Technology for End Stage Renal Disease (ESRD) therapy differs in various parts of the world; it is expected that these differences would be related primarily to the ability of the payer to afford advanced technology. The United States has a per capita gross national product that is comparable to wealthy European and Asian countries; however, those countries apply more advanced technology to ESRD therapies than does the U.S. I believe there are three general reasons for these differences which include regulatory, educational, and economic constraints. In this manuscript I give examples illustrating these limitations to the application of state-of-the-art ESRD technology in the U.S. This article is intended to give the perspective of a research scientist who has tested the effectiveness of advanced ESRD technology and who is also a member of a U.S. academic dialysis program which is a potential end-user of such technology. I preface this article by noting that I am a research scientist who has tested ESRD technology for its effectiveness and who is a member of an academic U.S. dialysis program which potentially is an end-user of this technology. I am not an expert on regulatory issues regarding medical devices nor am I currently involved in developing new ESRD technology. My intention here is to give the perspective of an end-user of ESRD technology.

**Background**

It is a widely held belief that technological advances lead to national wealth, and conversely, that national wealth leads to the accumulation of advanced technology. The United States is one of the wealthiest nations in the world and has a per capita gross national income or product (GNP) of approximately $40,000 (1). A number of European and Asian countries have similar per capita GNPs, and one would expect that the technology for treating ESRD patients in the U.S. would be comparable to that in the many wealthy European countries and Japan. Despite many similarities in equipment design, ESRD technologies in many European countries and Japan are more advanced than those in the U.S.

There are several reasons why I believe ESRD technology is not as advanced in the U.S. as in these other countries. I categorize these reasons into three distinct groups: regulatory, educational and economic. I also briefly discuss some specific examples to explain why I believe advanced ESRD technology is limited in the U.S. I preface this article by noting that I am a research scientist who has tested ESRD technology for its effectiveness and who is a member of an academic U.S. dialysis program which potentially is an end-user of this technology. I am not an expert on regulatory issues regarding medical devices nor am I currently involved in developing new ESRD technology. My intention here is to give the perspective of an end-user of ESRD technology.

**Regulatory Constraints on Advanced Technology**

Regulatory hurdles in the U.S. for new technological developments are high. Over the past few decades of the 20th Century, device and drug developers commonly tested and first introduced new products in Europe where the process of medical device approval was more efficient (2). More efficient approval of medical technology has been traced to the differing missions of the U.S. Food and Drug Administration (FDA) and the European system (2). The mission of the FDA is to protect public health, but the mission of the European system is to promote trade, in addition to protecting public health. Recent changes, such as The Food and Drug
Modernization Act of 1997 and the Medical Device User Fee and Modernization Act of 2002 in the U.S., have made the U.S. system more similar to the European system (2, 3); however, there are still many differences in the goals and implementation of the two systems. It is difficult to predict future trends in the current environment; however, it is unlikely that it will be dramatically easier to introduce new ESRD technology into the U.S. market in the near future.

Two examples of regulatory concerns regarding new ESRD technology development in the U.S. can be noted. First is the uncertain future of hemodiafiltration (HDF) in the U.S. HDF is a common alternative to hemodialysis in some European countries and has the advantage of higher clearances for both small solutes and other uremic toxins, such as middle molecules (4). As currently practiced, HDF requires a significant volume of sterile solution to be infused intravenously to the patient, and these HDF fluids can be prepared using two fundamentally different approaches: 1) the use of commercial fluids prepared in bags or 2) on-line generation of practically sterile fluids. Recent data suggest that HDF is routinely used in a number of European countries and Japan. Data from the Fresenius Medical Care international network, which collects data from 122 countries, estimates that approximately 4% of all patients worldwide undergoing extracorporeal therapies (43,000 total patients) were receiving hemofiltration (HF) or HDF treatments in 2004 (5). There was a higher incidence of HF and HDF treatments in Europe and Japan of approximately 10% and 5% of all extracorporeal therapies, respectively. Further, the 2003 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry reports that the total number of European patients treated by HDF in 2003 was greater than 11,000, although more than 80% of those patients were treated in the two European countries of Germany and Italy (6). Thus, the acceptance of HDF throughout Europe is significant, but non-uniform. In addition, these data do not identify whether the
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HDF fluids used were commercially prepared in bags or generated on-line.

