PEN

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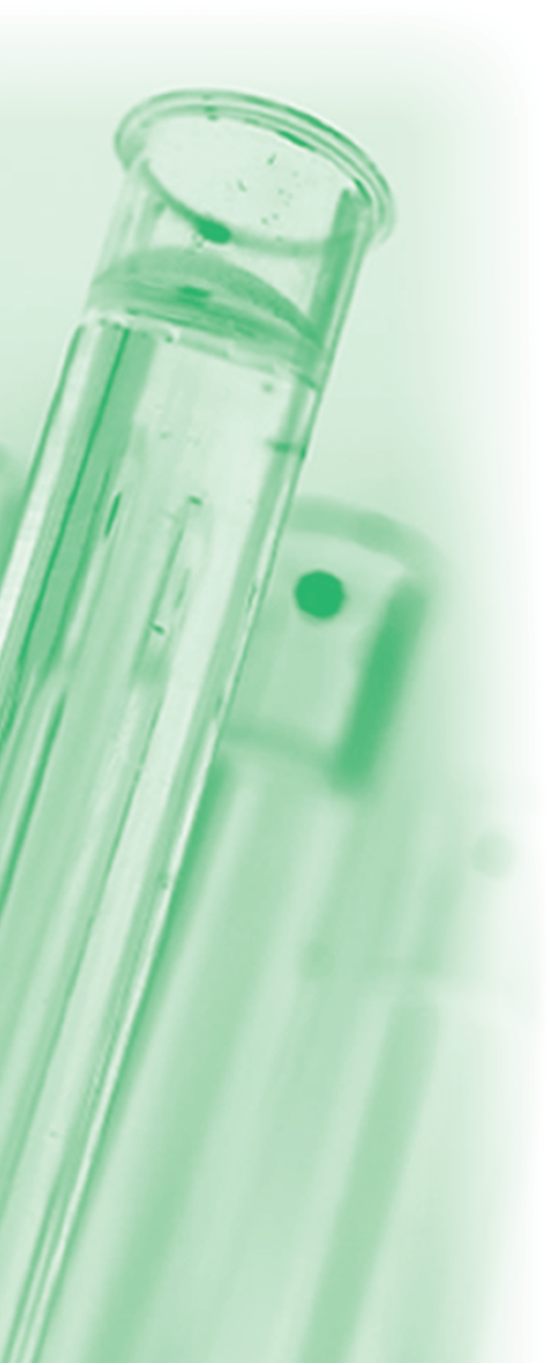
New Treatments in the New Decade:

Longer Acting, Purely Human, and Possibly Cheaper

Laurie Kelley and Chris Lamb



Octapharma, a Swiss manufacturer of blood-clotting products, received an early holiday gift. Its new product wilate®, a plasma-derived factor concentrate, was approved in early December for sale in the United States. Wilate is the first high-purity product indicated specifically for treating bleeds in patients with von Willebrand disease (VWD).[1]

It's big news: The last time a completely new competitor with a new product entered the US bleeding disorder market was in 1999, when Danish company Novo Nordisk's NovoSeven was approved in the US for patients with inhibitors. Wilate enters a market dominated for 25 years by Humate-P®, produced by CSL Behring, and including Alphanate®, produced by Grifols and approved for VWD only in 2007. Why would any manufacturer enter a market already saturated with products, especially when insurers may try to limit product choice?

Be prepared for more surprises. Right now, many blood-clotting products are in the pipeline for the American bleeding disorder community, products that could radically change treatment options and perhaps even the cost of treatment. From longer-acting factor requiring fewer infusions per week, to potentially cheaper generics, our marketplace is changing. Competition is heating up, so wise consumers will want to know what's ahead: What products will appear in the new decade? Which companies are on the cutting edge of research? What's the good news for treatment?

General Market Facts

To understand the new products in the pipeline, and to learn how they might affect your choices and treatment, you need to know how the manufacturers view us, the consumers with bleeding disorders.

