



A lifelong quest to make home hemodialysis simple, safe, and effective: A review of outcomes of 12 major projects

Abstract

In the course of over four decades, I have worked with an R&D team on 12 major R&D projects, all with the goal of making hemodialysis simple, safe, effective, and suitable for use in the home. Our team has worked within a University and in private companies and has collaborated with major healthcare drug and device companies. As a practicing nephrologist, my definition of success is when I see the device or drug we helped to develop in widespread clinical use. By this measure, two of the projects were highly successful, but seven failed. Most failures were due to decisions made by various corporations, governmental agencies, and venture capital groups, out of the hands or control of the R&D company. Three projects are still ongoing. There is no shortage of creativity or new ideas in nephrology and in dialysis. The major challenge is in the commercialization of the products.

1 | INTRODUCTION

I remember the first time I saw a hemodialysis machine in operation. It was in 1970 on the second floor of the University of Kansas Medical Center in Kansas City, where I was a third-year medical student. It was a Baxter Travenol RSP machine with a 100-L tank of dialysate, and a Kolff coil kidney and the access was two single-lumen catheters, one in the femoral artery and the other in the femoral vein. I was amazed by two things. First was how remarkable it was that the function of the human kidney, so selective in determining the excretion of thousands of various metabolites and toxins, could be somehow replicated by a collection of cellophane membranes and saltwater. Second was how beautifully simple but how crude the machine was. A roller pump propelled blood through vinyl tubings, then through a dialyzer with cellulosic membranes and returned it to the

body. Pressure in the circuit was monitored by a mercury switch. Ultrafiltration rate was measured by the increase in the volume of a 5-L container. My undergrad training in physics kicked in, and I said “there must be a simpler way.”

By that time, I was already fascinated by the kidney, with its complex interplay of so many tissues in providing so many functions to the body. Especially I was amazed by its regenerative capacity. Dr. Jared Grantham had shown me how to dissect living kidney tubules and how to measure their function in vitro. Each summer of my first two years I worked in the pathology laboratories, and I wrote my first scientific article on the metabolic changes that occur when the kidney decides to regenerate.

For Internship, Residency, and Fellowship I went to Indiana University Medical School, mostly because my young wife Marianne wished to be closer to her home in Indiana. My training at IUMC was a great experience, tiring, but great. I decided on Nephrology as a specialty, and when I had the chance to do research during my Fellowship, I studied the origin of cells which regenerate kidneys and attempted to form artificial tubules (they did not work, however). By then I already realized that hemodialysis was going to be very impractical as a long-term therapy for end-stage renal disease (ESRD) and I decided to make this therapy safe, simple, and better suited for use in the home.

At the conclusion of the Fellowship in Nephrology, I traveled to the University of Utah to work for three months in the Department of Nephrology but also in the Artificial Organs Division, with Dr. Willem Kolff in testing the Wearable Artificial Kidney (WAK). On returning to Lafayette, Indiana I joined the Arnett clinic (a multispecialty group) and opened the Hemodialysis Laboratory within the newly formed Bioengineering Department at Purdue University. That was in 1975, and still today my research focuses on making dialysis simple, safe, and suited for the home environment. The research continued from the Bioengineering Department into private companies formed by my business partner, Mr. Bob Truitt. Each company has its own interesting story of the pathway to success or failure with the projects.

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As I began to reflect on my “career” of R&D projects over the course of 45 years, I realized that most of the projects were started because of my frustration with dialysis as a therapy for end-stage kidney disease (ESKD). Some were started because we lacked a therapy at all for serious diseases, such as support of patients with liver failure. A great deal of thought and planning went into the decision to start each project, and a great deal of enthusiasm (and money) was invested in each one. Table 1 includes a synopsis of 12 major projects I have worked on during my career. All of these projects had the general goal of making hemodialysis simpler, safer, and more suited for use in the home. The table includes a synopsis of each project, the location of work, the product, and the eventual outcome. Figure 1 includes a pictorial display of the projects, and how far each project progressed along the numerous steps necessary to carry an idea for a new product to market introduction. The vertical lines show the course of each of the 12 projects and indicate the step at which many of the projects failed or succeeded.

