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1. Meeting Agenda (Draft)

**GASTROENTEROLOGY AND UROLOGY DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE**

June 8, 2005

Panel Chair

Mark Talamini, M.D.
Professor of Medicine
Johns Hopkins School of Medicine
Baltimore, MD

Location: Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland

NOTE: *Two ten-minute breaks and a one-hour lunch break will be determined at the discretion of the panel chair*

<u>CALL TO ORDER:</u>	9:00 a.m.
Agency's Critical Path Initiatives	9:00 to 9:15 a.m.
OSB Post Market Studies	9:15 to 9:30 a.m.
<u>OPEN PUBLIC HEARING*</u>	9:30 to 10:00 a.m.

Public attendees will be given an opportunity to address the Panel to present data or their views on the Panel's activities.

OPEN COMMITTEE DISCUSSION

1. Regulatory briefing – Carolyn Neuland, Ph.D.	10:00 to 10:15 a.m.
2. Overview of Conventional Hemodialysis Systems – Josh Nipper, M.E.	10:15 to 10:30 a.m.
3. FDA Presentation - Claudia Ruiz. M.D.	10:30 to 11:00 a.m.
4. Human Factors – Mike Mendelson, D.D.S., M.S. Biomed Eng	11:00 to 11:15 a.m.
5. Questions for the Panel	11:15 a.m.
Proposed lunch – 1 hour	12:30 p.m.
6. Continued: Questions for the Panel	1:30 p.m.

<u>OPEN PUBLIC HEARING*</u>	4:30p.m.
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Public attendees will be given an opportunity to address issues specific to the matter before the committee.

7. Final Comments	4:50 p.m.
8. Adjournment	5:00 p.m.

*OPEN PUBLIC HEARING

Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee.

After the scheduled public speakers have spoken, the Chair may ask them to remain if the committee wishes to question them further. Dr. Talamini will recognize unscheduled speakers as time allows.

Note: Only the Chair and members of the Panel may question speakers during the open public hearing.

2. Background Information

The most common form of renal replacement among the End Stage Renal Disease (ESRD) patient population in the United States is hemodialysis. This takes place most commonly in a center for hemodialysis (often independent from a hospital). Patients typically receive hemodialysis three times a week for four hours each visit. This is also known as conventional hemodialysis. In conventional hemodialysis, all aspects of patient care, from obtaining patients' weight, assessment of well being, vascular access, and dialysis prescription to connection, initiation, troubleshooting, and monitoring of the procedure, are performed by medical personnel. The patient is a passive part of the treatment.

This panel meeting is for the purposes of evaluating a different form of delivering hemodialysis, specifically at night, at home, while the patient is sleeping. Nocturnal home hemodialysis (NHD) is not a new concept; however, it is uncommon in the United States. Among hemodialysis patients, reported as 281,594 by the United States Renal Data System (USRDS) in 2002, only 0.3% or 843 were home hemodialysis patients, of which an even smaller portion received nocturnal hemodialysis (1). In 2001, 115 patients in 13 centers in North America were receiving NHD (2). Currently, there are no devices specifically labeled to perform NHD.

2.1 Guidance Documents

The FDA has developed guidance documents to aid manufacturers and reviewers in the preparation and processing of submissions. In the dialysis field, FDA developed guidance documents to address the review of hemodialyzers, hemodialyzer reuse, hemodialysis delivery machines, and water treatment systems. The latter two documents are included in this package, as they may be relevant in the consideration of NHD hemodialysis devices. Additionally, general use guidance documents on patient labeling and the incorporation of human factors into reviews are provided.

- 2.1.1 Guidance for the Content of Premarket Notifications for Hemodialysis Delivery Systems (Appendix A)
- 2.1.2 Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Hemodialysis (Appendix B)
- 2.1.3 Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers (Appendix C)
- 2.1.4 Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (Appendix D)

2.2 Definitions and nomenclature

Nocturnal Hemodialysis (NHD), also referred as Nightly Hemodialysis and Nocturnal Home Hemodialysis, is a type of hemodialysis performed at home, typically at night, and while the patient sleeps. Other types of similar modalities include in-center nocturnal hemodialysis, long nocturnal hemodialysis or slow nocturnal hemodialysis, and daily hemodialysis. In NHD, blood flows (QB) are generally 200-300 ml/min, and dialysate flows (QD) of 300 ml/min are usual, although dialysate flows as high as 800 ml/min have been reported in small non-controlled trials (3). In addition, NHD is done in the absence of medical personnel. The frequency and length of NHD, although not rigid, has ranged from 5-7 nights a week, and 6-10 hours per night, depending on the individualized dialysis prescription.

