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Parent Empowerment Newsletter

Hemophilia, Incorporated

How the Hemophilia Business Works in America, and What Threatens to Change It

by Laureen A. Kelley

First in a two-part series

What if you were suddenly told that you could use only one factor brand–a brand you didn't choose? What if you could order only three vials of factor at a time? What if you had to prove that you really needed your current order of a month's supply of factor? Be prepared. Like a storm quietly brewing, massive changes are poised to hit the hemophilia community. Both the federal government and private insurers are slashing the amount they'll pay for biological drugs–and they've targeted hemophilia.

What's at risk? Freedom to choose the product you need through the factor provider you want, at a price that will preserve adequate coverage. There's a lot you can do to prepare for this storm. But first, you'll need to understand "Hemophilia, Incorporated" in America: how blood-clotting medicine is produced, sold and distributed, and how this model currently meets our needs. Then in February, read "The Coming Storm," part II in our series, to learn what changes are happening right now, what to expect in the future, and what actions you must take to preserve product and factor provider choice and insurance coverage.

Hemophilia is big business in America. With an estimated $2 billion in products[1] treating approximately 20,000 US patients annually, hemophilia is one of the most expensive diseases per capita.[2] Hemophilia is also a complicated industry that is undergoing massive change. During the past 12 months, the hemophilia industry has been impacted by company acquisitions, changing product lines, and a US Food and Drug Administration (FDA) crackdown on pharmaceutical advertising claims and home infusion company giveaways. Skyrocketing costs of new biological products that treat other chronic disorders, like rheumatoid arthritis and asthma, have caught the attention of the entities that pay for these medicines–private insurance companies and the federal government. Intense scrutiny of the cost of treating these other disorders has put hemophilia on the cost-cutting radar screen. And payers are now determined to change the way hemophilia therapy is provided today.

"We are entering a new era where the hemophilia community is red-flagged," warns Ann Rogers, executive director of the Delaware Valley Chapter of the National Hemophilia Foundation (NHF). "We are the most expensive chronic disease. We are being watched." Much is at risk. As a parent, you need to provide your child with safe and effective treatment and adequate insurance coverage until he is a working adult–that's 18 to 20 years of coverage. As an adult, you want reliable healthcare coverage through your employer or from the government, enabling you to lead an independent life. Yet what if you were told that you could use only a specific, single factor provider–offering no home services, customer support,

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[1] Calculated using approximately 1.7 billion international units sold in 2003 times $1.20 average reimbursement per unit across all factor products. Source: Market Research Bureau, various homecare companies.
[2] Per capita means "per person." Other diseases, like HIV, may cost more in total dollars annually, but also have a vastly higher number of patients. Total healthcare dollars spent on a disease or disorder, divided by total number of patients, gives the amount spent per person that allows for equal comparison of expenditure. For hemophilia, this is approximately $100,000–$125,000 per person annually.

inside PEN

welcome

I've always been one of those national hemophilia advocates who insists, "You have options. You have choices. Be a savvy consumer!" But the joke was on me. Last year I learned that I had *no* choice of factor provider–and I was using a homecare company I didn't want, with no power to negotiate a lower factor price.

What was I paying per unit? No one would tell us. The homecare company and insurance company had a confidential and legal agreement, to be sure. But if I found out the per unit price they negotiated, might I possibly find another vendor on my own and negotiate a lower price? Would I "upset" the system? I was told, *Trust us: contracting with one homecare company exclusively is saving everyone money*. But how much money? We decided to find out.

After three months of digging, we eventually deduced the price we were paying. It was high–meaning higher expenditures against our son's $1 million lifetime cap. After the $1 million was used up–and we were well on our way–then what? Not letting us negotiate a lower per unit price meant that the homecare company and insurance company were playing Russian roulette with our son's healthcare. A rival homecare company then offered us a $.34 per unit reduction for contracting with them. Do the math: Tommy is 17, and at 130 pounds he requires 2,000 units of factor VIII per shot. He takes about 50 shots a year. This would mean *$34,000 a year in savings* to our insurance company! Best of all, with the rival company we could better preserve Tommy's million dollar cap, which he has had for ten years.

$34,000 a year. What a bargain–but would the insurance company accept? No. *Saving $34,000 isn't worth the time*. And no one cares whether Tommy runs out of insurance. I realized that when our insurance company says "cutting costs," it means cutting its costs to please its stockholders–not cutting costs for the people it insures.

Our shocking experience led to this two-part series in *PEN*. When your child is young, you may think that a million dollar cap will last a long, long time. But you'll eventually find yourself with a 17-year-old leaving for college soon and running out of insurance. What happened to us is just the tip of the iceberg: right now, the same thing is happening to thousands of families across the country. So prepare for the coming storm. Watch the horizon, check the climate and take some readings, or you'll find yourself lost in a wave of massive insurance change.

Our community is just beginning the fight to protect our choice of product and provider; so far, we've had only isolated skirmishes. We must band together now, united as a national community, to defend against arbitrary cost-cutting and restriction of choice. Read our feature story "Hemophilia, Incorporated" to learn how the US hemophilia business is structured and operates. This issue will prepare you for *PEN*'s February 2005 issue, where our feature "The Coming Storm" will explain who is trying to restrict your choice, security and quality of life, and how you can defend your healthcare.

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letters

I WAS TOUCHED BY THE STORY ABOUT THE gentleman with the tumor ["Galo Villamil: A Teacher's Courage," *PEN*, August 2004]. The strength in this community is incredible.

Debbie de la Riva
Texas

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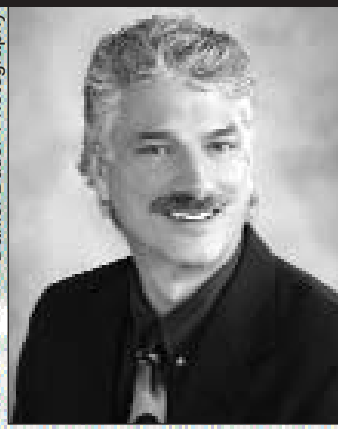
by Dana Kuhn, Ph.D.

Changes in the Provider and Reimbursement Climate


Daniel Butler Photography

WHEN YOU SEE DARK CLOUDS COMING OVER THE horizon, it's often a warning that a storm is approaching and the weather will change. There are some dark clouds in our hemophilia industry, signalling coming changes in the pharmaceutical and reimbursement businesses that can affect your service, lifetime maximums, and choice of product and provider.

For the past two decades, reimbursement of blood-clotting products has been influenced by two climates: the establishment of Average Wholesale Price (AWP, or the way prices are set), and Medicare and Medicaid discounts. Presently, reimbursement is taking on a new climate, resulting in troubling changes. This new climate can be described as stormy, and there are indications that a stormy forecast is in our near future.

First, Congress has directed the Centers of Medicare and Medicaid Services (CMS) to seek equitable reimbursement between the public sector (Medicare/Medicaid) and the private sector (well-known insurance companies). Congress has also directed these entities to decide upon a unified method for setting the baseline for reimbursement, selecting among methods that include AWP, Best Price, and Average Sale Price (ASP) of the products. This is a stormy and controversial subject: every agency, pharmaceutical, distributor, and provider company has its own opinion, and the outcome of the decision about which unified method to use will impact the profit margin of each.

Second, Congress has addressed the availability of prescription drug coverage for all Medicare recipients, whether senior citizens or people using expensive prescription treatments. Previously, prescription drugs and treatments were reimbursed by Medicare only if administered in a physician's office. Due to lobbying efforts, blood-clotting factor and end-stage renal disorder treatments were exceptions to this ruling. While prescription drugs were not previously covered under Medicare for senior citizens or for people using expensive treatments, in 2005 the new Medicare Modernization Act (MMA) will begin to cover some of these in a demonstration project; and will most likely cover them fully in 2006. Congress has addressed these reimbursement issues in the MMA.

Third, as a result of these Congressional initiatives, pharmaceutical companies, providers of service, and insurance companies are seeking ways to protect their profit margins in two obvious ways:

1) **Pharmacy Benefit Management Corporations** (PBMs) are specialty pharmacy companies that contract with insurance companies in order to become the main provider of service to patients and create savings for the insurance companies. PBMs then help insurance companies decide which pharmacies and homecare companies will become the network providers. This means that as a patient, you will have to get your prescription product *from the provider that the PBM and insurance company chooses*. The PBM then negotiates with pharmaceutical companies for discounted volume prices for their products, and decides which products to carry. Often, these decisions aren't good for the patient, who may have a reaction to a certain product and needs a choice of at least one other product. Patients may not be able to purchase product from the pharmacy or homecare company of their choice, and may be limited to only one or two products. Furthermore, physicians may be limited in the reimbursable drugs they can prescribe for their patients–to a choice of perhaps one or two medicines for a specific use.

2) **Acquisitions** ("buy-outs") of PBMs, pharmacies and homecare companies is another way to protect profit margins. In a buy-out, the acquiring company gains more buying and negotiating power, along with immediate earnings growth. This simply means that the new, merged company can now get a better discount for buying more product from the manufacturer, and earns bigger profits.

That's a snapshot of the changing climate of the prescription reimbursement business in this decade. Is it bad for patients? The answer is paradoxical. The climate is good for patients if the changes create a fair and equitable reimbursement system for both the public and private sectors. It's bad for patients if the changes eliminate or narrow patient choice of product and service provider. It's also bad if buy-outs sacrifice patient services for increased profits. Patients should be aware of these changes, and become proactive by advocating for patient choice and patient rights. Why? Because the bottom line in the reimbursement business is primarily the survival of healthy profit margins–while patients are interested in the survival of personal health, finances and choice.