Out of the 12 projects on different potential products, nine have been completed but only two of these have entered widespread clinical use and become a market success in the United States. I have written short history or “chapter” on each of these projects for the upcoming issues of *Artificial Organs*. The first of these history papers is included in this issue of the journal. At the end of each chapter, I reflect on what misconceptions we had and what mistakes we and our industry partners made, which sometimes contributed to the failure of a new technology to reach wide-scale marketing. To the credit of my colleagues in our research projects, we generally made each mistake only once. And perhaps, success is just being so persistent that you just “run out of mistakes.”

On reflecting on my so-called career in the development of devices and drugs, it appears that it lack any continuity or focus. However, there are some unifying threads. The first is that all of these projects were attempts to make hemodialysis simple, safe, and effective. Second, there is a technological similarity in some of the projects. The anti-bacterial products came from knowledge gained in storing chemicals for dialysis. Our dialysis machine projects have focused on sorbents for the removal of toxins of kidney failure and liver failure. But the real driving force was my frustration with almost every aspect of dialysis therapy.

It is often said that necessity is the mother of invention. But no one asks “so who is the father?” I can tell you that frustration is the father! What has driven me in all of the above projects is frustration in my treatment of ESKD by dialysis, and with the numerous problems, we see in implementing this therapy at in-center dialysis units. One project adapted sorbent dialysis to treat hepatic coma and hepatorenal syndrome, conditions which only get worse

with standard dialysis. What can be learned from a review of these 12 projects (drugs and devices) conducted by our small companies and the licensees? Here are the lessons I’ve learned from the R&D projects above:

1. There are plenty of new ideas and approaches to the treatment of ESRD among nephrologists and engineers.

Today, many of the new ideas for the treatment of kidney failure are well-founded and logical, and should be able to make dialysis much more suited for the home market. Turning the ideas into reality is one problem, but convincing major companies in the dialysis field to develop and market these new products is the real road-block. They not only have the challenge to create a new type of product and produce it, but to then convince nephrologists to learn about new therapies and adopt them into their practice. Truthfully, the companies are already aware that nephrologists, nurses, and patients are pretty complacent and appear satisfied with dialysis as practiced in-center. So in a way, the problem is us.

2. Many good ideas “die on the vine” because the inventors don’t have the resources, time, or dedication to develop workable prototypes.

Of the 12 projects I reviewed above, every one of them began with a laboratory prototype of some form or other, and some type of testing to prove the physical or chemical principles it embodies. Of course, just having a prototype is no guarantee of success in funding or in the marketing of the device. For revolutionary devices with new technology, the first devices to treat a disease (like liver failure), or those where therapy will be done in special settings (like home dialysis), the start-up company may have to carry the project much further down the road before a major company is interested in cooperating. However, a successful prototype serves to boost confidence in the product and in that small company, in colleagues, and in early investors.

3. For small companies and inventors, finding the funds to carry the project forward is usually the first consideration; however, finding the right corporate partner is equally important.

Even for revolutionary products which will require clinical trials to prove efficacy and safety, it is never too early to begin the discussion with major companies. After obtaining patent protection, begin communicating with companies that currently market the



TABLE 1 Twelve projects aimed at making hemodialysis simple, safe, and effective in the home environment (Ash and many collaborators)