For the purposes of this document, conventional hemodialysis will be considered to take place in a center for hemodialysis, typically independent from a hospital. It includes thrice weekly therapy for four hours each sitting. As noted earlier, the patient is a passive recipient, while one or more trained professionals perform all aspects of the treatment.

At this point it is also practical to define other terms used in this information package, such as human factors, patient labeling and physician labeling.

- Human Factors – According to Alphonse Chapanis, a pioneer in the field, human factors discovers and applies information about human behavior, abilities, limitations, and other characteristics to the design of tools, machines, systems, tasks, jobs and environments for productive, safe, comfortable, and effective human use. In the field of medicine, the objective is to improve human performance, reduce the burden on training and labeling, and reduce the likelihood of use error and patient injury.
- Physician's Instructions for Use - The manual that accompanies a medical device including the indications for use statement, contraindications, precautions and warnings. It should also include relevant data from clinical studies and instructions for using and caring for the device.
- Patient Instructions for Use - Same as above, but written for a person with no medical training.
- Training - The teaching provided by the manufacturer of the product that allows the medical expert to train the lay user, and the lay user to successfully use the device.

2.3 Device Description and Regulations

Hemodialysis delivery systems are described and classified in two sections of the Code of Federal Regulations (CFR). Under 21 CFR §876.5820, a conventional hemodialysis delivery system is defined as a system that **“consists of mechanisms that monitor and control the temperature, conductivity, flow rate, and pressure of the dialysate and circulates dialysate through the dialysate compartment of the dialyzer.”** Under 21 CFR §876.5860, a high permeability hemodialysis system is defined as a machine that

contains an “ultrafiltration controller and mechanisms that monitor and/or control such parameters as fluid balance, dialysate composition, and patient treatment parameters (e.g., blood pressure, hematocrit, urea, etc.).”

These classifications also contain hemodialyzers and extracorporeal and associated tubing lines. For the purpose of this document, a NHD system could be from either classification listed above. The discussions in this document and at the Advisory Panel meeting, however, will center on hemodialysis delivery systems, rather than on dialyzers and tubing lines.

Both classifications above specify that dialysis delivery devices are Class II products and are thus appropriate for review and clearance under Premarket Notifications or 510(k)s. In performing the device reviews, FDA compares the new proposed device to a “predicate” device (a device already cleared by FDA or one being marketed prior to the enactment of the Medical Device Amendments in 1976) in terms of safety and effectiveness to demonstrate substantial equivalence. These reviews include an evaluation of the devices’ technological characteristics (device design and components), functional validation, and labeling.

2.3.1 Device Components

The following is a list of components typically required of conventional hemodialysis delivery devices:

- **Blood Pump** – The blood pump is responsible for pumping the blood from the patients’ arterial access, through the hemodialyzer, and back to the patients’ venous access. Blood pumps are designed to pump blood from 0 to 600 mL/min, and are monitored for accurate speed. During most alarm conditions, the blood pump is stopped to protect patient safety.
- **Dialysate Pump** – The dialysate pump is responsible for pumping the dialysate fluid from its origination point through the dialyzer, and back to waste. Dialysate pumps are designed to pump blood from 0 to 800 mL/min, and are monitored for accurate speed. During most alarm conditions, the dialysate pump is stopped to protect patient safety.
- **Anticoagulant Pump** – An anticoagulant pump, usually in the form of a small stepper motor with a syringe, is required to administer anticoagulant (e.g. heparin or sodium citrate) to the patient.
- **Ultrafiltration (UF) Controller** – An ultrafiltration controller is required to ensure adequate patient fluid balance. The UF controller uses data supplied from the blood pump, dialysate pump, pressure monitoring system, and/or scales to control the amount of excess fluid that is removed from the patient during each dialysis session.