No matter what the changing climate brings, Patient Services Incorporated (PSI) will continue to encourage the reimbursement entities to keep patient service a priority, and to establish fair reimbursement systems that help patients maintain their health, finances and choice. PSI provides the perfect model to maintain this balance, and offers a win-win solution for reimbursement entities as well as for patients.

Dana Kuhn is president and co-founder of Patient Services, Inc., and a person with hemophilia. PSI is a nonprofit organization that helps people with expensive chronic illnesses find solutions for health insurance problems, and helps pay expensive premiums and co-payments. For more information about the changing reimbursement scene, or for insurance premium assistance, contact PSI at (800) 366-7741. Background information for this article came from the monthly Drug Cost Management Report, *published by Atlantic Information Services, Inc., Washington, DC.*

by Paul Clement

From Plasma to Prophylaxis

Forty years of progress in the treatment of hemophilia

The past forty years have seen dramatic improvements in treating hemophilia. Where have we come from, and where are we heading?

Prior to 1965, treatment for people with hemophilia was bleak and involved frequent, prolonged trips to the hospital for transfusions of whole blood or fresh frozen plasma (FFP). Because these treatments contained only small amounts of clotting factor, it was necessary to infuse large volumes. To enable the body to process such high volumes of fluid and avoid fluid overload and possible death, the infusion had to proceed slowly. This slow treatment was largely ineffective at controlling severe bleeds. In addition to frequent trips to the hospital, life with hemophilia meant casts and splints, crutches and wheelchairs, joint damage, chronic pain, and the prospect of an early death.

Breakthrough Treatment: Cryo

In 1964, American researcher Dr. Judith Graham Pool of Stanford University discovered a gelatinous material that formed when FFP was thawed slowly. This material, which she called *cryoprecipitate*, or "cryo," contained 50 times more factor VIII than an equal volume of plasma. Dr. Pool announced the first effective treatment for hemophilia A. Cryo revolutionized hemophilia treatment, and within a year it became the standard of care. Although a visit to the hospital was still required, cryo stopped bleeds faster, reducing the pain and joint damage caused by uncontrolled bleeding.

With concentrated factor in the form of cryo, the door opened for another breakthrough in hemophilia treatment: powdered factor VIII concentrate that did not require freezing. Introduced in 1966, factor VIII concentrate was convenient and effective, and enabled people to treat at home by simply reconstituting the powder with sterile water. Bleeds could be stopped sooner and joint damage reduced or prevented. Unfortunately, these early concentrates were not virally inactivated. Fractionators–the commercial companies that separate factor from blood plasma to produce factor concentrates–combined plasma collected from as many as 400,000 donors into one giant lot. These donors included people considered at high risk for viral infections. Eventually, thousands of hemophilia patients became infected with hepatitis C and Human Immunodeficiency Virus (HIV). By the early 1980s, it was estimated that up to 90% of people with severe hemophilia A were infected with HIV.

In 1982 the first factor VIII concentrate using heat treatment to kill viruses–including HIV–became available. In 1988 the first factor concentrates using a solvent/detergent viral inactivation process were released. Then, in the late 1980s, highly purified factor concentrates were produced using new monoclonal antibody purification techniques.

Although the latest monoclonal purified factor concentrates were now considered safe, pure and effective, the HIV epidemic left a psychological scar on the hemophilia community. Never again would the hemophilia community be the "canary in the coal mine" for the nation's blood supply. The pharmaceutical industry, with the urging of the hemophilia community, sought to develop a factor concentrate that would contain *no* blood products, and be free of the risk of transmitting blood-borne infections or other pathogens.

Recombinant: Factor Without Blood Plasma

But how could factor VIII be produced without blood or plasma? Between 1982 and 1984, the human gene for factor VIII was characterized and cloned. By the late 1980s, researchers were able to insert the human gene for factor VIII into non-human cells, such as baby hamster kidney cells or Chinese hamster ovary cells. This "recombinant DNA" enabled the cells to produce human factor VIII, and the new technology was scaled up for commercial production of factor. Factor concentrates produced using this technique are called "recombinant" and are not derived from blood plasma. The first commercial recombinant factor VIII product was available commercially in 1992, and the first recombinant factor IX product in 1997.

While these first recombinant factor VIII concentrates didn't use blood plasma as their source, they did require the addition of another blood protein, human *albumin*, to stabilize the fragile factor VIII protein and prevent it from breaking down. In fact, these "first generation" recombinant factor concentrates, like their plasma-derived predecessors, contained mostly albumin. Although albumin is treated to destroy or inactivate viruses and has a good safety record, some types of viruses that are resistant to heat and/or solvent/detergent viral inactivation processes may survive the viral inactivation step.[1]

Researchers continued to explore ways to remove animal proteins such as human albumin or cow plasma from the

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[1] Fortunately, these resistant viruses do not cause serious diseases.

A Guardian Angel

by Annie Schwechheimer


photo:

Dodong T., age 16, is the elder son of poor, hardworking parents who live in Ozamiz City, Philippines. Dodong's father drives a bicycle cab, and can barely meet his family's basic needs. Dodong and his younger brother Jobert were forced to beg to help the family. One day in 2003, Father Don Kill, a Colomban priest who runs a home for abused and neglected children, noticed the boys. When he asked why they weren't in school, Dodong replied that he couldn't walk and relied on his younger brother to get around. Father Don asked the boys to live at the home he runs. With permission from their father, the next day Dodong and Jobert moved into Father Don's home.

Dodong's story is sad. At age eight, he ran a high fever. His parents rushed him to a public hospital where he was diagnosed with leukemia. Told that they would need to pay for a blood transfusion to save his life, Dodong's parents sold most of what they owned. But the transfusion didn't work: Dodong's body and joints began to swell. The doctor believed that Dodong contracted polio from the blood transfusion, and told his parents that Dodong probably would die.

But Dodong didn't die. Instead, he languished as a beggar on the streets for eight years until that fateful day when a guardian angel walked into his life. Intrigued by Dodong's malady, Father Don questioned the diagnosis of leukemia and polio. He took Dodong to the University of Santo Tomas Hospital in Manila, an international hemophilia treatment center. There, Dodong was properly diagnosed with hemophilia. Father Don set out to help Dodong receive the treatment he was unknowingly denied for years.

Partners in care: Father Don Kill visits with Laurie Kelley (left) and Annie Schwechheimer (right).

Father Don contacted St. Jerome's, his home parish in Ohio. The parish put him in touch with the Northern Ohio Chapter of the NHF, which referred him to Project SHARE. Father Don emailed us requesting factor and educational materials. But SHARE cannot donate factor to patients who are untrained in infusions.

Undaunted, Father Don called hematologist Dr. Mary Chua at Santo Tomas Hospital. Within a week, we received a surprise, upbeat email from Father Don: he had sent Dodong to Santo Tomas Hospital, accompanied by a local nurse, to learn how to infuse. Dodong also had a complete physical and dental exam. SHARE immediately sent a small donation of factor to Dodong, with a check to cover the cost of transportation to Manila. Dodong is now infusing himself!

Dodong's life has been transformed by the international teamwork of Project SHARE, the Northern Ohio Chapter, Santo Tomas Hospital, St. Jerome's and Father Don. Although Dodong acknowledges that he will never walk again, he has accepted his limitations and is grateful for his many blessings, all due to his guardian angel.

Father Don Kill visited Project SHARE in August to express his gratitude, learn more about hemophilia, and bring more factor to Dodong. We are currently trying to raise $600 for a wheelchair ramp for Father Don's van, to make traveling easier for Dodong. Would you like to help us? Please contact Project SHARE to make your donation, and make a difference in the life of this special teen.

To learn more about Project SHARE℠ and how you can help patients like Dodong, please visit www.kelleycom.com/iha/projshare.html or contact Director Annie Schwechheimer at (978) 352-7657 or annie@kelleycom.com.

Hemophilia, Incorporated... continued from cover

or even syringes and needles? What if an insurance company representative showed up on your doorstep, asking to inspect your refrigerator?[3]

"There's been a major paradigm shift in how payers are making their coverage decisions," explains Michael J. Russo, partner at The Bruckner Group and expert in the payer decision-making process. "Factor products and other expensive biologics that require chronic use will be scrutinized as never before. Community involvement will be essential to ensure that the extraordinary value of factor to the patient is accounted for in the payers' *economic* assessment of therapeutic value."[4]

This may be a glimpse of things to come. Only through coordinated community action–by parents, clinicians, patients and the national organizations that serve us–will we be able to preserve our current choice, methods of care and quality of life. But first, we must understand the current hemophilia "business model," or how the American hemophilia market works. Then we must examine the way it's changing. And the current model *is* changing. Don't be lulled into complacency, believing that these changes won't affect you. The good news is that there's still time to act as a national community to stop the machinery already set in motion by the restriction–even elimination–of product choice, factor provider choice, and adequate insurance coverage.

Who Are the Industry Players?

To understand the American hemophilia industry, you need to know the players, their roles, and how their involvement affects the way you get factor products. Who are the players? Factor **manufacturers** make the product. Factor **distributors** deliver the product. **Hospitals** treat patients and sometimes distribute factor. The **consumer**–you or your child–uses the product. And private **insurance companies** and the **federal government** pay for the product. In a nutshell, factor products are made at manufacturing facilities, sold to distributors and delivered to your home. Your distributor bills your payer, and is eventually "reimbursed" by that payer for each shipment or "sale." Private payers, like Blue Cross/Blue Shield or Aetna, reimburse for factor used by people who either have health insurance through their employers or purchase insurance privately. Public payers, like the federal government, reimburse for factor used by people who are classified as low income (Medicaid), or are elderly or disabled (Medicare).