You probably know about the three main bleeding disorders: hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency), and VWD. But manufacturers see four markets: hemophilia A, hemophilia B, VWD, and inhibitors. Each market has its own unique products. And each product manufacturer carefully studies these four markets to monitor how its product is selling: the greater the sales, the higher the product market share. Manufacturers also study healthcare reform and clinical study outcomes, to analyze how these may impact their product's growth.

As in any market, the more consumers, the higher the sales. How many consumers are in these four markets? Of the estimated 17,500 Americans with hemophilia A and B, about 80% have hemophilia A. About 15% have hemophilia B, and the rest have rare factor deficiencies like factor XIII or factor V.

About 1% to 2% of Americans have VWD. Unlike hemophilia, VWD affects males and females equally. But of the estimated 150,000 Americans with VWD, many are not identified. Why?

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welcome


Sherrell Portrait Design

In the late 1990s we were all talking about, and hoping for, gene therapy for hemophilia. National Hemophilia Foundation launched its Campaign for a Cure, and millions of dollars poured in. A new decade was looming – and a new millennium – when everything seemed possible.

But in 1999, 18-year-old Jerry Gelsinger became the first person known to die while in gene therapy trials (unrelated to hemophilia). The brakes slammed on gene therapy clinical trials around the world. The millennium ushered in concern and hesitation about gene therapy. NHF eventually shut down the Campaign for a Cure.

At the beginning of this new decade, it's time to look beyond gene therapy for now, and get a glimpse of what's far more likely to come down the road. But we still have reason to be excited. One day soon, we may be injecting factor once a week – and have it last *all* week. We may see products from completely human cell lines, not animal cell lines. And how about less expensive factor? It's all possible.

This time in PEN, we offer an overview of current factor products in development. From factor VIII to IX, from von Wllebrand disease to inhibitors, research is underway to bring you better products.

In this issue's Inhibitor Insights, Paul Clement explains the manufacturing processes that bring us bypassing agents for inhibitor patients. And in honor of Valentine's Day, Kevin Correa writes about how to handle dating when you have a bleeding disorder. Richard Atwood reviews a romance novel that features hemophilia! Share PEN with your favorite loved one with hemophilia, and stay hopeful for new products to make life easier.

inbox

I AM A MOM OF TWO ADULT boys who have severe hemophilia. I met you, Laurie, many years ago at a conference, and *Raising a Child With Hemophilia* still sits in my library. I have referred to it often, and it was crucial in helping me realize that my son was having a cerebral hemorrhage when he was younger. I was excited to find that you are still active in the hemophilia community. I have been withdrawn for the past several years and have just now begun to reconnect.

Patty Bond

Tennessee

PEN November 2009

THANK YOU FOR THE IN-depth article on the factor provider industry in the US. For those of us who are newer to working with patients with hemophilia and their families, this is a thorough background on the evolution of the marketplace. And as always, PEN makes sure to bring focus back where it belongs – on the patients at the center of the story. Well done.

Chris Core

Associate Director, Hematology

Talecris Biotherapeutics, Inc.

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PARENT EMPOWERMENT NEWSLETTER • FEBRUARY 2010

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Andy Matthews

Andy's Healthcare Cost Solution

Get Fit America! Sounds like a reality television show, but if you think about it, the actual reality is this: if everybody in this country would start getting fit, we could save hundreds of billions of dollars in healthcare costs that are affecting our healthcare system. According to a new study, the United States spends about $1.8 trillion a year on medical costs linked to diabetes, heart disease, and cancer – conditions associated with habits like smoking and overeating.*

Many things influence our skyrocketing healthcare costs, but there's one area where we can all have an impact. Many of the costs in our healthcare system are caused by lifestyle: people are overweight, eating the wrong foods, smoking, and not getting regular exercise! Chronic health problems and the pressures they put on our healthcare system could be relieved greatly if people changed their lifestyle and eating habits, and got into shape.