- Pressure Monitoring System – Hemodialysis delivery devices contain multiple pressure transducers in order to monitor the operating pressure of the blood and dialysate. Generally, the patients’ venous pressure is measured, along with the transmembrane pressure (TMP) of the hemodialyzer. Arterial pressure is also frequently measured.
- Air Detection System – An air detection system is required after the blood pump to ensure that an air embolus is not returned to the patient. If an air embolus is detected, the device alarms and the blood pump is stopped.
- Blood Leak Detector – A blood leak detector measures the color of the dialysate fluid exiting the hemodialyzer and alarms if blood is detected. The presence of blood in the dialysate fluid signals a leaking hemodialyzer.
- Temperature Monitor – Hemodialysis delivery systems have temperature transducers to measure the temperature of the dialysate.
- Disinfection System – Any hemodialysis delivery system that has dialysate supplied from a central supply, or contacts patient fluid (including ultrafiltrate) must be periodically disinfected. The hemodialysis delivery system is responsible for ensuring that adequate disinfection parameters (e.g. disinfection mix time, temperatures, etc.) are established. Hemodialysis delivery systems that use closed systems, and do not directly contact patient fluid, are not responsible for disinfection.
- User Interface – Hemodialysis delivery systems are software-controlled devices, and require a user interface for entering the prescription information, monitoring treatment, and communicating alarms. Most modern systems contain sophisticated interfaces that display treatment times, operating pressure, remaining time left, ultrafiltration rate, volume of fluid removed, etc. The user interface may be text based, or may be designed as a graphical, touch-screen display. The user interface can be designed to limit certain features based on passwords in order to prevent misuse. For instance, home use devices may have their dialysis prescription pre-set by the physician, and prevent the patient from altering certain parameters. The user interface can also be designed to assist in setup and trouble-shooting of the device by giving the user of the device clear visual instructions on-screen. In this capacity, the interface works in conjunction with the labeling of the device (discussed next). The user interface of any hemodialysis delivery system should be designed with human factors in mind.
- Labeling – A comprehensive Operator’s Manual must be included with every hemodialysis delivery system. This manual should demonstrate the proper setup and use of the device, as well as how to respond to any alarm conditions.
- Blood rinse-back – A fail-safe design allowing blood rinse-back, either using battery backup power or mechanical means, in the case of power failure.

In addition, depending on the design of the device, a hemodialysis delivery device may include the following components:

- Fluid Heater – Some hemodialysis delivery systems contain built-in fluid heaters to warm dialysate to physiologic temperatures, while other systems use fluid heaters as an optional accessory. Systems that use a heater as an accessory may have electrical interfaces with the heater, or these heaters may be independent. Any system with a fluid heater should also contain temperature monitors to prevent fluid over-heating.
- Conductivity Monitor – Hemodialysis delivery systems that are responsible for proportioning purified water with dialysate concentrate must have a conductivity meter and a pH sensor to ensure that the dialysate composition is adequate.
- pH Sensor – See the conductivity meter description above.
- Water Treatment System - Some hemodialysis delivery devices have built-in water treatment systems (discussed later) as part of the device. Other devices require a separate device to purify the water, and some delivery systems use pre-mixed dialysate.
- Scales – Hemodialysis delivery systems that use pre-mixed dialysate may have scales to monitor the amount of dialysate remaining and the amount of dialysate that has been used. These scales can interface with the UF controller to ensure that the proper amount of fluid has been removed from the patient.

2.3.2 Device Alarms

Hemodialysis delivery devices monitor ongoing treatments, and provide visual and audible alarms in the event of an unsafe situation. These devices typically prioritize alarms in order to ensure that the most serious problems are addressed by the user first. Often, the system will have different levels for alarms conditions. For instance, a high return pressure may first trigger a “Caution” at a designated level, and then a “Warning” alarm at a higher lever. Alarms present on hemodialysis delivery devices may include the following:

- Pressure alarms – Blood pressure alarms are present for both over-pressure and under-pressure situations. In addition, the dialysate pressure is monitored, and an alarm is triggered if the transmembrane pressure exceeds safe levels.
- Temperature alarms – Temperature alarms are triggered if the incoming dialysate fluid is higher or lower than pre-set limits.
- Blood leak alarm – As discussed above, blood leak alarms monitor the spent dialysate for the presence of blood, and respond accordingly.

- Air embolism alarm – As discussed above, air embolism alarms monitor the venous return line of the blood tubing for air embolism, and respond accordingly.
- Vascular access disconnect alarms – Vascular access disconnect alarms monitor the status of the patients return access, to ensure that needle pull-out or catheter disconnection has not occurred. Most current systems rely on the venous return pressure to monitor for vascular disconnect, since disconnection should result in a noticeable drop in venous pressure. However, inherent resistance in the blood tubing and small gauge needles can cause enough back-pressure in the system to prevent the venous return pressure alarm from triggering. This situation could result in significant blood loss and eventual exsanguination of a patient. Other systems rely on single-needle modes of dialysis, so that a venous access disconnect would be detected by air embolus detectors.
- Conductivity / pH alarms – Hemodialysis delivery systems that proportion purified water with dialysate concentrate are required to have conductivity and pH alarms to ensure that the resulting dialysate does not fall above or below pre-set limits.
- Water quality alarms – Hemodialysis delivery systems that include a water treatment component should contain alarms to indicate that the water quality has not met the required purity standard.
- System level alarms – System level alarms are designed to alert the user of device hardware and/or software issues.