Each player has a role in the marketplace that affects prices and supply. In a perfectly free market, high demand for a product drives up price, and low demand reduces price. Scarce supply drives up price, and a glut of products lowers price. Increased competition also lowers price. Even with limited competition, prices may drop naturally over time, as manufacturers recoup profits. But the hemophilia industry is not a perfectly free market.

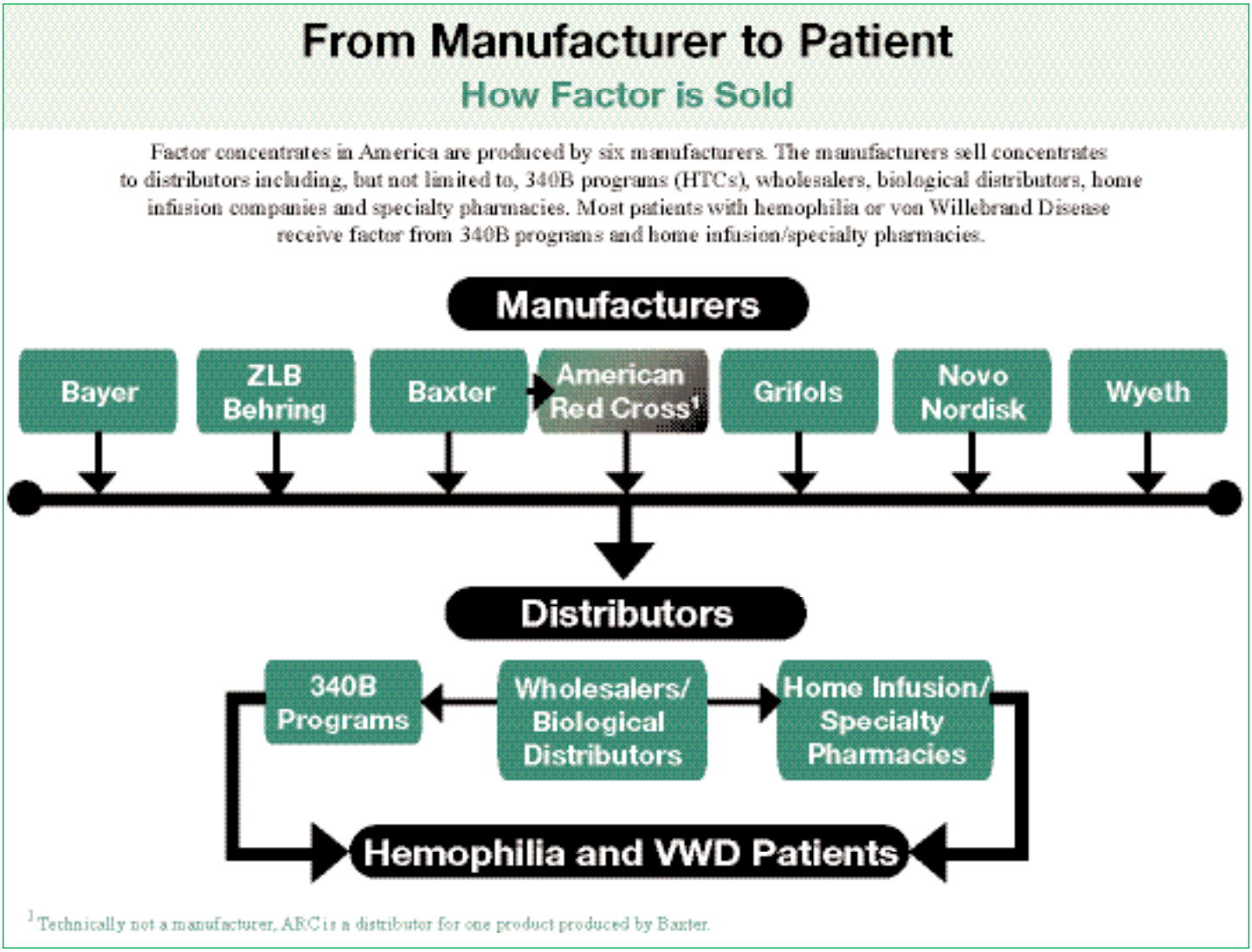
What Matters Most?

The things that matter most to hemophilia consumers are changing. If you asked parents and patients five years ago, *What's most important to you in hemophilia treatment?* the majority would have ranked "product safety" first. This is a legacy of the HIV crisis of the 1980s. Two years ago, "product availability" ranked highest, after a frightening shortage of recombinant factor VIII products. What will consumers rank highest next year? Most likely "treatment coverage" and "product choice."

In some ways, we have less to worry about today: all US products are considered safe from viral transmission, and currently we have plenty of products. But you don't need a Ph.D. in economics to understand that times are changing in America: budgets are being squeezed and insurance companies are slashing costs, including the amount they will reimburse factor distributors for hemophilia products. The government has also reduced what it will reimburse federal recipients—through Medicare and Medicaid—for hemophilia products. Some small homecare companies, feeling the pinch, have sold out to larger ones. At least one factor manufacturer has tried to strike a deal with one state payer to become a sole provider of factor. These attempts to manage costs may affect your choice of product and choice of provider.

Many parents innocently ask, "When will factor pricing come down?" In general, factor prices are insulated from the perfectly free market forces that affect regular consumer goods like cameras and computers. This is because the factor market is an *oligopoly*, with only a few sellers controlling production and supply of a particular product. The factor market is similar to the international oil market, in which an oil cartel, consisting of a few major producers, controls output and price for a captive consumer audience dependent on oil.[5] Hemophilia patients are also a captive consumer audience. We have no choice but to use products from one of the licensed US manufacturers. Hemophilia patients can't shop for cheaper imports, discounted products or wholesale deals, or simply wait until prices drop. We are people with a life-threatening blood-clotting disorder who must buy factor when we need it.

[3] This incident actually happened in August 2004 to a family with hemophilia in the Mid-Atlantic region.
[4] The Bruckner Group is a strategy and research firm working exclusively in the pharmaceutical and biotechnology industries. BGI has extensive experience examining the evolution of managed care in the US, and most recently has explored the specific issues facing biological products. For more information visit www.brucknergroup.com.
[5] There is an important difference between an oil cartel and the factor manufacturers: Although an oil cartel can collude to set prices in the marketplace, US firms are forbidden to collude on prices due to strong anti-trust laws.



On the other hand, this isn't an ordinary market for manufacturers either. Researching, developing and licensing a biological product takes years–and hundreds of millions of dollars. These extraordinary costs can't be absorbed by low per unit prices spread across millions of consumers. The American hemophilia market has only 20,000 consumers. Costs are bound to be high, and there are few ways to reduce them.

Your role as a consumer in the hemophilia marketplace is paramount: you consume the products. Your opinion helps drive research and determine production. Public outcry about viral safety, for example, is the reason that we now have products that include far fewer human and animal proteins than the first recombinant products. Your individual choice of product helps determine which products stay in the marketplace and which products disappear. But politics, marketing and economics also influence what consumers purchase and what's available to purchase.

Know the Manufacturers

The hemophilia business starts with the manufacturers of blood-clotting products. These are the companies that research, develop and produce factor concentrates. Six manufacturers are licensed to sell products in the US: Baxter BioScience, Bayer Healthcare, Grifols, Novo Nordisk, Wyeth® and ZLB Behring.[6] Each company manufactures specific blood-clotting products. All blood-clotting products are either *plasma-derived* or *recombinant*. Plasma-derived means that the product originates from human blood sources–donations of blood or blood plasma, both paid and volunteer. Recombinant means that the human gene responsible for producing factor VIII or IX is identified, isolated from human cells, and then spliced or "recombined" into an animal host cell (Chinese hamster ovary cells or baby hamster kidney cells). These original host cells serve as the starting point for each production batch of recombinant factor.[7]

[6] The American Red Cross (ARC) is often referred to as a manufacturer of factor concentrates, but is not. The ARC is a distributor of the factor concentrate Monarc-M™, produced by Baxter for the ARC.

[7] A fairly small number of these cells is added to a large tank containing a nutrient-enriched growth medium, and as the cells grow and multiply they also produce factor and secrete it into the medium. The secreted factor is purified into concentrate, ready for injection.

Whether
you or your children use plasma-derived or recombinant products, you should be aware of four important facts:

1. All US hemophilia products are considered safe.
2. No plasma-derived US product has transmitted hepatitis C or HIV since 1986.
3. Recombinant products are generally more expensive per unit than plasma-derived products.
4. NHF's MASAC recommends the use of recombinant products in hemophilia treatment.

The major difference between the two types of product is their source material. Recombinant products do not use human blood as their source, so have a reduced risk of transmitting human blood-borne viruses. First and second generation recombinant products use human and/or animal protein (such as albumin) either in the growth medium or as a stabilizer in the final formulation. But third generation recombinant products use no human or animal products anywhere in the production process, and are completely free of blood-borne viral transmission risk.

Each manufacturer focuses on specific market "segments." Wyeth produces only recombinant products, both factor VIII and IX. Grifols makes only plasma-derived products, both factor VIII and IX. Baxter and Bayer offer both recombinant and plasma-derived products. Bayer offers only factor VIII products, while Baxter's product line includes factor IX complexes, factor VIII and inhibitor products. ZLB Behring produces plasma-derived factor VIII and IX, as well as the only FDA-approved factor product for von Willebrand Disease. ZLB Behring also distributes a recombinant factor VIII product. Novo Nordisk offers a recombinant factor VII product for inhibitor patients.