Year	Location	Project	Clinical Trials	FDA approval	Outcome
1975	Artificial Organs Dept, U. of Utah	1. WAK: Invented by Dr. Kolff and Dr. Jacobsen, a single access machine with charcoal regeneration of dialysate, plus small dialysate tank for removal of small m.w. toxins ¹	Yes	N/A	Successful device, licensee decided to make it more complete, but not “wearable.” Device never marketed
1975–1983	Bioengineering Center, Purdue Univ.	2. SSRD: Wearable HD system using sorbent suspension and reciprocating membranes to pump blood through single access. Cooperation with Union Carbide in developing calcium-loaded zeolites for binding potassium and ammonium+ from urea ²	No	No	Ca- loaded zeolites worked perfectly but released aluminum and/or silica to dialysate during animal trials. Project funding cancelled by major company
1983–1988	Ash Medical Systems	3. BioLogic-HD™ with dialysate regeneration (Redy™), single access, plate dialyzer membranes as blood pump, airless blood circuit, controlled filtration, and automatic fluid replacement ³	No	1986	Worked well physically, some technical problems that were resolvable. CMS canceled home helpers and in 1986 and the home dialysis market evaporated in 1987. Our venture capital companies “walked.”
1989–1997	HemoCleanse	4. BioLogic-DT™ similar to BioLogic-HD but with 2-L sorbent suspension. Indications: hepatic encephalopathy and drug overdose ⁴	Yes	1997	Licensed to spin-off company HemoTherapies, marketed therapy as Liver Dialysis. They failed to focus on A-on-C hepatic failure, and on the large liver transplant centers as planned. Clinical results were variable. Licensee went bankrupt
2000–2007	HemoCleanse and spin-off Renal Solutions	5. Allient™ HD machine with hollow-fiber dialyzer, single- or dual-access, pressure-actuated blood pumping, dialysate regeneration (Redy™), controlled filtration, and automatic fluid replacement ⁵	Yes	2006	Company (including Sorb, Inc.) sold to FMC in 2007. The plan was to redesign the machine but this never happened and the project eventually was canceled
2002–2015	HemoCleanse and spin-off ZS Pharma	6. Zirconium cyclosilicate: After the above project using zeolites, Union Carbide and UOP developed a crystal designed for binding monovalents like potassium and ammonium+. HemoCleanse performed early animal studies to test ZS as an oral sorbent and helped to form ZS Pharma as the sole licensee in 2008. HemoCleanse helped direct product development and plan clinical trials ⁶	Yes	2018	ZS Pharma was sold to AstraZeneca in 2015. The highly successful oral powder for removing potassium is now on market as Lokelma. HemoCleanse retained rights to use of as extracorporeal sorbent

(Continues)

TABLE 1 (Continued)

Year	Location	Project	Clinical Trials	FDA approval	Outcome
1996–2000	Ash Access	7. Ash Split-Cath™ chronic central venous catheter (CVC) for hemodialysis ⁷	Yes	1997	Highly successful, first split-tip CVC for dialysis. Patent was more restrictive than needed, so competitive catheters appeared on the market. Royalty arrangement with MedComp ended with a buy-out
1997–2000	Ash Access	8. Concentrated sodium citrate catheter lock: We showed the antibacterial and anticoagulant effects of concentrate sodium citrate in a published paper with clinical results in 2000. We stated that 47% concentration left catheters quickly due to density. The article recommended a concentration of 23% sodium citrate as catheter lock, made by diluting 47% sodium citrate (instructions for use repeated this direction) ⁸	Yes	N/A	US and PCT patents were issued. The patent was contested by a Netherlands company in PCT court and they won on appeal. After one accidental over-injection of the product, FDA issued a warning and limitations on product use in 2000. Remains on the market in Europe and worldwide today and its use has been shown to decrease CRBSI incidence
2004–2014	Ash Access	9. Zuragen®: A catheter lock at 7% concentration (for density equal to blood) and parabens and methylene blue to provide antibacterial function. Sponsored large randomized clinical trial to demonstrate safety and benefits ⁹	Yes	No	FDA decided the product was a drug due to antibacterial functions. Clinical trial showed a significant decrease in infections by concordant cultures, but lock not approved to market. Licensee abandoned project, product re-licensed
2014-present	Ash Access and spin-off Zurex Pharma	10. Zuragard™: Skin preparation solution with components of Zuragen and 70% isopropyl alcohol ¹⁰	Yes	Yes	Zuragard has been shown in clinical trials to be more effective than Chloroprep® in decreasing skin bacteria. Beta site testing is now being performed. Zuragen catheter lock is a potential product also
2014-present	Ash Access	11. 7% sodium citrate with benzyl alcohol: Concentration of sodium citrate the same as Zuragen® but added benzyl alcohol as a preservative ¹¹	Planned	503B now, regular approval planned	Now marketed through a compounding pharmacy. Clinical trial planned for general approval as a routine catheter lock for dialysis patients
2010-present	HemoCleanse	12. Sterile carbon block: Designed to regenerate dialysate in CVVHD, to maximize the removal of middle molecule toxins and minimize the number of bags of sterile dialysate needed for treatment ¹²	Planned	Planned	A partial solution for dialysate regeneration, but a way to separately control the removal of mm toxins and small and charged toxins