The regulatory concern with HDF is the requirement for intravenous infusion of significant quantities of sterile solutions, unlike conventional hemodialysis (HD) where body fluids are generally only removed from the patient. Bag fluids are convenient when sterile solutions are needed in relatively small volumes (9-12 L), but there are no commercial fluids which are approved by the FDA for current use during HDF in the U.S. The FDA regulates such fluids as they regulate drugs, and such commercial development would require the strict regulations that apply to drug development. This is an expensive undertaking that limits the ready development of such products. Alternatively, on-line generation of sterile fluids by dialysis monitors or other free-standing equipment can produce solutions as needed in the dialysis unit (7, 8); the volume of solution used in such treatments can be relatively large (25-60 L) (7-9). This approach for the generation of sterile fluid at the bedside was first demonstrated in 1978 (10) and has been ongoing in certain dialysis units for more than two decades without significant adverse reactions (11). Such technology is not currently approved for use by the FDA in the U.S. The equipment which could be used for on-line generation of sterile fluids would be regulated by FDA as a medical device, i.e., differently from the regulations for bags containing sterile fluids. The FDA must ensure that such on-line fluid generation is safe, but the amount of evidence required for approval is uncertain. The manufacturers of such equipment do not believe that widespread testing should be required because of the extensive experience with similar equipment in Europe. Thus, there is debate over the degree of testing that should be required for FDA approval of this equipment. On the other hand, it is somewhat paradoxical to expect the FDA to impose lower standards on medical devices which are used to produce sterile fluids since the volume of solution infused intravenously is much larger by the medical device than when using bag fluids and both solutions are used for the same clinical purpose. It can also be argued that the extensive experience with equipment in Europe has not been widespread; such experience may not readily apply to the routine dialysis unit in the U.S.

A second example is the use of closed-loop, biofeedback systems for controlling fluid removal during HD. One such system determines the instantaneous rate of fluid removal or ultrafiltration and dialysate sodium concentration which are necessary to maintain a pre-set profile of intradialytic changes in relative blood volume during the treatment. Such equipment has been described in the recent scientific literature and has been associated with improved intradialytic hemodynamic stability (12-16). The regulatory concern with these devices is that it is not the dialysis staff but the dialysis machine that, using complex algorithms, determines the variable rate at which fluid is removed and the level of dialysate sodium concentration administered during the treatment. Thus, the dialytic prescription parameters, dialysate sodium concentration and the ultrafiltration rate, are dynamically adjusted throughout the treatment by the dialysis machine, largely independent of human input. There are two significant scientific concerns with these systems that require tangible evidence. First, the cumulative clinical experience with these systems is relatively short and the mechanisms for the improved intradialytic hemodynamic stability remain incompletely understood (17). Second, there is little evidence regarding the effect of such systems on long term blood pressure control. These systems avoid intradialytic hypotension largely by increasing the dialysate sodium concentration, which has been associated with elevated blood pressure in HD patients (18). This is of concern since approximately 90% of all HD patients in the U.S. are hypertensive (19). The regulatory requirements for the introduction of such systems into the U.S. market will likely require both short-term and long-term evidence to document their efficacy and safety.

Educational Constraints on Advanced Technology

The effect of education and training of technical staff in the dialysis unit on technology development has not been studied extensively. The training requirements for dialysis staff members in the U.S. are defined by state and federal regulations, and the number of highly trained staff in dialysis units in the U.S. is often limited. For example, the number of highly trained staff in dialysis units in Europe is higher than in the U.S. (20), and this may limit the types and quality of ESRD technology that can be routinely applied in dialysis units in the U.S. Thus, the use of advanced ESRD technology may be limited in the U.S. because highly trained dialysis staff may be necessary to use these devices effectively.

One example of ESRD technology where staff training may be a concern is the blood volume monitor which
can be used to measure relative changes in blood volume during extracorporeal treatments in real time. Several technologies are currently available for making such measurements, determining either blood hemoglobin concentration (21), hematocrit (22), or total plasma protein concentration (23), to infer intradialytic changes in relative blood volume based on relative changes in the measured parameters. The abilities of current devices to accurately measure relative changes in blood volume have been shown to be excellent (24). In order for these devices to be accurate in the determination of relative changes in blood volume, there must be no change in the total mass of hemoglobin or total protein during the hemodialysis treatment and the blood compartment must remain well-mixed during rapid intradialytic removal of fluid. Neither of these assumptions apply exactly (25, 26), but the effects of these assumptions on accurate determinations of intradialytic changes in relative blood volume are unlikely to be clinically significant.

A reason why blood volume monitors are not currently essential in dialysis units in the U.S. is that there are many common clinical and physiological factors that can influence the output of these devices. Thus, accurate use of blood volume monitors may require additional clinical staff training and an advanced degree of understanding of these clinical and physiological factors. For example, it is known that intradialytic changes in relative blood volume are altered by patient posture (sitting versus lying down), food intake, intravenous administration of protein-containing solutions (such as albumin solutions or packed red blood cells), and exercise using a stationary bicycle (17). The interpretation of these data in a busy dialysis unit may be problematic when the dialysis staff is not sufficiently trained in these physiological principles. In the U.S., the number of years of nursing education is less than in other countries; therefore, the output from blood volume monitors may not be interpreted accurately and the usefulness of these devices not as readily appreciated.

If true, this example suggests that additional human engineering is required in the development of advanced ESRD technology for use in the U.S. than is necessary for use in other countries. This will also require either more educational support from the device manufacturer or, alternatively, the device will need to be modified to be used in an environment where the staff has less training. Efforts along these lines by companies developing new ESRD technology may allow more rapid introduction of advanced technology into the U.S. market.

