectiveness of the reprocessing procedure. Seeded dialyzers were placed in the oven at room temperature, the oven was turned on with the temperature set point at 95°C. Test dialyzers were pulled at specified hour increments, blood side drained and flushed and the contents serially plated to determine number of viable organisms. These data were used to calculate the log reduction potential of the reprocessing procedure. Three test runs were conducted. The results are enclosed in **Attachment 3**. Results demonstrate that at least 18 log reduction in the test organism was achieved with the 95°C/1.5% citric acid for 24 hours (from room temperature to the test temperature) program. These results demonstrate that the heat reprocessing procedure of 95°C exposure with 1.5% citric acid results in an additional 12 log reduction of the indicator organism over standard accepted sterilization log reduction processes of 6 log. In addition to the above tests, a reprocessing run was also carried out at 90°C for 24 hours with the same procedure. The results of this single run demonstrate at least a 12 log reduction of the test organism. Lastly, 24 dialyzers were seeded with the test organism *B. stearothermophilus*, heated at 95°C for 24 hours, let set for 96 hours, blood side drained and serially plated and the dialyzer blood side filled with SCD media. No growth was observed. The data demonstrate that with worst case conditions (maximum dialyzer loading, largest dialyzer, multiple blood contact, heat from RT. to 95°C for 24 hours, oven opened to remove test samples and closed, 5°C below standard temperature) that disinfection and, in fact sterilization has been attained. In addition, 1.5% citric acid was shown to be bacteriostatic.

Toxicity testing was carried out according to the ISO 10993-1 guidelines with the exception that only one of three carcinogenicity tests was performed on dialyzer samples that were reprocessed a minimum of 15 times. The data are enclosed in **Attachment 4**. Results indicate no evidence of toxicity.

Attachment 5 contains the *in vitro* performance data for each membrane family of Fresenius polysulfone dialyzers; low (F4, F6 and F8), mid (F60M and F80M) and high flux (F60 and F80) compared to membrane performance data for 1.5% formaldehyde (HCHO) and 40°C based on the guidelines specified in the dialyzer reuse 510 (k) document. The materials and manufacturing process used in the production of all Fresenius polysulfone dialyzers are identical. Flux rates are manipulated by accelerating the membrane precipitation rates and wall formation only. The data demonstrate that there is no difference in membrane performance due to heat reprocessing with 95°C/1.5% citric

acid when compared to non-reprocessed dialyzers or dialyzers reprocessed with 1.5% HCHO and 40°C incubation.

Attachment 6 contains *in vivo* product performance data for all Fresenius polysulfone membrane configurations compared to *in vivo* product performance of dialyzers preprocessed with 1.5% HCHO with 40°C incubation. The results show no difference in product performance due to heat reprocessing with 95°C/1.5% citric acid compared to non-reprocessed hemodialyzers or dialyzers reprocessed with 1.5% HCHO with 40°C incubation.

Attachment 7 contains *in vivo* clinical data of comparison of patients dialyzed with hemodialyzers reprocessed with 1.5% formaldehyde and 40°C incubation who were then transferred to dialyzers heat reprocessed with 95°C/1.5% citric acid. Patient parameters and intradialytic episodes (hypotension, reactions, etc.) were followed. No differences were noted between the two reprocessing procedures.

Attachment 8 contains proposed clinical reprocessing procedures, convection oven operator's manual and brochure for a typical temperature recorder, and proposed manual for citric acid reprocessing with a Fresenius DRS-4 Dialyzer Reprocessing System.

Based on the enclosed information, Fresenius requests that the Commissioner find that hemodialyzer reprocessing using 1.5% citric acid/95°C for 24 hours is substantially equivalent to other reprocessing procedures in clinical use now and prior to 1976.

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Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850Mr. Tom Folden
Director, Product Development
Fresenius Medical Care
2637 Shadelands Drive
Walnut Creek, CA 94598Re: K974090
Multiple Use Labeling for Hemoflow hemodialyzers
Reprocessed with 1.5% Citric Acid/95+ 2 °C
Dated: May 20, 1998
Received: May 29, 1998
Regulatory Class: II and III
21 CFR §876.5820 and §876.5860
Product code: 78 MSE and 78 MSF

Dear Mr. Folden:

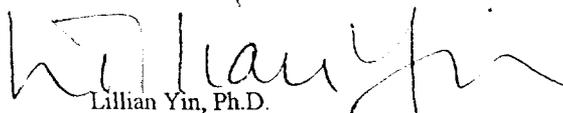
We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Pre-market Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4613. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

Lillian Yin, Ph.D.
Director, Division of Reproductive,
Abdominal, Ear, Nose and Throat
and Radiological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure



Fresenius Medical Care
North America
Renal Product Technologies

Indications for Use Statement

“Hemoflow dialyzers are designed for acute and chronic hemodialysis. Hemoflow dialyzers are also appropriate for single or multiple use when reprocessed with 1.5% Citric Acid/95°C.”

(Division Sign-Off)
Division of Reproductive, Abdominal, ENT,
and Radiological Devices
510(k) Number K974090

Prescription Use
(Per 21 CFR 801.109)