2.3.3 Accessory Devices

Below is a brief listing of additional devices that may be required to perform hemodialysis. This listing does not include basic medical supplies such as gauze, access needles, tape, or other such items. In addition, this listing does not include the dialysate or dialysate concentrate prescribed by the physician, or any anticoagulant that may be prescribed (e.g., heparin or sodium citrate). Again, the discussion in this document and at the Advisory Panel Meeting will center on hemodialysis delivery devices, although information on these accessories is valuable for background purposes.

2.3.3.1 Water Treatment Systems

Water treatment systems for hemodialysis are regulated by the FDA under 21 CFR §876.5665, and are Class II devices. The FDA guidance document “Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Hemodialysis” (enclosed in Appendix B) identifies the suggested information to include in a premarket notification for one of these devices. Water treatment systems are required to convert potable (tap) water into water meeting the requirements of the Association for the Advancement of Medical Instrumentation (AAMI) RD62 water quality standard. In a clinical setting, these systems are typically customized to meet the individual site needs. A water treatment system can include some or all of the following

components: sediment filters, carbon filters, water softeners, reverse osmosis (RO) systems, a deionization (DI) system, holding tanks, ultrafilters, and ultraviolet lights. Water treatment systems require routine maintenance and regular monitoring to ensure that the output water is meeting the AAMI RD62 standard.

Individual or single patient water treatment systems are also available. These devices are much smaller than traditional water treatment systems, and typically lack the flow rate capabilities to handle more than one patient. In addition, single patient water treatment systems usually require a minimum quality of inlet water, and pre-treatment or filtration may be required to ensure that AAMI quality water is met.

An alternative to using a water treatment system is to use pre-mixed, bagged dialysate. Pre-mixed dialysate may be preferable to a water treatment system in situations where a water treatment system cannot be installed due to space limitations or water quality issues. However, large amounts of pre-mixed dialysate must be purchased and a proper storage environment must be found.

2.3.3.2 Blood Tubing

Blood tubing for hemodialysis is regulated by the FDA under 21 CFR §876.5820, and is a Class II device. Hemodialysis blood tubing is sterile tubing designed to route the patient's blood from the arterial access, through the hemodialyzer, and back to the patient through their venous access. This tubing, which is typically constructed from polyvinyl chloride (PVC), is designed to interface with specific hemodialysis delivery systems. Depending on the delivery system used, this tubing may contain the following components: arterial and/or venous drip chambers, infusion ports, infusion tubing lines, tubing lines for pressure monitoring, and transducer protectors designed to prevent patient blood from contacting the pressure transducer. Proper setup of this blood tubing is crucial, since the hemodialysis delivery system typically relies on proper tubing placement for pressure monitoring, blood leak detection, and monitoring of venous air embolism.

In a home use setting, a patient would be required to connect tubing for dialysate delivery, as well as blood tubing. In the clinical setting, dialysate delivery is usually controlled from a centralized water treatment system and dialysate concentrate mixing system. Concentrated dialysate is then proportioned with purified water by the hemodialysis delivery device.

Hemodialysis blood tubing can also come in pre-formed sets, or cartridges. This type of tubing reduces the number of connections that the patient is required to perform. These cartridges can be supplied with or without a pre-attached hemodialyzer.

2.3.3.3 Hemodialyzers

Hemodialyzers are regulated by the FDA under 21 CFR §876.5820 (conventional, low-flux hemodialyzers) and 21 CFR §876.5860 (high-flux hemodialyzers), and are Class II

devices. These devices have a blood inlet port and a blood outlet port that attach to the hemodialysis blood tubing. They also contain a dialysate inlet port and dialysate outlet port that attach to either dialysate tubing or central supply lines. The choice of hemodialyzer is based on physician prescription, and depends on patient needs. Hemodialyzers are labeled with the following information: effective surface area, priming (blood) volume, maximum transmembrane pressure (TMP), maximum blood and dialysate flow rates, the ultrafiltration coefficient, pressure drop across the blood and dialysate compartments, and in-vitro clearance data for urea, Vitamin B₁₂, and inulin. As noted in the hemodialysis blood tubing section above, some blood tubing cartridges are supplied with a pre-attached hemodialyzer.