To prepare for changes in our industry, consumers should know which company produces which type of product. Know the brand names. Be aware of changes in the factor manufacturers: acquisitions, name changes and staff changes. One father wrote recently to *PEN* that his factor IX deficient son didn't use Wyeth's product, but used one by "Genetics Institute." He didn't realize that Genetics Institute was purchased by American Home Products in 1992, and later renamed Wyeth.[8] In just the past ten years, Armour Pharmaceutical Company became Centeon, then Aventis Behring, and finally ZLB Behring when it was recently purchased by CSL Limited of Australia. Alpha Therapeutics was purchased in 2004 by the Spanish-based company Grifols. Name changes are sometimes cosmetic only, as when Baxter Healthcare updated its name to Baxter BioScience: same company, same products. Other changes produce drastic differences: a company may drop or sell an entire product line. As of this writing, Bayer is in the process of selling its plasma division, including its plasma-derived factor VIII product Koate®-DVI.

You may want to know your manufacturer's country of origin. Bayer is a German company, Grifols a Spanish company, ZLB Behring an Australian-owned company, and Novo Nordisk a Swedish company. Although they operate in the US, foreign companies may have differing budget or market priorities, which can affect how they act in the marketplace. Baxter and Wyeth remain the only American-owned companies that manufacture factor. In addition, Advate is manufactured in Switzerland and ReFacto in Sweden. Helixate/Kogenate and Recombinate are manufactured in California. Regardless of a company's origin, most of its American operations are staffed by Americans; and all products registered and marketed in the US must adhere to strict US FDA testing and guidelines, making them the highest quality factor concentrates available in the world.[9]

Why is it good to know about ownership, staff and name changes in the manufacturers? These changes may mean changes in the product you use and the services offered by these companies.

Know Your Product

Although six manufacturers currently produce factor, only a few products dominate the hemophilia marketplace. The high cost of entry into this industry, the limited pool of patients, and the protection of patents[10] adds up to very little chance that new hemophilia pharmaceutical companies will appear. So to preserve consumer choice, the hemophilia community must work to ensure a continued variety of products. The table on page 9 shows the full range of blood-clotting products in the American hemophilia marketplace.

As of 2000, the NHF's Medical and Scientific Advisory Council (MASAC) recommends the use of recombinant products to treat hemophilia.[11] Does the US market still

[8] In 1992, American Home Products (AHP) acquired a 60% share of Genetics Institute, which became a wholly owned subsidiary of AHP in December 1996. On March 5, 1998, AHP announced the integration of Wyeth-Ayerst Research and the research and development organization Genetics Institute. AHP's vision to meet the soaring demand for new biopharmaceutical products led to the commitment of $2 billion in the Wyeth BioPharma organization. In March 2002, AHP changed its corporate name to Wyeth.
[9] The FDA also inspects and licenses overseas manufacturing facilities that produce products for sale in the US.
[10] Patents are legal safeguards ensuring that a technology developed by one company will not be used illegally by another company for profit. Hemophilia products take many years and millions of dollars to develop for a very small market. Patents ensure that a company with new technology will be able to recoup its financial investment in research and development without worrying about competitors. Without patent protection, it's unlikely that any company would invest in hemophilia treatment.
[11] MASAC Recommendation #106, "MASAC Recommendation Regarding the Use of Recombinant Clotting Factor Replacement Therapies." November 11, 2000, National Hemophilia Foundation.

need plasma-derived products? Yes. Plasma-derived products offer choice. They are considered safe, effective, available–and they're less expensive. They may help preserve insurance coverage for people with lifetime maximums facing soaring medical bills. And they can be substituted for recombinant products in an emergency. Remember the factor "shortage" of 2001? Many families were afraid that no factor VIII was available in America. In truth, there was a temporary recombinant factor shortage. While many in the community were alarmed that patients might die, tens of thousands of units of safe, effective plasma-derived factor VIII products were sitting in warehouses. Being informed about products and product choice leads to better decision-making.

To preserve choice of product, you must know which product you use and why. You probably use either a factor VIII, factor IX, factor IX complex, inhibitor or von Willebrand Disease product. Your product is either plasma-derived or recombinant. If it is recombinant, is it first, second or third generation? Are you able to explain your choice of product to your insurance company, which may one day ask you to switch to a less expensive product? If you want to replace your current product, worry that supply might shrink, or fear that the company will stop production, do you know which company produces similar products?

It's not unusual to find parents or people with hemophilia who don't know which product they use or which company produces it. Knowing about the different products will help you make better choices. One mother wondered whether to use Kogenate® FS or Helixate® FS. She didn't realize that she could easily switch products–because Helixate FS *is* Kogenate FS, relabeled.[12] Yet she refused to believe this! Unaware of how the hemophilia business works, she asked, "How can the same product have two different names?"

You should also be able to respond to every item in the list on page 12. If you don't know which company makes your product and supplies dry up, you may assume that you can choose among plenty of other products. Not necessarily. The supply of Helixate FS is directly dependent on the supply of Kogenate FS. Since there is currently only one recombinant factor IX supplier, you have no other choices. But there are two plasma-derived factor IX makers. Not every consumer understands the choices available. If Novo Nordisk's product is unavailable, you'll have only one other choice for inhibitor medicine: FEIBA®.[13] Most people with von Willebrand Disease use Humate-P®, but did you know that two other products can also be used? If the supply of Recombinate is disrupted, up to 60% of the US market will be scrambling to find a replacement. This last concern reflects the vital importance of knowing each product's *market share*. Awareness of changing market shares can help our community track the relative importance of each product to the market–and may help preserve choice.

US Factor Concentrates

Which Product Do You Use?

Manufacturer	Product: Recombinant – Factor VIII	Recombinant – Factor IX	Recombinant – Inhibitor	Plasma-Derived – Factor VIII	Plasma-Derived – Factor IX	Plasma-Derived – Inhibitor
American Red Cross[1]				MONARC-M™ [2]		
Baxter BioScience	ADVATE rAHF-PFM RECOMBINATE rAHF			HEMOFIL® M	Proplex® T Bebulin® VH	FEIBA® VH
Bayer Healthcare	Kogenate® FS			Koate®-DVI		
Grifols Biologicals, Inc.				Alphanate®	AlphaNine® SD Profilnine® SD	
Novo Nordisk			NovoSeven®			
Wyeth®	ReFacto®	BeneFix®				
ZLB Behring	Helixate® FS [3]			Monoclate-P® Humate-P® [4]	Mononine®	

[1] Technically not a manufacturer, ARC is a distributor of one product produced by Baxter.
[2] MONARC-M is produced by Baxter, but uses separate sources of plasma and separate facilities.
[3] Helixate FS is exactly the same product as Kogenate FS.
[4] FDA-indicated for treating von Willebrand Disease, Humate-P can also be used to treat hemophilia A.

Note: RECOMBINATE is a first generation product. Kogenate, Helixate and ReFacto are second generation products. ADVATE and BeneFix are third generation products.

[12] Kogenate FS is manufactured by Bayer, which sells a set amount to ZLB Behring (formerly Aventis Behring) as part of a settlement from a patent lawsuit. ZLB Behring relabels Kogenate FS as Helixate FS and sells it. They are exactly the same product.
[13] Two other inhibitor products have already been phased out of production: Hyate C (porcine factor) and AutoPlex T. This leaves only two inhibitor medicines, NovoSeven® and FEIBA.

Factor Distributors

Any business entity that sells factor and is not a manufacturer is a factor distributor. Factor distributors include:

- Wholesalers (purchase factor and entire product lines from manufacturers and sell to hospitals and pharmacies)
- Biological distributors (wholesalers that primarily distribute injectables)
- Hospital pharmacies and blood banks
- Hemophilia Treatment Centers (HTCs) with 340B programs
- Home infusion companies (provide nursing services)
- Specialty pharmacies (focus on certain chronic therapies; may directly provide or subcontract nursing services)
- Mail order pharmacies
- Physicians' offices
- Retail pharmacies

Only licensed pharmacies or physicians can sell factor to patients. How you receive your factor depends on which of these distributors is approved by your payer—your private insurance company or federal or state government (Medicare or Medicaid).

Understand Market Shares

"Market share" refers to how much money a product earns out of the total earnings of all related products in its industry. For example, Coca-Cola™ has a 44% market share of the US carbonated beverages industry, making it the market leader. In other words, more Coca-Cola products are purchased than any other brand of carbonated beverage.

Why should you know about hemophilia product market share? More knowledge helps you ask better questions. If a company's product has a large market share, does it have more supply, more resources, greater production capacity, even better products? Maybe. Does it give back to the consumers who support it? Quite possibly. What if a company's product has a small market share? Will that company struggle, or does its product fill a niche–a particular need–that no one else's product provides?[14]

In the US hemophilia marketplace, declining market share has caused only a few products to be phased out; despite occasionally drastic changes in market shares, most products remain viable and necessary. Recombinant factor VIII and IX products have the largest overall market share. Baxter is the dominant factor VIII manufacturer. Wyeth is the dominant factor IX manufacturer. Wyeth has captured the largest factor IX market share because it offers the only recombinant factor IX product. Baxter, already the dominant factor VIII manufacturer, captured an even larger market share during the recombinant factor shortage of 2001. In 2001, Bayer closed its Kogenate FS production plant to investigate quality control concerns–and supplies of Kogenate FS began to dry up. Wyeth's recombinant factor VIII product ReFacto had just been licensed and couldn't meet the sudden increased demand. Consumers who wanted only recombinant factor VIII turned to Baxter, the only company able to fulfill so many orders at the time. In an industry like blood-clotting medicine, where parents inject a substance directly into their children's veins, consumers don't like to switch brands. Once they choose, patients tend to remain brand loyal.

