This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

GUIDANCE FOR HEMODIALYZER REUSE LABELING

FINAL Draft October 6, 1995

The Food and Drug Administration (FDA) has determined that hemodialyzer labeling should reflect the actual commercial marketing and clinical use of a hemodialyzer. Whether a hemodialyzer is intended for single or multiple use, this information should appear prominently on the device label.

Manufacturers of hemodialyzers who distribute to facilities known to reuse that manufacturer's product will now be required to provide adequate instructions for safe and effective reuse of the device in accordance with 21 CFR §801.4. Manufacturers of reusable hemodialyzers will be expected to recommend at least one method for reprocessing and are to provide FDA with scientific documentation of the safety and effectiveness of each recommended reprocessing method on their hemodialyzers.

The clinical studies described in this guidance are intended solely to collect data to support hemodialyzer reuse labeling. If the hemodialyzer and the reprocessing agent and/or process are currently legally marketed devices and have a clinical history of hemodialyzer reuse in the United States, a clinical study would be considered non-significant risk and an Investigational Device Exemption (IDE) would not have to be submitted to the FDA. For a new hemodialyzer (e.g., new membrane, new design, etc.) or a reprocessing agent and/or process that do not have a clinical history of hemodialyzer reuse in the United States or are not legally marketed devices, the manufacturer will need to meet the IDE requirements for a significant risk study as described in 21 CFR §812.

1. General Requirements

All hemodialyzer premarket notifications will be expected to meet the content requirements outlined in the "DRAERD Premarket Notification [510(k)] Screening Checklist". A copy of this guidance can be obtained by contacting the Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597. Submissions for hemodialyzers that have not yet been cleared for marketing will be expected to meet all current requirements for single use hemodialyzers as well as the

requirements discussed in this guidance.

2. Preclinical Testing Requirements

a. In vitro testing

Laboratory data to determine the effect of each recommended reprocessing agent and/or process on the performance of the hemodialyzers should be provided in tabular form. For conventional (low flux, Class II) hemodialyzers, ultrafiltration coefficient [k_{uf}] data (ml/hr/mm Hg) should be provided at transmembrane pressures (TMPs) of 0, 100, 300, 500 and maximum TMP (when different from these TMPs). For high permeability (high flux, Class III) hemodialyzers, k_{uf} data should be generated by measuring the slope of the ultrafiltration rate versus TMP at ultrafiltration rates between 600 and 1800 ml/hr using a minimum of four data points. The k_{uf} data should be measured using bovine blood at 37 ^{o}C with a hematocrit of 32% ($\pm$ 2%) and a minimum protein content of 5 g/dL (albumin). Clearances should be provided for urea, creatinine and vitamin B_{12} or inulin, at blood flow rates of 200 ml/min, 300 ml/min, 400 ml/min, 500 ml/min and maximum rate when different from these rates. The composition of the aqueous test solution should be specified. For conventional (low flux, Class II) hemodialyzers, the clearance data should be collected at 0 and maximum TMP. For high permeability (high flux, Class III) hemodialyzers, the ultrafiltration rate (Q_f) at which the clearance data was collected should be provided.

Each model of hemodialyzer should be tested with each recommended reprocessing agent and/or process, unless the hemodialyzer is a member of a family. If the chemical composition of the membranes and the processing of hemodialyzers are identical, these models may be considered a family. In lieu of testing each model, the manufacturer may certify that the model is a member of a family, including the specific family name or identifier. In that case, for the conventional hemodialyzers of a family, only the smallest and largest models need to be tested. For the high permeability hemodialyzer of a family, a medium size should be tested in addition to the smallest and largest models. The tests should be performed with hemodialyzers that have been exposed to the reprocessing agent and/or process 0, 1, 5, and 15 times.

b. Biocompatibility/Toxicology Testing

For each recommended reprocessing agent and/or process, biocompatibility data should be provided, as recommended by Bluebook

Memorandum G95-1 "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part I: Evaluation and Testing" (5/1/95). A copy of this guidance can be obtained by contacting DSMA at the telephone numbers listed above. The tests should be performed with polar and non-polar solvents, and the amount of solvent and the extraction times used should reflect the anticipated clinical use of the hemodialyzer. These test results will be expected for the largest model of each family of hemodialyzers after it has been exposed to the reprocessing agent and/or process a minimum of 15 times. If the manufacturer does not certify that the chemical composition and processing of each model in a family is identical, then each model of hemodialyzer should be tested after 15 exposures to each recommended reprocessing agent and/or process.