2.3.3.4 Remote Monitoring Systems

Remote monitoring systems for hemodialysis are regulated by the FDA under 21 CFR §876.5820, and are Class II devices. These devices interface directly with a hemodialysis delivery system, and can transmit patient treatment information electronically over a local area network (LAN) or the internet.

2.3.4 Existing Medicare Regulations

The CFR requires that centers offering home dialysis to their patients must monitor the patient and the home environment. Sections 42 CFR §405.2137(b)(6) and (7), as well as §404.2163(e), state that these facilities are required to periodically monitor home adaptation with visits. In addition, diet, fluid intake, medications, hematocrit, and iron stores must be monitored. The dialysis prescription must be reviewed and blood tests performed. Training should be provided to identify hypo- and hypertension. The training should be under the charge of a registered nurse and social work and dietary consultants should be available. The facility is required to keep records, install and maintain the equipment as well as test and treat the water.

Training is defined in 42 CFR §405.2102 as "a program that trains ESRD patients to perform self-dialysis or home dialysis with little or no professional assistance, and trains other individuals to assist patients in performing self-dialysis or home dialysis."

Home dialysis is defined in the same section as "dialysis performed by an appropriately trained patient at home."

3. Nocturnal Home Hemodialysis

NHD differs from conventional hemodialysis in that the patient is not only the receiver of the treatment, but the giver of the treatment, as well. In addition, it is presumed that the patient will be asleep through most of the treatment. Therefore, when considering what a hemodialysis device to be used at home should include, safety becomes a primary concern. Any device malfunction, access problems, or break in the seal of the hemodialysis circuit (e.g., dislodged access needle, blood leaks) would be life threatening, even with the lower blood flows used in nocturnal home hemodialysis. It is important to consider building

redundancy into the design, so that safety is assured in the event of a component failure during treatment. Additional safety alarms at different sites of the hemodialysis circuit may become necessary for a successful hemodialysis session. Considerations regarding alarms include their loudness, sensitivity, and ease of understanding and correction. In addition, the device should be user-friendly for patients to be successfully trained in performing the procedure without medical personnel assistance.

Some device and treatment parameters that differentiate nocturnal from conventional hemodialysis are mentioned below as background for your discussions at the panel meeting.

3.1 Device Components

The following additional safety features, compared to those included in conventional hemodialysis devices, should be considered for NHD devices:

- a. Additional safeguards to prevent blood access disconnections;
- b. Alarms to detect fluid (blood or dialysate) leaks, and a moisture detector at the site of hemodialysis access;
- c. Software incorporated in the NHD device allowing connection to the internet for remote monitoring;
- d. Central monitoring of treatment and patient parameters, such as blood pressure, pulse, venous and arterial pressures;
- e. Instructions that are user-friendly, containing clear, easy to follow, and accessible instructions for treatment set up, discontinuation, troubleshooting, and disinfection of the device;
- f. Alarms that are sensitive and loud, with clear explanations of what they mean and how to respond; and
- g. User interface that contains the instructions for the set-up, use and troubleshooting of the device (e.g., displayed screens and menus).

3.2 Human Factors Issues

Human factors (HF) is the study of how people use technology. It involves the interaction of human abilities, expectations, and limitations, with work environments and system design.

In the application of human factors to medical devices, it is important to ensure that devices are "user friendly" so that users are able to install, calibrate, operate, maintain, and ultimately, dispose of devices safely and effectively with minimal dangerous error and minimal dependence on labeling and training. It should be noted that users are not merely the operators of devices; any task involving interaction with a medical device may have an adverse impact on safety and effectiveness if it is performed improperly. This is accomplished by refining the device "user interface."

The consideration of human factors in the design, training program and labeling of NHD devices is crucial to their success. Therefore, you will be asked to discuss how human factors should be incorporated into the design process and how a device's training program and labeling can be developed to minimize the potential for user (patient) errors. General information on human factors engineering, background material and issues to consider regarding NHD devices has been provided in Appendix E.

3.3 Water Quality

Water quality is another concern in the consideration of nocturnal home hemodialysis. In conventional hemodialysis, patients are exposed to about 360 L of dialysate per week; while in nocturnal hemodialysis, assuming dialysate flows of 300 ml/min for 6 hours per treatment, 6 times per week, patients will be exposed to 648 L per week (up to 1080 L if using a dialysate flow rate of 500 ml/min). This raises the concern as to whether the standard water quality for hemodialysis is sufficient for NHD, or if higher standards should be considered (e.g., lower levels of toxin contaminants). Also, as with all home hemodialysis procedures, storage of water is a major issue and on-line production of water of acceptable quality may be preferred.