Are there dangers in the dominance of one or two products? Potentially. For example, America is heavily dependent on Saudi Arabia for oil imports. Events that affect Saudi Arabia affect the oil market worldwide, but a disruption in supply especially hurts the US. Similarly, Canada offers a classic example in the hemophilia community. Canada has a socialized healthcare system. The Canadian government sole-sourced its factor purchases and chose Kogenate FS. As a result, Bayer captured a whopping 95% market share in Canada. This arrangement worked well. But when the worldwide shortage of Kogenate FS hit, Canada suffered. Fortunately, shortfalls in production have not been a consistent problem overall. Meeting the demands of the hemophilia marketplace requires strong production capability, and if market leaders are able to sustain production they can usually meet demand.

All factor concentrate manufacturers are vying for market share, all the time. As a consumer, you are an important player in determining market share. Work with your physician to understand your product choices. Learn which products meet your medical needs within your healthcare budget and lifestyle. But beware the physician or factor provider who recommends only one product without stressing choice. Your physician should be able to tell you which products are available, how they work, who manufactures them, and approximately how much they cost.[15] Remember that a consumer is a customer, and meeting customer needs is the hemophilia market's job.

How Factor Gets Distributed to You

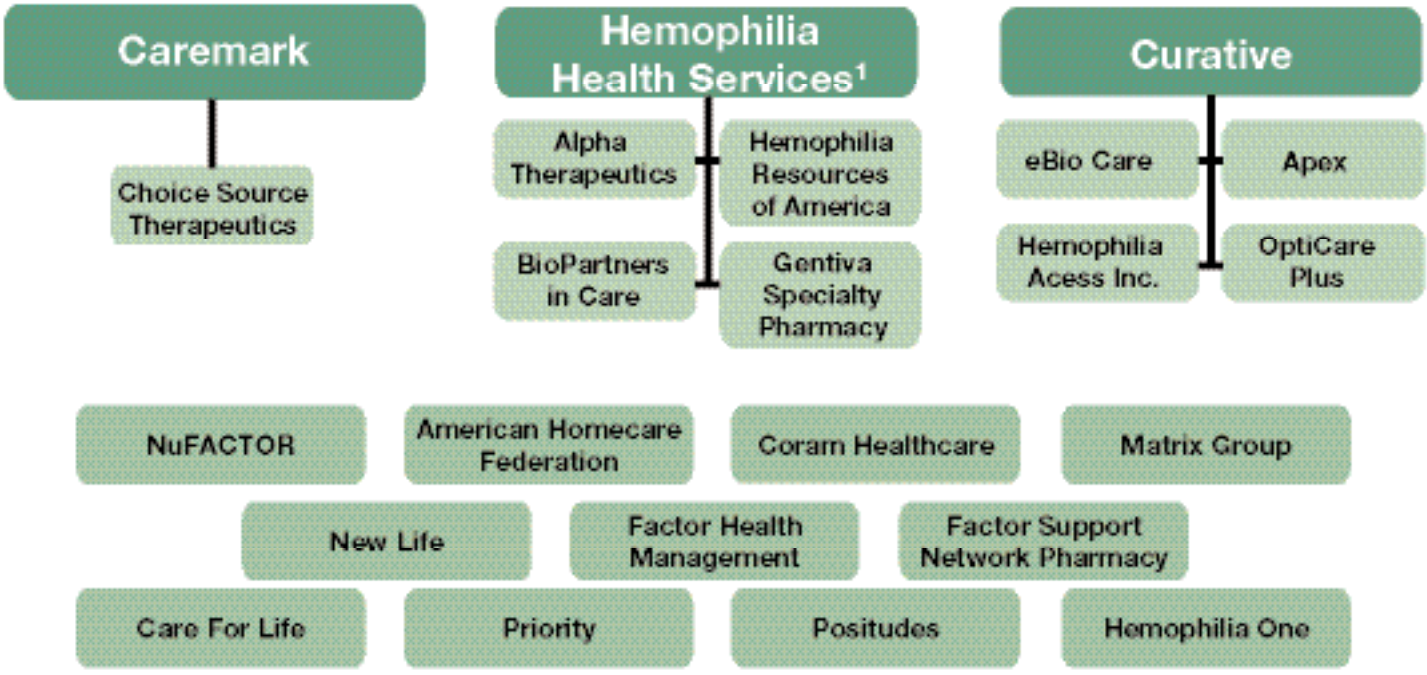
Although you're the consumer, you're not the manufacturer's *direct* customer. You can't buy Coke directly from the Coca-Cola Company–and you can't buy factor directly from the manufacturer. To buy Coke you need a third party, like a grocery

[14] For example, Apple Computers has only a 3% market share of the world's computer market. It has smaller supply and resources than its competitors, but its products are considered cutting-edge. Apple has found a niche, especially among publishers.

[15] Order *A Consumer's Guide to Hemophilia and von Willebrand Disease Products* from LA Kelley Communications. See page 15.

Recent Homecare Company Acquisitions

Recent acquisitions of smaller home infusion companies and specialty pharmacies by larger ones have consolidated more resources and budgets into the three biggest factor providers. There are still many independent homecare companies, but coming reimbursement restrictions may put pressure on their ability to grow and maintain profitability.



[1] Owned by Accredo.

store. Similarly, the factor manufacturers' direct customers are factor distributors. When factor concentrate leaves the warehouse at the manufacturing plant, it's shipped directly to distributors. Who are the factor distributors? The most important are homecare companies (specialty pharmacies/ home infusion companies[16]), 340B programs (HTCs), and biological distributors.

Biological distributors differ slightly from the other distributors. Unlike homecare companies and 340B programs, biological distributors do not ship directly to patients, and indeed rarely ever meet them. Their customers are the *other* distributors. Biological distributors like BioMed Plus and ActSys often buy huge quantities of injectable products from a single manufacturer at deep discounts. Then they sell the products to your homecare company or HTC at substantial markups. Your homecare company or HTC may pay more per unit, especially during a shortage or other crisis, but can at least meet its patients' urgent needs. Like all players in the marketplace, biological distributors have a role.

Most hemophilia patients get factor from homecare companies or 340B programs. Homecare companies are the chief distributors of factor in America. Homecare companies purchase drugs and ancillaries for all types of chronic diseases and disorders from the manufacturers, and ship these biological and prescription products directly to patients' homes nationwide. Homecare companies may hire in-home IV and nursing services, or may have staffing to provide this. Most donate a percentage of their profits to the community by funding local hemophilia nonprofits, supporting fundraisers, providing college scholarships, assisting camps and creating educational booklets. They develop software to track bleeds, provide medical identification bracelets and cards, and offer splints and orthopedic devices. Homecare company workers have direct contact with patients, often track factor usage, and take an active role in ensuring that adequate factor supplies are ordered.

About two dozen homecare companies service hemophilia, and some are entirely devoted to hemophilia. Perhaps no other disorder has so many entities shipping medicine for a single disorder. Hemophilia's traditional high profits have made the homecare company a lucrative business.

The three largest American homecare companies are Hemophilia Health Services, Caremark and Curative. During the past few years, larger homecare companies have purchased smaller homecare companies, increasing and consolidating their customer bases and resources. Why this growing consolidation? "Consolidations are a sign of the general economic system we have," notes Derek Robertson, attorney-at-law and consultant for the Hemophilia Alliance.[17] "Small telephone companies

continued on page 13

[16] While there are subtle distinctions between specialty pharmacies and home infusion companies, for simplicity here we'll call them "homecare companies."
[17] The Hemophilia Alliance is a trade association representing over half of the HTCs participating in 340B programs.

As a hemophilia consumer, you must know the following information:

1. My child has/I have factor _____ deficiency.
2. The brand name of my factor is _____.
3. The company that manufactures my factor is _____.
4. A distributor ships my factor to me. My distributor is:
   a) a homecare company
   b) a 340B program (HTC)
   c) other
5. (If you use a homecare company) My homecare company name is _____.
6. The product I use is:
   a) recombinant
   b) plasma-derived
7. (If you use a recombinant product)
   The product I use is:
   a) first generation
   b) second generation
   c) third generation
8. I pay $_____ per unit of factor.
9. I have a lifetime maximum, after which my insurance will be terminated.
   ☐ True ☐ False
10. I have a lifetime maximum of $_____.
11. Currently my child has/I have used _____% of my lifetime maximum.
12. I can easily switch employers if I need to get different insurance.
    ☐ True ☐ False
13. I can easily switch insurance plans if I need to get different or more insurance.
    ☐ True ☐ False
14. My factor costs are covered by:
    a) private insurance
    b) Medicaid
    c) Medicare
    d) state-based program, such as GHPP or CIDP
    e) no payer
    f) don't know
15. I have noticed a change in the way my insurance company handles my factor usage and expenses.
    ☐ True ☐ False
16. I am worried about the way my insurance company handles my factor usage and expenses.
    ☐ True ☐ False
17. I read and stay aware of changes in the insurance, homecare and hemophilia healthcare industry.