I know that I'm just one little voice, but if every person reading PEN would commit to achieving an optimal weight, doing regular exercise, and eating a healthy diet, that alone could make a big impact! If all the children and adults living with hemophilia would maintain some kind of fitness routine, they would have healthier joints. If you're dealing with problem joints, then even a moderate amount of fitness, along with proper factor dosage, can help rebuild muscles around the joint areas and minimize future bleeds. Think about how much better you'd feel with strong, healthy joints! I am living proof that eating right and adhering to a fitness program with strict discipline can change your life with hemophilia.

I know fitness is the answer because I am healthier than most people living *without* hemophilia! In the 1990s, when many of my friends with hemophilia learned they had HIV, most of them figured they would die. I thought that mentality was crazy, so I chose to get more serious about what I ate, keep a positive outlook, and most important, develop a workout regimen with regular cardiovascular exercise. Yes, I had a bad target ankle joint to worry about, but I still stayed true to the physical activities that worked for me: mountain biking and fast walking.

Did you know that making simple changes to incorporate fitness into your daily routine can get you in much better shape? If you'll just commit to parking in the farthest parking space, taking the stairs instead of the elevator, and walking whenever possible, you'll be amazed! Heck, just think about how much power walking you can do around the Home Depot or the mall. You can get exercise anywhere by just walking as if you're in a hurry – and you'll look important while you're doing it!

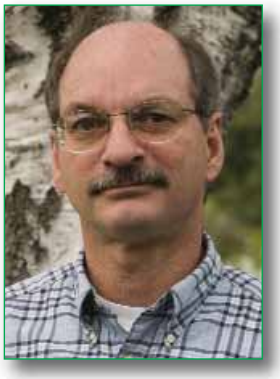
The great thing about fitness is that it's a sure thing. I can advise you to do many things in life that are *not* sure things. I can tell you to work harder, but that won't mean you'll make more money. I can tell you to improve your appearance, but that won't mean you'll get more dates. But I can promise you this: if you commit to it, you'll get results from a fitness program. How much success you achieve is up to you. Rich or poor, tall or short, skinny or fat – with proper training, healthy diet, and good clean living, your body will become your temple!

Start now. First, visit your HTC and get the green light to begin. Then start by just walking. Next, try some light weight lifting or swimming. Put on your helmet and try some biking – maybe even mountain biking once you're ready. Make sure you factor up to prevent bleeding and get better results. I guarantee you will start dropping cumbersome weight and start building stronger muscles and joints. You'll have more energy and begin to feel better. In these uncertain economic times, this is the single best thing you can do for yourself and your children. And it's the best beginning for true healthcare reform: start with yourself.

Andy Matthews, age 43, has severe factor VIII deficiency and is HIV positive. Andy has worked in the bleeding disorder community for 18 years, and is currently a motivational speaker on topics including education, making career choices, and insurance. He lives in Dallas, Texas, with his wife Patti, son Keeton, and new baby daughter Kelsey. Visit Andy at www.sweetaffliction.com

* Nanci Hellmich, "Rising Obesity Will Cost U.S. Health Care $344 billion a year." http://abcnews.go.com

Andy Matthews



Paul Clement

Bypassing Agents: Which Product Is Better?

As you'll read in this issue's feature article, people with hemophilia A or B without inhibitors have a variety of choices for stopping bleeds. People with hemophilia and inhibitors don't have that luxury. They must use special factor concentrates called *bypassing agents*. Currently only two bypassing agents exist to help them stop bleeding: FEIBA®VH, made by Baxter BioScience, and NovoSeven® RT, made by Novo Nordisk. Which product to use depends on a number of things, including type of inhibitor. Sometimes patients don't have a choice; only one product works to stop their bleeds. If that one product is made from human plasma, should people with inhibitors worry about product safety?