3. Clinical Testing Requirements

Clinical data on a minimum of 12 patients selected by the submitter should be provided to validate the preclinical test results of the hemodialyzer performance, using the model chosen for the in vitro testing, with each recommended reprocessing agent and/or process. The data should be provided in tabular form. In vivo ultrafiltration coefficients and extent of removal of urea, albumin and β_2-microglobulin should be provided for hemodialyzers after the first use and after the first, fifth and fifteenth reprocessed uses. Removals should be determined from blood samples taken pre- and post-dialysis. (The time at which the samples were obtained should be provided.) A minimum of 50% of the patients should have reused the hemodialyzer 15 times. (NOTE: The requirement for β_2-microglobulin testing may be waived for manufacturers of conventional hemodialyzers who are not making any claims for β_2-microglobulin removal in their labeling or promotional material.)

Existing clinical data (e.g., studies published in the scientific literature) that support the safety and effectiveness of each recommended reprocessing agent and/or process for the manufacturer's hemodialyzers may be submitted to the FDA. However, such data must have been collected under conditions reflecting current hemodialysis practice in the United States.

4. Labeling Requirements

Proposed labels, labeling, and advertisements sufficient to describe the hemodialyzer and its intended use should be provided. The directions for use should contain a specific intended use statement and any warnings, contraindications, or limitations. This may be provided in draft form. The label of the device must bear the caution statement required in 21 CFR §801.109(b)(1): "CAUTION: Federal law restricts this device to sale by or on the order of a physician." Guidance on labeling issues is provided in Bluebook Memorandum G91-1 "Device Labeling Guidance" (3/8/91). A copy may be obtained from DSMA at the telephone number listed above.

A. The labeling for the hemodialyzer should include at a minimum the device name, U.S. point of contact, corporation name, address, and phone number, manufacturing concerns unique to this device, storage conditions, priming volume, sterility status and method, sterilization date, lot number, surface area, and an indication whether the device is for single or multiple use.

In addition, labeling for the hemodialyzer should address the following:

(1) The intended use statement should include specific indications and intended patient population.

(2) Contraindications, warnings, and precautions should be included to reflect the conditions after first use and after multiple uses. If the test data demonstrate significant changes in the k_{uf} after reprocessing, warnings should be included to use appropriate control of the ultrafiltration rate.

(3) The directions for use should include at a minimum the following:

(a) Comprehensive instructions for the preparation of the hemodialyzer, initiation of dialysis, troubleshooting, and discontinuance of dialysis should be included.

(b) Hemodialyzer clearances, k_{UF} <u>in vitro</u> correlation (bovine and human blood), β_2-microglobulin with human blood, and maximum recommended TMP should be included.

(c) Instructions for adequate cleaning and rinsing (including the maximum water flow velocities and pressures) should be included. When applicable, instructions for header and "O"-

ring disassembly, cleaning and assembly should also be included as well as instructions for the proper storage and handling of reprocessed hemodialyzers.

The instructions should include the recommended reprocessing agent(s) and/or process(es), a method for determining chemical residuals and a precaution that any other reprocessing agent or process has not been tested with the manufacturer's hemodialyzer.

The instructions should include a warning against the use of any reprocessing agent(s) or process(es) known to adversely affect a manufacturer's hemodialyzer.

(d) Instructions for the user on the performance tests needed prior to each reuse to determine whether the hemodialyzer can be safely reused should be included.

(e) A summary of the in vivo and in vitro performance data, described in the preceding sections, should be provided for the user in tabular form.

B. Advertisements or promotional literature for the hemodialyzer should be provided. Literature or labeling may not imply approval by FDA in any manner or extend the intended use beyond those cleared in the 510(k).