If you can't fill out every item on this list, you need to read, ask questions and learn more. Look in your refrigerator to see which factor brand you use. Call your doctor to learn which type of product you use. Call your insurance company to learn how your factor is delivered. Call your factor provider to learn the cost per unit. Call your insurance company or your product distributor to learn your lifetime maximum usage. Record the name of every person you contact, and write down what is said. Take notes—because you may meet resistance when you start asking questions. If you encounter roadblocks and can't get the answers you need, call your HTC, manufacturer reimbursement specialist, factor distributor reimbursement specialist, insurance company or local chapter. *Ignoring any item on this list means putting your child's or your own future healthcare in jeopardy*.

Hemophilia, Incorporated... continued from page 11

are bought by larger ones. Consolidation is happening in insurance and accounting as well." Robertson adds, "In our economic model, as industry becomes more profitable you have more entries into the market. The larger players will want bigger market share. One way to do this is to buy your competition. Companies will buy to gain the services they lack or geographical areas they do not dominate." Another reason for consolidation? Cost-cutting by payers–private insurance companies and the federal government–who reimburse the distributors for the factor they purchased. As funds for reimbursement decrease, to maintain profitability homecare companies must increase the volume of factor sold.

Homecare companies compete fiercely for patients. Consumers can use this to their advantage by attempting to negotiate lower per unit prices when possible. For example, a father of a child with hemophilia recently revealed that he was being charged $2.00 per unit for recombinant factor VIII. By anyone's standards, this is outrageously high. Knowing the price was too high and that he could go to another distributor, this father could try to negotiate for a lower price. This is the beauty of competition. Yet in too many cases, prices are set by contracts between the insurance company and the factor distributor, and kept confidential from the consumer. Without knowing your per unit price, and without choice of provider, you will never control your hemophilia costs. If you have a cap on your insurance–and about 65% of hemophilia patients with private insurance do[18]–you are in trouble. It pays to know your choices.

"Patients should most definitely try to understand this industry. The cost of factor is the single highest cost; the payment mechanism is changing even now."
—Derek Robertson, attorney-at-law, consultant for the Hemophilia Alliance

Without knowing your per unit price, and without choice of provider, you will never control your hemophilia costs. If you have a cap on your insurance—and about 65% of hemophilia patients with private insurance do—you are in trouble.

Lowering Per Unit Price with the 340B

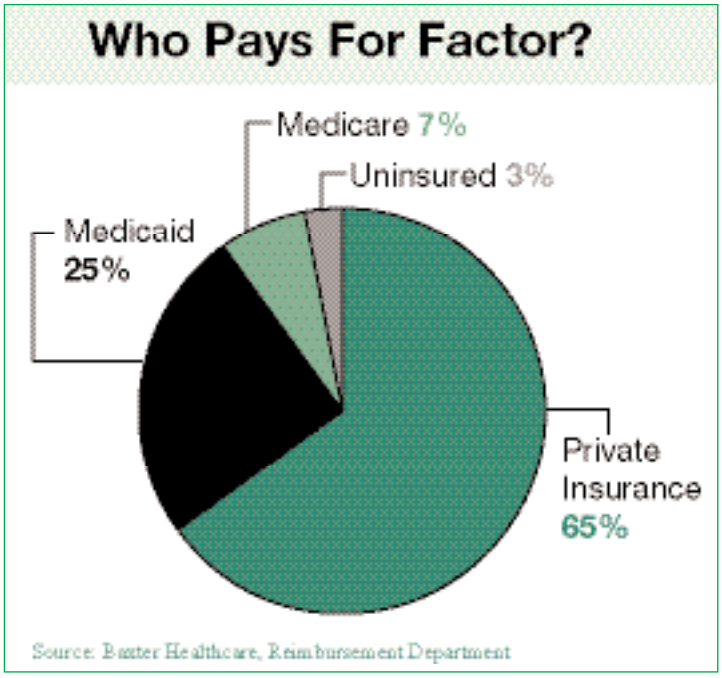
Another choice of factor distributor might be your HTC, if it participates in a 340B program.[19] The 340B program allows HTCs to purchase factor from manufacturers at reduced, government-determined prices, and then resell the factor to their hemophilia patients. In other words, your HTC can serve as your homecare company, with the added competitive advantage of accessing substantially lower manufacturer prices than those available to homecare companies. Out of approximately 150 HTCs in the US, about 70 participate in the 340B program. These HTCs have become the competitors of homecare companies.

In theory, the 340B program seems like an efficient way to manage costs, offer choice, and channel profits back into the HTC. Currently many HTCs are facing federal budget cuts. Selling factor at a below market price could still yield a good profit for HTCs because they can purchase factor at the lowest possible prices. Discounts can then be passed along to consumers in the form of lower per unit prices. A hemophilia patient with a $1 million lifetime cap, who can choose between paying $1.00 and $1.30 per unit, might choose to buy from the lowest-cost provider in order to preserve his insurance coverage over time. But in reality, things aren't so simple. Buying and selling factor is complicated and time consuming; it requires expertise to navigate insurance policies, alert patients about withdrawals and recalls, and manage inventory. Some HTCs perform these tasks well, and also pass along savings. But some don't. The father who admitted paying a high $2.00 per unit price was quoting his HTC, which has a 340B program.

Any factor provider, whether a homecare company or 340B program, can charge varying prices–sometimes high and sometimes low. It's up to you as a consumer to *know what you pay per unit.* Sometimes, the only way to find out is to ask repeatedly. Many factor sellers don't want you to know what you pay per unit, even though your insurance coverage may depend on it. Higher prices will diminish your lifetime maximums. You can see why knowing your products, price

[18] Source: Patient Services, Inc.

[19] In 1992 Congress passed the Veterans Health Care Act (VHCA), which established section 340B of the Public Health Service Act. The PHS Act allows the lowest manufacturer purchase prices on prescription outpatient drugs for certain federally funded entities and public hospitals that treat a disproportionate share of Medicaid and Medicare patients. The intent of Congress was to "…enable these entities to stretch scarce Federal resources as far as possible, reaching more eligible patients and providing more comprehensive services." (H.R. Rpt.102-384, 102nd Cong., 2d Sess., pt. 2, at 12 [1992]). These "covered entities" serve special groups of patients, typically the uninsured or low income, those facing catastrophic medical costs, or those who are underserved in the healthcare of certain diseases, such as AIDS. Federally funded covered entities named in the VHCA include community health centers, black lung clinics, family planning centers, Native Hawaiian Health Centers and HTCs that receive grants from the Maternal and Child Health Bureau (MCHB).



and distributor options can really pay off, helping us all preserve choice and coverage.

The Looming Threat

The high prices of biological products used to treat many chronic conditions are causing payers to sit up and take notice. Because hemophilia fits into this category, it's being scrutinized along with other therapies. For the first time in hemophilia history, payers are making a concerted effort to slash costs nationwide. If the per unit price won't drop, what can payers do to lower costs? They can request a switch to less expensive products. They can question the need for prophylaxis. They can engage in exclusive "sole supplier" deals with the manufacturers, in which one brand only will be reimbursed. Another ominous possibility: insurers may request to inspect factor logs–or even your refrigerator. Doesn't sound like healthcare in America, does it? But this Orwellian version of the future of hemophilia care is here: some of these scary changes are happening right now.

The first major impact of our changing healthcare model has been felt by the Medicaid programs in Arizona, Florida and Pennsylvania.[20] Medicare recipients nationwide will also feel the impact in January 2005, when the first phase of the Medicare Modernization Act takes effect. Under this act, federal reimbursement for hemophilia therapies will be dramatically reduced, possibly causing some factor providers to stop offering certain products and services. As players in this unfolding drama, you will be affected, either directly or indirectly, as the entire hemophilia community feels the loss of revenue. Reduced revenue may affect home nursing services, donations to hemophilia state chapters, and hemophilia programs like camps and scholarships.

Preserving Choice

To enjoy the best healthcare for their chronic disorder, hemophilia patients need to maintain product and factor provider choice. If recombinants were the only products available, some patients would quickly burn through their insurance lifetime caps–a million dollars doesn't last long in hemophilia treatment.[21] If plasma-derived products were the only choice, some would fear viral transmission from as yet unknown sources. If factor VIII products were the only ones available, factor IX patients would suffer. If the "American Pharmaceutical Company" was the sole producer of factor in our country, we would all be at the mercy of its supply capacity. Supply could be disrupted by foreign company mergers, possible divestiture of a division or product, or even natural disasters that damage the manufacturing plant. One company cannot produce enough factor to meet all needs.

If factor were distributed only by biological distributors, we'd be paying the highest prices, and distribution would be uneven. If factor were distributed only through homecare, we might not get the discounts available to HTCs. And if only HTCs were allowed to distribute factor, services would be provided only locally at the HTC.

Admittedly, the hemophilia industry isn't perfect, but currently it does offer us a system of checks and balances. We must be willing to monitor our industry, acting as watchdogs for our own care. "We need to be informed consumers, and not just accept what is prescribed or given to us," advises Ann Rogers. As watchdogs, we should now be growling: insurer and government cost-cutting is already limiting or eliminating choice within certain states and patient groups in the hemophilia community.

In a national climate of healthcare cost-cutting, why should hemophilia patients feel entitled to get their preferred products, providers and treatments? "The hemophilia community has paid its dues," asserts Michael Rosenthal, executive director of Hemophilia Association, Arizona, referring to the 10,000 young American men and boys with hemophilia who contracted HIV. "We've earned the right to demand product choice due to what happened to our community in the 1980s."