To answer that question, let's look at how the two products work and how they are manufactured.

FEIBA is an *activated prothrombin complex concentrate* (aPCC), also called an anti-inhibitor coagulant complex (AICC). It contains inactivated forms of clotting factors II (prothrombin), IX and X, and activated factor VII, as well as small amounts of factor VIII. FEIBA works by bypassing, or skipping, the missing factor (the one the inhibitor attacks) and then moving on to the next level of the clotting cascade. FEIBA is a *plasma-derived* product, manufactured from blood plasma that has been collected and processed under the QSEAL (Quality Standards of Excellence, Assurance and Leadership) program of the Plasma Protein Therapeutics Association. These voluntary standards include (1) a *qualified donor standard*, in which a potential plasma donor must pass two separate medical screenings and testing for HIV, hepatitis B (HBV) and hepatitis C (HCV) on two different occasions; (2) an *inventory hold*, in which plasma is held in inventory for a minimum of 60 days to allow units to be retrieved if a donor later discloses high-risk behavior or tests positive for one of the screened viral diseases; and (3) *Nucleic Acid Amplification Technology* (NAT) screening, a highly sensitive viral test that allows detection of infected units of plasma much sooner than do conventional viral tests. FEIBA also undergoes a vapor heat-treatment process to inactivate lipid-enveloped viruses.[1] And aPCCs have been used to treat bleeding in patients with inhibitors for more than 30 years.

NovoSeven RT contains only activated factor VII, which skips the need for factor VIII and factor IX in the clotting cascade to form a clot. NovoSeven RT is not produced from blood plasma. It's a *recombinant* product manufactured through recombinant DNA technology. In this process, the cloned gene for human factor VII is inserted into host cells (baby hamster kidney cells), making them capable of producing the human factor VII. When the host cells with the recombinant (human) DNA divide, their offspring also contain the human DNA and the ability to produce factor VII. In the production process, the recombinant host cells are allowed to reproduce and grow to large numbers in a nutrient solution called a *culture medium* inside large stainless steel vats called *bioreactors*. The recombinant cells continually express, or secrete, human factor VII into the culture medium. Periodically, some of the culture medium is removed and the factor VII is separated from the other proteins in the medium. This purified factor then undergoes a solvent-detergent viral inactivation process to eliminate any lipid-enveloped viruses that theoretically could infect the host cells. No human serum or other proteins are used in NovoSeven RT production, and none are added to the final product. NovoSeven RT is theoretically free of the risk of viral contamination.

So which product is better? Does plasma-derived or recombinant make a difference? First, know that *all* FDA-approved blood clotting products are considered safe. You should use plasma-derived and recombinant products with confidence. What about effectiveness? In many cases, there is no one answer. Currently, neither product used to treat bleeds in people with inhibitors is as effective as treating bleeds with pure factor VIII or factor IX in people without inhibitors. As a result, people with inhibitors tend to bleed for a longer time, increasing their risk of hemophilic arthropathy (joint destruction caused by repeated bleeds), life-threatening hemorrhages, and possible side effects of their treatment. Some people with inhibitors report that one product or the other is more effective for them. Some people report that

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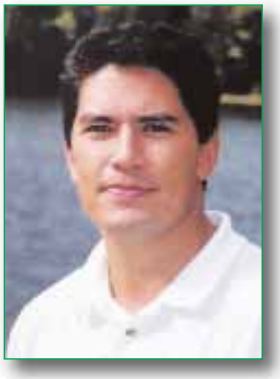

Kevin Correa

"Come Here Often?"
Hemophilia and the Dating Scene

Venture into any card shop in the late afternoon on Valentine's Day and you'll find it packed with men searching for the perfect card that says, "No, I didn't wait until the last minute." We all know this annual ritual. But have you let your hemophilia keep you out of the dating game?

Chances are good that at some point you've met an interesting girl* and wondered, *How will she react when she learns I have hemophilia?* And chances are also good that you allowed that thought to stop you from striking up a conversation.