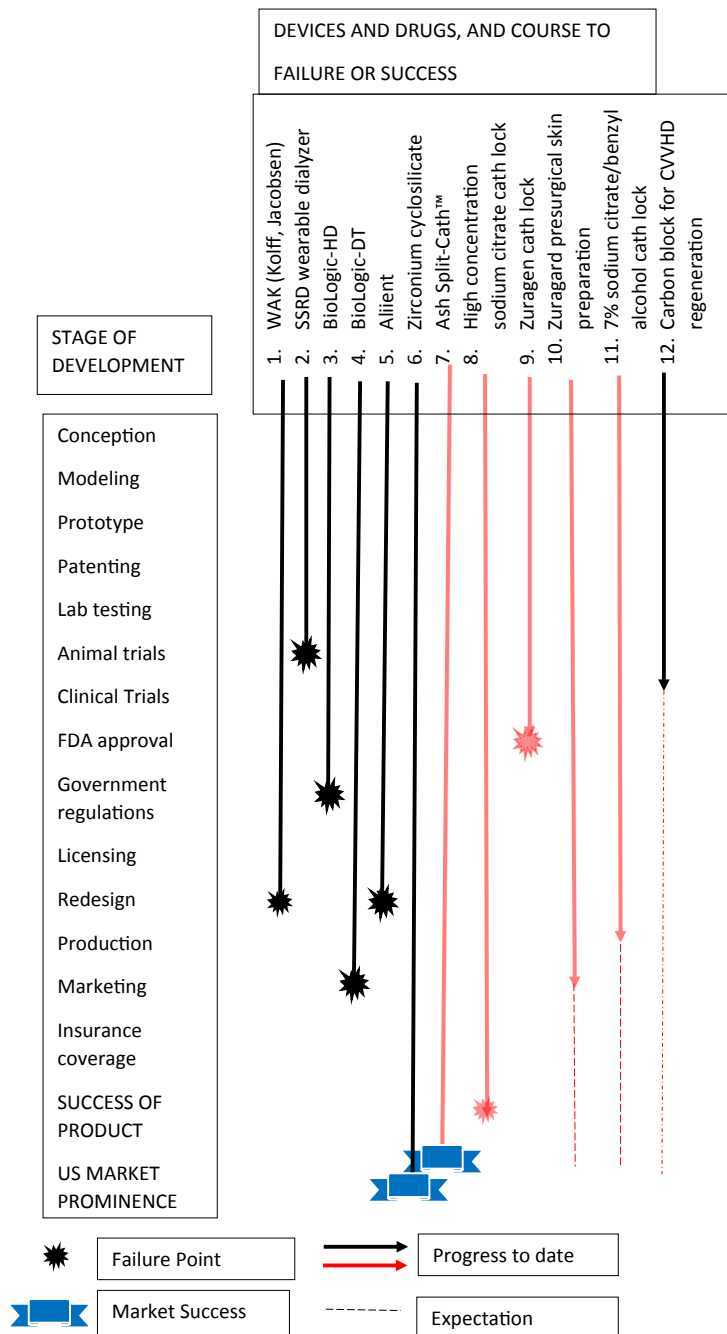


FIGURE 1 Progress of various research projects to make dialysis simple, safe, and effective in the home environment. Note that project failures occurred at many of the steps from invention to widespread clinical use. Black lines: sorbent-based dialysis and oral therapies. Red lines: catheter, catheter placement, and use therapies [Color figure can be viewed at wileyonlinelibrary.com]

products most similar to your product. It takes considerable time to convey all that you’ve learned about the disease you’re treating, the market, current technology, how your product works, and what would be the benefits. Contacts within the company will be open lines for news on your progress. Some companies just seem to “fit” with you, your product, and your needs. Find one. For a medical product to survive the long pathway to commercialization and market success takes the cooperation of an entire team, including the inventors, the R&D scientists, the manufacturer, and the healthcare institutions providing the medical service.