An argument can also be made that U.S. nephrologists and non-physician practitioners, such as nurse practitioners and physician assistants, who prescribe and monitor the effects of ESRD therapies, are not well educated about advanced ESRD technology and its potential benefits. Manufacturers of these technologies must be prepared to educate physicians and their colleagues to the effectiveness and benefits of advanced ESRD technology. Once U.S. nephrologists are aware of the clinical benefits of advanced ESRD technologies, they will likely demand such technologies for the benefit of their patients.

**Economic Constraints on Advanced Technology**

The economic constraints on government funding for ESRD therapies in the U.S. are well known; reimbursement for ESRD therapy has decreased substantially in inflation-adjusted dollars since the 1972 amendment to the Medicare Act of 1965 which allowed all dialysis patients to be eligible for Medicare. These financial constraints have resulted in various cost-saving options: older equipment, dialyzer reuse, fewer supplies, and less-advanced ESRD technology. Furthermore, the majority of dialysis in the U.S. is delivered in a for-profit setting, in contrast to the not-for-profit setting in many other countries. In such an environment, the addition of new technology means added cost and requires rigorous clinical justification. In general terms, this situation can be described graphically as shown in Figure 1. Simply stated, as the profit margin for ESRD therapy decreases, the scientific or clinical evidence necessary to justify the introduction of new ESRD technology into the dialysis unit increases. Thus, the addition of advanced ESRD technology in the U.S. requires more rigorous scientific evidence than in other countries.
One example of the level of scientific evidence necessary in the U.S. to justify advanced ESRD technology is the use of monitoring devices to assess vascular access function. There is great clinical need for new devices to assist in monitoring vascular access function. Methods for monitoring the vascular access began in recent times with the observations by Schwab and colleagues who showed that elevated pressure in the venous line, which returns blood to the patient, indicates potential vascular access stenosis and subsequent access thrombosis (27). This approach was widely adopted in U.S. dialysis units because it was simple and could be performed without additional cost; however, this approach was later shown to be an imperfect method for the identification of vascular access stenoses (28). Others have developed methods for measuring the rate of blood flow through the vascular access, using Doppler ultrasound (29) or various other methods (30-32). These methods showed great promise in detecting poor vascular access function without other obvious clinical signs or symptoms, and several reports have suggested that routine vascular access monitoring could be used to decrease access thromboses and increase access survival (33-37).

To more rigorously test the usefulness of these technologies, several randomized clinical trials have been performed to assess the ability of these devices to assess vascular access dysfunction during routine HD (38-40). These clinical trials clearly showed that various monitors and monitoring methods could detect poor flow within the vascular access, which could subsequently be increased by angioplasty. However, none of the devices tested was shown to decrease the access thrombosis rate or increase access survival. A recent presentation summarizing the results from these clinical trials at the 2005 American Society of Nephrology meeting by Dr. Michael Allon convincingly demonstrated that such advanced ESRD technology is not necessary to improve vascular access care; rather, routine medical care provides the same outcome. Based on this presentation, it is not expected that vascular access monitors, at least in their current form, will be readily adopted in the U.S. for routine vascular access surveillance.

**Summary**

ESRD technologies in many other countries are more advanced than those available in the U.S. In this article I have discussed three main reasons, in general terms, for these differences. Of the three, economic constraints are the most critical and can only be overcome by obtaining additional scientific evidence that ESRD technology improves patient outcomes. For example, justification for widespread U.S. adoption of HDF must address the increased costs associated with this therapy. Certain results from the HEMO Study, a randomized clinical trial that suggested improved patient outcomes (especially cardiovascular outcomes) in patients treated with high flux vs. low flux hemodialysis (41, 42), indirectly supports that HDF would be a superior therapy. Further, an observational investigation from the Dialysis Outcomes and Practice Patterns Study, or DOPPS, (presented only as an abstract) has shown that European patients treated by HDF and HF had a 23% lower risk of mortality than those receiving standard hemodialysis (43). After adjustment for differences in urea Kt/V, however, the differences in patient outcomes were no longer significant. Taken together, these observations support the contention that HDF will produce improved patient outcomes in ESRD patients; however, the data are not particularly compelling. Fortunately, two randomized controlled clinical trials evaluating the importance of high flux membranes (44) and HDF (45, 46) are ongoing in Europe. The data obtained from these trials will be crucial in supplying additional evidence supporting the advantages of HDF in treating ESRD patients.

While ESRD technologies are more advanced in the rest of the world, there is little scientific evidence that the use of such technologies leads to better patient outcomes. Comparison of patient survival in various geographical regions of the world has shown superior patient survival in Japan than in Europe and in Europe than in the U.S. (47). Many of the reasons for these findings are differences in patient characteristics and practice patterns; however, the evidence for specific advanced ESRD technologies in improving patient outcomes is sparse. Advanced ESRD technology is always welcomed by the dialysis community in the U.S., but only as long as its economy is favorable, it is designed to be used by dialysis staff who may have limited clinical knowledge of patient physiology, and it can be shown to improve patient outcomes.

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