The London Daily/Nocturnal Hemodialysis Study (4) used a Service Deionization (SDI) Tank water treatment system composed of pretreatment, purification, and post-treatment components. The water treatment equipment requirements from the London Daily/Nocturnal Hemodialysis Study included:

- tempered water control/mixing valve (Fotopanel);
- water quality indicator lights/alarm;
- product water connection hose;
- water supply pressure of 20 to 105 psi; and
- wall switch to remotely activate a deionization tank recirculation pump.

The pretreatment components required:

- Fotopanel;
- Water softener; and
- Activated carbon filters.

The purification component of the SDI system model included:

- Two, 9-inch medical grade, mixed-bed SDI tanks connected in series; and
- A recirculation pump to extend the tanks' servicing interval.

The post-treatment component of the water treatment system included:

- Ultraviolet light sterilizer; and
- Submicron filter/ultrafilter to trap endotoxins and remaining bacteria.

Another issue to consider is how to handle changes to the water quality or composition by municipal water suppliers. In such cases, procedures should be in place so that notifications about water changes are communicated appropriately and responses are mounted accordingly.

3.4 Use of a Partner and Remote Monitoring

Some studies have suggested that home hemodialysis can be done by the patient without the need of an assistant or partner (5). This raises safety concerns, however, that warrant being addressed by the device design, patient training, and/or monitoring performed.

Patients receiving in-center conventional hemodialysis are under constant monitoring by medical personnel. This is not the case for patients doing home hemodialysis during the day or night. Further concerns arise from the fact that NHD patients are typically asleep during treatments. The London Daily/Nocturnal Hemodialysis Study, a prospective, comparative, non-randomized study, suggested that “Monitoring is essential for the initial 3 months of nocturnal HD therapy until the HD team is convinced the patient is stable and compliant” (6). In cases where a partner is not available and remote monitoring is not used, additional treatment and device safeguards may be necessary to ensure patient safety.

3.5 Vascular Access and Extracorporeal Circuit Connections

Traditionally the vascular access of patients on hemodialysis has not been a part of the device labeling or regulation. However, NHD cannot be safely delivered without a properly evaluated and secured vascular access and a discussion is valuable. Available types of vascular access include arteriovenous fistulae and synthetic grafts, or alternatively, long-term, cuffed hemodialysis catheters. The preferred type of vascular access is arteriovenous fistulae, because of the high patency and lower infection rates. Evidence suggests that the increased rate of cannulation of AV fistulas in daily hemodialysis, compared to three times a week, does not increase the rate of complications or infections (7). Synthetic grafts are technically more easily placed by the surgeon, and are ready to be used sooner than fistulae; however, the patency rate is inferior to that of fistulae. Long-term, cuffed catheters for hemodialysis have the advantages of immediate use after placement, and needleless access for each hemodialysis treatment; however, the disadvantages are the associated higher complication rates, which range from infections to thrombosis. The access location should also be considered for NHD.

In addition to the access itself, the connection of the access (patient) to the dialysis device may pose a source of risk. Training in self cannulation, use of locking devices, enuresis alarms, and moisture sensors are all issues that should be considered in NHD

3.6 Labeling

Typical conventional hemodialysis machines contain labeling in the form of an Operator’s Manual (list of warnings, cautions and precautions, device specifications,

instructions for the use of the device, troubleshooting information, and instructions for the maintenance, cleaning and disinfection of the device) and package labels for the disposable sets (if available). Such labeling is insufficient for nocturnal home hemodialysis systems, as it does not include information directed to the patient. Patient labeling should be included to convey to the patient information about the device and its use, about the treatments to be performed, and about anticipated adverse events and complications.

In addition to the risks and adverse events typically associated with conventional hemodialysis systems, and contained in those devices' labeling, additional risks and potential problems may need to be included in the labeling of nocturnal home hemodialysis devices. At the panel meeting, you will be asked to discuss such risks, including:

- a. Increased risk of inadvertent disconnections;
- b. Increased blood loss from increased frequency of treatments;
- c. Potential increased rate of vascular access infection due to increased use of access; and
- d. Psychological effects (e.g., impact of treatments on patients, such as loss of social interaction and the impact of increased responsibility on the patient) requiring need for adjustment or discontinuation of therapy.