4. Before proceeding to clinical trials, be sure that the device or drug is absolutely as perfect as you can make it.

Every blood treatment system is a complex collection of a number of technologies. Especially for components that have been specifically developed for your device, they must be completely satisfactory in performance. There is a great advantage in using components that exist on the market in building a new machine or therapy. However, if the components are not exactly what you need or don’t work very well, or are likely to disappear from the market at some time, it is better to design and build the



appropriate components. This makes your project more expensive and lengthy, but the products will be much more successful and sustainable in the market.

5. Of those ideas which are proven effective and safe in clinical trials, there are still innumerable hurdles between the proven success of the device and widespread market adoption (the real goal of the inventor and company).

Every step along the way from idea to market success is highly important and decreases the risk of the project. Of our 12 projects, none failed in the steps of prototyping, patenting, lab testing, or clinical trials. Only one failed in animal testing, from an adverse effect we could not have predicted, the wearable dialyzer (#2, in Figure 1). Failure of FDA approval stopped only one of our projects, the Zuragen catheter lock solution, which was a drug-device (# 9). An unexpected change in Medicare payments and regulations ended the marketing of our first home dialysis machine (#3). Dr. Kolff's WAK and our Allient™ machines each failed *after* the license to major manufacturing and marketing companies (#1 and #5). The companies in each case decided to re-design the machine to become much more like a traditional dialysis machine. Our concentrated citrate lock solution was a market success in Europe, but was taken off the market in the United States because *one* physician badly misused the product (#8).

6. The final step towards market success requires that practicing physicians are as frustrated and dissatisfied with current technology as you are, so that they will want to use the new product.

Not all physicians have the same degree of frustration with dialysis technology. It is the older physicians, who have seen the many complications and failures who have the most frustration. Further, physicians develop their practice within the boundaries and practices of large dialysis organizations and hospitals. Even if a physician has read about your new improvement in the therapy, and is enthusiastic about it, they realize that convincing the Large Dialysis Organization (LDO) or hospital to acquire the product will be an arduous process. If the product will cost more and is covered by the "bundle" or is made by a competing company, then convincing an LDO to adopt it is nearly impossible. Early adopters are those physicians willing to put significant effort into changing local practices or performing clinical trials of new products. Most physicians are average adopters, who will use the product when available, but will not demand the use of it, even if it's better.

7. In the medical market, the probability of overall success is greater for products that are evolutionary than those that are revolutionary.

There is always significant resistance to truly new medical therapies, from patients, physicians, manufacturers, and healthcare-delivery companies. Being the first product in a class means it will be hard to find a company with the skills to make it and market it, and criticism will come from every "expert" in the field. Our team's greatest market successes have been with products which were evolutionary than revolutionary. Zirconium cyclo-silicate was not the first cation exchanger to be used as an oral sorbent for potassium. The Ash Split Cath™ was not the first tunneled dialysis catheter. It was an improvement of the older single-body Mahurkar catheter. But on the other hand, when the inventor is young and the product has unique technology and exciting potential, enthusiasm in the investment community and company supporters come naturally. Any inventor is fortunate to live long enough to complete a major invention and see it change to an innovation in the market. So at some point, just focus on projects which are a little less far-fetched.

8. Keep the faith.

Most of the approaches we use in dialysis came from physicians and engineers searching for the right technology, just like you and me. But realize that just coming up with the idea is only the start of a long, long commitment that's needed before an invention (idea) becomes an innovation (market success). Even after the idea is proven, the patent is issued and FDA approves the product to market, you can see the project and product fail. Learn the lessons from the first project, apply them to your next project and you will probably be successful. As Winston Churchill said, "Never give in—never, never, never, never." Whether it was your main goal or not, you have furthered the science of medicine by your development of a new drug or device. Perhaps, you may have stimulated some young physician or scientist to come up with an even better idea.



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