Elena Bostick, executive director of Hemophilia Association of New Jersey, adds, "Hemophilia care as we know it today is significantly jeopardized. In South Carolina in 2003, use of recombinant products was banned! Unless we organize and scream bloody murder, the system as we know it today will no longer be available. Our choice of product and our coverage are at risk." Rogers, Bostick and Rosenthal are champions already leading the fight against reduced choice. These leaders are trying to wake our drowsy and innocent hemophilia community.

continued on page 19

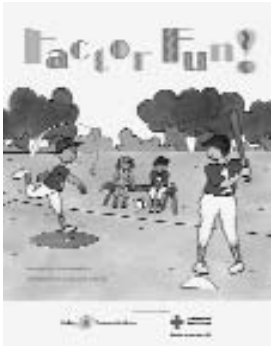
[20] These cases will be discussed in the February 2005 issue of *PEN*.
[21] A study by Towers Perrin in 2000 revealed that approximately 10% of hemophilia patients were likely to reach their private insurance maximums within eight years. Source: Patient Services Inc., which contributed to the study content.

Consumer's Guide to Hemophilia and von Willebrand Disease Products

For the first time, people with hemophilia or von Willebrand Disease have a guide to compare all US blood-clotting and specialty products. This colorful and easy-to-use flipchart is the best way for parents of the newly diagnosed to get an immediate overview of all products. It also helps veteran parents and patients learn about new products on the market. Made possible by a grant from the Factor Support Network Pharmacy, a specialty pharmacy for hemophilia and von Willebrand Disease products, the *Consumer's Guide to Hemophilia and von Willebrand Disease Products* is available through LA Kelley Communications at www.kelleycom.com and through FSNP at www.FactorSupport.com.

Factor Fun! is Back

The long-awaited reprint of *Factor Fun!* has arrived. This popular activity book about hemophilia for preschool children was written by Diane Horbacz, mother of two with hemophilia. The colorful and sturdy activity book teaches about hemophilia, treatment and self-esteem with mazes, matching, glyphs and counting. Funded by a grant from the American Red Cross, *Factor Fun!* is for children ages four to seven. Provided by LA Kelley Communications and available at www.kelleycom.com.



New *Hole In Wall Gang Camps*

Paul Newman's *Hole in the Wall Gang Camps* is a nonprofit organization providing a worldwide network of camps for children with life-threatening illnesses. When the new *Painted Turtle Camp* opened this summer in southern California, The Hemophilia Foundation of Southern California booked one week for 110 kids with hemophilia. *Jordan River Village Camp*, set to open in 2006 in Lower Galilee, Israel, plans to host Jewish and Arab children from Israel, Jordan, Lebanon and the Palestinian Authority. More than 70,000 children from 34 states and 27 countries have attended *Hole in the Wall Gang* camps free of charge. For more information visit www.holeinthewallgang.org.

Wyeth Announces ReFacto® R2 Kit

A new ReFacto reconstitution device called the R2 (for *R*apid *R*econstitution) is expected to ship soon. Wyeth received FDA approval for the device in September 2004. The R2 kit needleless reconstitution device consists of a pre-filled diluent syringe and a plastic vial adapter. The vial adapter is pushed onto the factor bottle, puncturing the rubber seal. The pre-filled syringe is then screwed onto the adapter, and the diluent injected into the concentrate vial. The mixed factor is withdrawn from the vial with the same syringe. The R2 kit eliminates exposure to the filter and transfer needles previously used in the reconstitution of ReFacto. For more information visit www.hemophiliavillage.com.

Bayer Biological Products Launches Initiative to Aid Kogenate® FS Patients

Bayer Biological Products has launched a patient assistance initiative in the US for eligible patients receiving treatment with Kogenate FS. The *Bayer Kogenate® FS Assure Program* (BKAP) has four components: a coupon-based program, patient assistance program, insurance support program and HELP*line*. The program is designed to help patients continue treatment with Kogenate FS in the event of a lapse in private health insurance coverage. Call the HELP*line* at (800) 288-8374 for more information.

Hemalog Discontinued

Hemalog, the quarterly hemophilia publication published by Materia Medica/Creative Annex Inc. with a grant from ZLB Behring (formerly Aventis Behring), is being discontinued after more than 17 years in circulation. This insightful and comprehensive journal was consistently rated one of the best publications for people with hemophilia. It will be greatly missed by our community.

Letters... continued from page 2

I AM A BIG FAN OF *PEN* AND WAS DISAPPOINTED to see the latest issue [*PEN*, August 2004] feature a picture of bicyclists on the cover. *These bike riders were not wearing helmets*. As a parent of a child with hemophilia, I know the importance of wearing protective gear. This photo sends the wrong message. Everyone, with or without a bleeding disorder, needs to wear safety gear while riding a bike.

Shari Bender
New York

Editor's note: *We agree that all children should wear safety gear while bike riding, and regret our unintentional publication of a photo that is contrary to this belief.*

Readers respond to
"Seven Reasons to Remove a Port"

I DON'T ALWAYS TAKE THE TIME TO READ EVERY

word of new information relating to hemophilia. But the article "Seven Reasons to Remove a Port" [*PEN*, August 2004] was extremely interesting and packed with information. Our son Jacob has severe hemophilia B. He had his port placed in January 2003. It has been a blessing for us to do weekly prophylaxis, although he did get an infection in July 2004. Since then, I have been contemplating removing the port; it worries me that an infection could happen again. However, the port has made things so much easier, and my son is now able to relax about getting a shot. We are going to wait until he has a better understanding about using the vein versus the port. I hope that we don't have port complications, and that when he goes to hemophilia camp with other kids–with and without ports–he'll be able to choose once he starts learning self-infusion. He'll go to camp in two years, so we'll see how things go.

Renae Crabtree
Minnesota

THIS ARTICLE WAS ESPECIALLY HELPFUL TO ME, as my child has just started a regimen that includes frequent infusions. Although he's an eight-year-old with "good veins," I was concerned about over-using his veins. But I can see clearly that when someone has healthy, available veins, it's in his best interest to use veins over a port, primarily because of the possibility of infection. Thanks for your continued support and concern for the welfare of people with hemophilia.

Name withheld

MY SON DOESN'T HAVE A PORT, BUT ARTICLES about them are still interesting to read. You can never have too much knowledge.

Vicki Hance
Kansas

I WAS AMAZED WHEN I OPENED THE AUGUST ISSUE of *PEN*. Our 12-year-old son Austin has a port that was placed in 1999. The port was a life-changing experience for us. It allowed Austin to go on prophylaxis, without worry about how many times we'd have to stick him each week. Austin has grown up a lot this summer, and started to self-infuse. He has been doing a great job, and we've started discussing port removal. Austin is self-conscious about the port because he is very thin and the port protrudes. He is a terrific swimmer on our local swim team, and wants to take his shirt off without feeling self-conscious. Reading your article gave us some wonderful discussion points. I knew that ports don't usually last as long as Austin's has, but I hadn't heard about the study showing an increased incidence of thrombosis. We're now planning to have his port removed in the next few months. Thanks for all the wonderful information. It has really made our decision easier!

Susan Henry
Kansas

I FOUND THE ARTICLE ABOUT REMOVING THE PORT very interesting, although my son doesn't have a port and he is terrified to get one. He thinks that a port is what made my husband pass away, although I tried to explain to him that the port was helping his father receive chemotherapy. This didn't help at all, and he is still terrified of ports.

Karen Melendez
New York

Editor's note: *If you think that a port would benefit your son and his infusions, talk to your HTC staff about how to approach the subject. Perhaps your son can meet other boys with ports to learn how ports help. A port might not be necessary if your son is not on prophylaxis, if he has mild hemophilia, or if he has excellent venous access.*

THANK YOU FOR MY FIRST ISSUE OF *PEN*. I HAVE two sons with hemophilia. Daniel is 14 months old and just had his first bleed from an injury to his chin and mouth. Matthew is four, and just had his first joint bleed in his knee. I still feel very new at this, and it's helpful and encouraging to have advice and support from other parents in the hemophilia community. I wonder whether we will eventually need to consider a port for Matthew or Daniel. I didn't realize that various problems could arise, or that a child could outgrow a port. Being armed with all the information in *PEN* will help when making a decision if a port is recommended in the future. Thank you for all you do for the hemophilia community!

Heidi Lyons
New York

My son Michael has had two ports. The first one was placed when he was three years old because he developed an inhibitor and needed to undergo immune tolerance therapy. That port lasted about five years and was removed because it began to disintegrate. Another port was placed. When Michael was 12 he wanted his port removed because he was beginning junior high school. He assured me that doing venipuncture would be fine. I didn't feel comfortable doing venipuncture and talked with our hematologist. My biggest fear was *What if I don't get the vein?* When I asked our doctor that question, she replied, "But if he isn't bleeding you can try again the next day." I soon realized that there was more danger of infection and blood clots than missing a vein. I am happy with the decision we made. Michael is now working on self-infusion. We've come a long way!

Kaaren Zielinski
New York

When and whether to remove a port is an individual choice. For us, the decision came from asking, *How do we best care for our child within our family context?*

When our son Isaac was two years old, we drove the 20 minutes to the pediatric division of a local hospital for infusions. We visited once a week. On good days we were done in 20 minutes. On other days–four- or five-stick pokes–Isaac cried as an hour or more passed before the nurses could access one of his tiny veins.