Physician labeling may also need to include non-device, treatment-related information, such as:

- a. Need for separate alarms (e.g., circuit disconnect alarms, fluid leak or moisture detection alarms);
- b. Need for a partner or for remote monitoring;
- c. Vascular access requirements (e.g., type of access and location);
- d. Need for dialysate additives (e.g., phosphorus);
- e. Water quality recommendations, and
- f. Support staff recommendations (e.g., who should be contacted in the event of a problem, who is responsible for supplying device parts and disposable sets, who is responsible for device repairs).

3.7 Lay-user Training

The training of patients and their partners is crucial in being able to conduct safe and effective NHD treatments. Since they do not have the background and experience of the professionals that operate these devices in a clinical setting, the training needs to be tailored to their circumstances. In published studies, training has been reported to last from 2 to 8 weeks, depending on the complexity of the hemodialysis device and the patient's familiarity with the hemodialysis process (8, 9). In certain circumstances, training has been as short as one day for patients who had previously been on home hemodialysis (3).

A complete training program should comprise not only the use of the hemodialysis device itself, but the entire array of safety features, accessories and the hemodialysis treatment itself; for example, training to manage the water purification system, the catheter lock boxes, the moisture sensors, and the monitoring device. The training program should also specify criteria to determine if a patient has been adequately trained and is ready to initiate self-care at home, who should do the training and how these providers should be qualified. Some of the topics that should be covered are required by the Center for Medicare and Medicaid Services (CMS), as discussed in section 2.3.4. It should be noted, however, that training needs to be device- and patient-specific and should cover the device's and the treatment's limitations.

4. Clinical Studies

The purpose of clinical studies is to demonstrate the safety and effectiveness of the NHD devices under actual use conditions. Clinical studies to be considered for NHD should also show that:

- a. The device can be used by a patient to deliver hemodialysis treatments with outcomes similar to those seen with in-clinic conventional hemodialysis, in terms of clearance rates and other acute findings;
- b. The adverse event rate is not greater than that observed with in-center conventional hemodialysis; and
- c. The patient can be trained to understand how to use the machine and troubleshoot should an alarm situation occur.

In addition, a device cleared for NHD should comply with the guidelines suggested for conventional hemodialysis devices (device performance). This type of clinical study is not intended to evaluate the long term safety and effectiveness of NHD as a therapeutic modality compared to conventional dialysis.

Regarding patient selection, several studies on NHD have selected highly motivated ESRD patients who have been stable on conventional or home hemodialysis (8, 10). This type of selection automatically excludes patients who undergo significant intradialytic hypotension, or patients who suffer from severe congestive heart failure, diabetes or cardiovascular disease (11).

Patients need to be able to learn to perform the entire treatment, from setting up the system to the after-treatment clean up and troubleshooting, either themselves or with the help of a partner. In addition, patients are expected to wake up to the alarms and be able to respond in a timely manner. The psychological effects of NHD on patients should also be considered in the selection of candidates for this modality, as they will be required to adjust to changes caused by the new treatments, such as needing to handle the responsibility of self-care, and dealing with the loss of interactions with other patients, as would occur in a treatment center. The impact on and the reaction of the patient's family members living in the house should also be considered. Besides the patients' ability to be trained and subsequently perform the hemodialysis process alone, other selection criteria

may prove important, such as home environment, patient's vascular access type and location, availability of a partner, patient's compliance, and psychological well being (9).

The design of clinical studies for NHD will be discussed at the panel meeting. In addition to your comments on study parameters, such as study design (e.g., retrospective or prospective), need for a control group, sample size, patient selection, clinical endpoints and evaluation of outcomes, treatment frequency and duration, study duration and length of follow-up, you will also be asked to discuss the importance of the evaluation of treatment aspects, such as dialysate composition (including the need for phosphate or other additives), type of anticoagulation (dose, bolus, monitoring), choice of dialyzer (membrane type and permeability), type of monitoring (e.g., partner present, partner awake, no partner but using remote monitoring, no partner or remote monitoring), choice of blood access type and location, and the practice of reuse of dialyzers.

5. References

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6. Discussion Points for the Panel (Draft)

Tentative Panel Discussion Points

Nocturnal Dialysis Advisory Panel Meeting

June 8, 2005

Device Design

1. Standard hemodialysis delivery devices contain monitors and alarms to assess blood pressure, pulse, venous and arterial pressures, blood and air leaks, temperature, dialysate and blood flow, ultrafiltration rate, acid and bicarb pumps, end of treatment, and other parameters particular to the specific device. Please consider and discuss the need for the following additional safety features in nocturnal home hemodialysis (NHD) treatments and provide suggestions for additional features. You should take into consideration the importance of human factors when discussing these features.

Blood Access

- a. Additional safeguards to prevent blood access disconnections;
- b. Alarms to detect fluid (blood or dialysate) leaks, and a moisture detector at the site of hemodialysis access;

Central monitoring

- c. Software incorporated in the NHD device allowing connection to the internet for remote monitoring;
- d. Central monitoring of treatment and patient parameters, such as blood pressure, pulse, venous and arterial pressures;

User-friendly design

- e. Instructions displayed on the machine itself that are clear, and easy to follow, for treatment set up, discontinuation, troubleshooting, and disinfection of the device;
 - f. Sensitive and loud alarms with clear explanations of what they mean and how to respond;
 - g. A justification for leaving out any standard alarms or features found in traditional hemodialysis equipment.
2. The quality of the water to be used to prepare dialysate is crucial for any dialysis treatment. Please discuss the water purification needs for NHD procedures, including the following:
 - a. Type of water treatment equipment (for preparation of water and verification of its quality) appropriate for nocturnal home use;

- b. Due to the potentially higher exposure of patients to the processed water, consideration as to whether the water quality recommendations be different for nocturnal home use as opposed to conventional, in-clinic use; and
- c. Procedures on how to handle changes to the water quality and composition by municipal water suppliers.

Clinical Study Design

- 3. FDA proposes that manufacturers evaluate NHD devices in clinical trials. The purpose of these studies is to evaluate the incidence of adverse events, the devices' ability to deliver prescribed treatments, and the patients' ability to conduct the treatments as prescribed in a home nocturnal hemodialysis setting, after appropriate training. Please consider the following aspects of the clinical study design, and provide input on the following elements of the study:
 - a. Study design (e.g., retrospective or prospective);
 - b. Need for a control group and if so, appropriate type of control (e.g., prospective, historical, patient as their own control);
 - c. Appropriate sample size;
 - d. Inclusion/Exclusion criteria (e.g., exclusion of patients previously on home dialysis);
 - e. Frequency and duration of treatments;
 - f. Study duration;
 - g. Safety endpoints;
 - h. Effectiveness endpoints; and
 - i. Length of follow-up.

- 4. Please address these additional issues and discuss whether or not they should be considered in a clinical trial.
 - a. Need for dialysate additives, such as phosphate, and monitoring requirements for these levels;
 - b. Type of anticoagulant appropriate for home use (e.g., dose, bolus, and monitoring issues);
 - c. Type of hemodialyzer membrane and permeability;
 - d. Type of monitoring (e.g., partner present, partner awake, no partner but using remote monitoring, no partner or remote monitoring);
 - e. Vascular access choice and location, and risks associated with these;
 - f. Practice of hemodialyzer reuse; and
 - g. Psychological effects (e.g., impact of treatments on patients, such as loss of social interaction and the effects of the increased responsibility on the patient, and the impact on and the reaction of the family members living in the house).

Training

5. The training of patients and their partners (if applicable) is crucial in performing NHD treatments. Please comment on the training needs for this modality in terms of the important aspects to be included in the training program, how long the training period should be and what criteria should be used to determine if a patient has been adequately trained and is ready to begin self-care at home. Please also consider who should do the training and how they should be qualified.

Labeling

6. Device labeling directed towards the patient should include information on NHD and on the device, including instructions for the use and care of the device, how to deal with alarms and how to run treatments. Please discuss other important aspects of NHD and the value of including them in the Lay User's Manual (e.g., treatment (not device) risks, psychological effects of the treatments, vascular access information).
7. The physician labeling (prescribing information) typically includes the indications for use, contraindications, warnings and precautions, instructions for use and clinical data on the use of the device. For NHD, there is other important information that clinicians need to know, such as the need for alarms that may not be part of the NHD device (e.g., circuit disconnect alarms, fluid leak or moisture detection alarms), the need for a partner or for remote monitoring, vascular access requirements, and the need for dialysate additives (e.g., phosphorus). Please discuss whether or not this and/or other treatment information should be part of the physician labeling.

Risk Analysis

8. FDA has identified the following potential risks associated with NHD, in addition to those related to conventional hemodialysis:
 - a. Increased risk of inadvertent disconnections;
 - b. Increased blood loss from increased frequency of treatments;
 - c. Potential increased rate of vascular access infection due to increased use of access; and
 - d. Psychological effects (e.g., impact of treatments on patients, such as loss of social interaction and the impact of increased responsibility on the patient) requiring need for adjustment or discontinuation of therapy.

To aid FDA in the development of a guidance document on NHD, please comment on the completeness and appropriateness of this list.