Then we were invited on a trip to Disneyland with relatives. We went happily but with some apprehension: *What if Isaac needs an infusion?* To prepare, we located the nearest hospital and the name of a person we could call if needed. We watched Isaac carefully on the trip, and all went well until our departing flight. As we waited in the Los Angeles airport, Isaac tripped and fell face-first into a metal divider between the chairs.

I held him as he cried and bled, trying to collect myself. Our flight was to leave shortly. We asked airport personnel to page any medical staff who could help us infuse. They called paramedics, and requested assistance from passengers with medical backgrounds: a physician and a pediatric nurse responded. Despite the stress, the nurse was able to access a vein and we did the rest of the infusion. I still recall our exhaustion and gratitude as we sat down in bloodstained clothing for our return flight. I held my boy, now asleep, nose swollen–but infused. A month later we put in a port.

For us, the port has been monumental. It has helped us transition smoothly through Isaac's infancy, toddler stage, and now young boyhood. We haven't returned to the hospital for an infusion in over four years. Isaac's port has dramatically shifted the way we live with hemophilia, enabling us to move from urgent hospital care to a simple home infusion process.

Why would we remove our son's port? We are somewhat concerned about external physical impact: Isaac is thin, and his port protrudes. Infection is our most serious concern: we watch carefully for fevers. We make sure that Isaac has an antibiotic before receiving dental work. And new research and experience, such as the port article in *PEN*, influences our decision-making.

Isaac still needs factor. He still bleeds. We still face the uncertainty of a world of infusions, infections, target joints, swelling joints. Having a port is just the best way we know, within our family context, to care for Isaac. When we're all ready, we will transition to infusing without using his port. His reaction will help us determine the next best step–just like each day with a bleeding disorder.

Tenneson Woolf
Utah

The article about port removal presented a lot of information to consider. We have two boys with severe hemophilia. We are transitioning to venipuncture with our oldest, Jacob, who is ten. He has had his port for almost seven years without complications. Along with our hematologist, Jacob has made the decision to have his port removed next month. Our youngest, Joseph, is six and has had his second port for two years. He is not yet ready to have his port removed, and his veins aren't easy to access. But I believe that the transition will be easier for him because he has watched his older brother, and they have worked together doing activities that help build up their veins. Thanks for publishing a great newsletter.

Rachel Gehartz
Minnesota

PENPAL WANTED

My son Jeremy is eight years old and has type 3 von Willebrand Disease. He began third grade in September. As a boy with VWD, I think Jeremy feels 'out of place' because the other boys at camp and HTC activities have hemophilia. Most VWD-related resources and programs are for girls. Jeremy is a playful little guy who is trying to fit in, but he isn't always successful. He has a great imagination and enjoys building things. He loves Legos, Star Wars and–even better–Star Wars Legos!

I would really like to find a penpal for Jeremy, perhaps another boy his age or older with type 3 VWD. Jeremy looks up to older boys, such as his camp counselors, for friendship and acceptance. I can't always tell how much having VWD bothers Jeremy, but I would like to help him feel "normal."

Jessica
New York

If you'd like to be Jeremy's penpal
send an email
directly to him at **JLKVWD@aol.com**
or write your letter to the
LA Kelley Communications, Inc.
address and we'll forward it.

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growth medium, and remove human albumin, used as a stabilizer, from recombinant factor concentrates. In 1999 the first recombinant factor concentrate that did not use albumin as a stabilizer was released, and others soon followed. These "second generation" recombinant factor concentrates still use human or animal proteins in the growth medium, but do not use albumin as a stabilizer in the final product. Contaminating proteins from the growth medium are essentially removed by the purification process, and there are only trace amounts of extraneous animal or human proteins in the final product.

The next step was to produce a recombinant factor product with no human or animal proteins in the growth medium *or* in the final product. The first long-awaited "third generation" recombinant factor VIII product hit the market in 2003.

Continuing Research in Hemophilia Treatment

What's on the horizon of research in hemophilia treatment? Today researchers are hard at work in several key areas that will enable manufacturers to produce more factor at lower cost, and make factor last longer in the blood stream, possibly with less likelihood of inducing inhibitors.

New "cell lines."[2] Researchers are hunting for new cell lines that can better "express" or manufacture recombinant factor VIII or IX. A cell line that could produce more factor would lower production costs and increase supply.

Half-life.[3] Factor VIII is a large and very unstable protein with a short half-life. Researchers are now studying the structure of the factor VIII protein molecule, and learning how it interacts with other compounds in the bloodstream–especially von Willebrand factor, which acts as the body's natural stabilizer for factor VIII. They hope to be able to modify the structure of the factor VIII molecule, making it more stable and increasing its half-life. Factor VIII with a longer half-life would last longer in the bloodstream, requiring less frequent doses.

Inhibitors. A major complication in factor replacement therapy is that 15%–20% of people with hemophilia A develop antibodies, known as "inhibitors," to infused factor VIII. Their immune systems attack the infused factor as a foreign agent, inactivating it and making it less effective, even useless, in controlling a bleed. Treating people who have inhibitors is very complicated and often extremely expensive. Researchers hope to learn what causes the factor VIII molecule to trigger the immune systems of some people but not others, then modify factor VIII to make it less *immunogenic*–less likely to trigger the immune system to mount a defense.

New ways to administer factor. Since the factor VIII molecule is so large, it isn't easily absorbed through the skin. If swallowed, most of it is digested before it can be absorbed by the intestines. For these reasons, the only effective method of administering factor VIII remains intravenous infusion. Conversely, factor IX is a much smaller molecule; researchers are currently exploring delivery methods for factor IX that don't involve intravenous infusion. Right now, these novel delivery methods can't get factor into the bloodstream efficiently, so researchers are working on a variety of methods to increase efficiency of delivery.

Pharming. Pharming involves techniques similar to human gene therapy. The human gene for factor VIII or IX is introduced into the genes of a farm animal–a pig, goat or cow. The animal then produces factor VIII in its milk. These "transgenic" animals can provide a steady source of factor in large supply. Pharming, however, has a few drawbacks: clotting factors are more difficult to separate from milk than from growth medium or blood plasma. And pharming involves animal proteins and the associated risk of viral transmission. Nevertheless, pharming may be a viable source of factor for countries lacking ready access to factor concentrates.

Human gene therapy. Right now, the primary goal of the hemophilia community is to eventually cure hemophilia by introducing good copies of the factor VIII or IX gene into the bodies of people with hemophilia, enabling them to produce their own factor. Hemophilia is a model disorder for gene therapy because the amount of factor produced by an individual doesn't have to be closely regulated–an increase in factor can be effective at anywhere from 1% to over 150% without causing problems such as excessive clotting. Numerous problems–such as selecting the appropriate "vector" capable of targeting and infecting the appropriate cells to produce factor without eliciting an immune response, increasing factor levels sufficiently for an extended time (longer than a few weeks), and avoiding transmission of the introduced gene through sperm cells–have arisen during gene therapy research, but many researchers are optimistic that these challenges will eventually be surmounted and gene therapy will become a reality.

Hemophilia, once a disorder with no effective treatment, is now easily treated. For most people with hemophilia who have access to modern treatment, life is good. Young people with hemophilia today can look forward to normal and relatively pain-free lives–in developed countries. But the vast majority of the world's estimated 400,000 people with hemophilia still live in the past, with substandard or no treatment for hemophilia. The challenge of the future is not just finding a cure through gene therapy, but finding a way to extend current therapy to all nations of the earth.

[2] "Cell line" refers to cells of a single type that have been grown in the laboratory for several generations (cell divisions), such as the baby hamster kidney cell line or Chinese hamster ovary cell line currently used to produce recombinant factor products.
[3] Half-life is the time required for the body to eliminate half the amount of a drug, such as clotting factor.

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Fighting for our rights isn't new to the community. "I think hemophilia patients are well educated and proactive on a lot of issues," notes Derek Robertson. "But most are not as aware of the changes that are taking place right now related to how payers are reimbursing for factor. Patients should most definitely try to understand this industry. The cost of factor is the single highest cost; the payment mechanism is changing even now. You need to know how this will impact your access to care, to get the product you need, to lead the life you choose."

End of Part I

Look for Part II of our series in the February 2005 issue of *PEN*. "The Coming Storm" will explain how factor pricing is set and reimbursed, and how a new model–with a new player, Pharmacy Benefit Managers–is threatening choice and may threaten our quality of life. How will these changes affect you or your child? Read what leaders in the hemophilia community have to say about what's happening and how you can get involved to preserve choice of product and provider–and your future.

Laurie Kelley is president of LA Kelley Communications, Inc., a worldwide provider of educational resources and leadership training for the bleeding disorders community. She is the author of ten books, including Raising a Child With Hemophilia *and* A Guide to Living With von Willebrand Disease. *Laurie holds a master's degree in international economics and business from the Fletcher School of Law and Diplomacy. She lives in Georgetown, Massachusetts with her husband Kevin, a process scientist for New England Biolabs, and their three children: 17-year-old Tommy, who has hemophilia A, 14-year-old Tara, and ten-year-old Mary.*

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by Laureen A. Kelley

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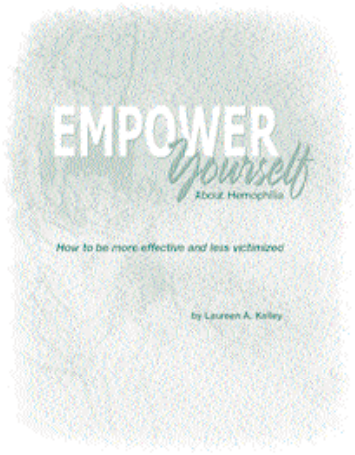

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