Here's a newsflash: as unique as you think you are, you're just like the vast majority of men on the planet who shy away from approaching a woman because of some self-perceived shortcoming. Sure, there are scores of reasons you might not take a chance, but above all is the simple fear of rejection. Hemophilic guys haven't cornered the market on this phobia. Guys without hemophilia have plenty to muddy their minds... *Maybe she won't like me because I'm too short; or too thin; or have brown hair; or don't drive the right car.*

Bottom line? Given the myriad reasons a girl might turn down the average guy, there's no sense in fixating on your hemophilia.

Warming the Bench

It's interesting that the peers who impress us change over time. When we're in elementary school, it might be the kid who runs the fastest. In high school, it might be the three-sport captain. But then there's a shift, and suddenly we're not so impressed by the jump shot or curve ball. Now the guy who dazzles us is the one who can walk up to a girl in any location – at school, the mall, a party – and strike up a conversation. The quality that makes him the envy of his friends? A complete absence of the natural fear of rejection.

That fear results from a lack of confidence. When hemophilia plays a role in this equation, you need to understand why.

Michael, a 29-year-old with hemophilia and HIV, is used to talking about his health issues as an advocate and educational outreach speaker. But five years ago, he had essentially given up the dating scene. "It was easier not to date than to deal with the stress of a girl learning about my various health concerns."

In spite of his public speaking experience, Michael still lacked the confidence to talk about his health one-on-one with a potential romantic interest.

It's normal to feel apprehensive about how a girl might react when she learns about your hemophilia. *Will she look at me differently? Will she be afraid? Will she think I'm damaged goods?* Ultimately, this apprehension results in a lack of confidence, which, in turn, fuels your fear of rejection.

And the only way to conquer that fear is to build your confidence and self-esteem.

Getting in the Game

If hemophilia has chipped away at the confidence you need to chat-up the ladies, one way to rebuild it is through mastery of the subject.

Says Greg McClure, licensed social worker with Chicago's Rush University Hemophilia and Thrombophilia Center (HTC), "We tell all of our guys to learn as much as they can about their hemophilia. The more you know about it, the more comfortable you are discussing it." If you aren't comfortable talking about your own disorder, you'll face an uphill battle trying to make someone *else* comfortable.

By learning everything you can about hemophilia, you won't be so nervous about the questions a girl might ask you when on a date, and you can respond to anything she may wonder: *Can I catch it? Would our kids have it? So you might bleed to death if you get a cut?*

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* To avoid cumbersome text, I'll describe relationships in terms of a hemophilic male and a female, but this can represent any of numerous relationship combinations.

Rachel Ruggles

Life Saving, Soul Saving

PROJECT SHARE

It's time to give back

Andrea Trinidad-Echavez is a USAID (United States Agency for International Development) consultant in the Philippines, and also a Filipino woman with a bleeding disorder. In November 2008, while doing outreach in the city of Cagayan de Oro, Mindanano region, Andrea heard about a child with a suspected bleeding disorder. She stumbled upon him by accident: a hospitalized boy whose foot looked like a grenade had hit it. An untreated ankle bleed had become infected and eaten nine-year-old Kirby's flesh and muscle. Luckily, Andrea knew how to submit a request to Project SHARE for factor to try to save the boy's leg.

Within days, Kirby's physician, Dr. Fedo Go, received our donation. Soon Kirby's condition drastically improved, and the bone infection subsided. His situation seemed ideal: shipping factor to spare a patient from amputation or further deterioration is one of Project SHARE's goals. As our optimism grew, however, so did the bacteria in Kirby's leg.

By May 2009, gangrene forced Kirby's doctors to amputate. Project SHARE again supplied factor. The 70,000 IU shipped to Kirby came from American donors who sent their unwanted factor to Project SHARE instead of throwing it away.

Project SHARE collects unused, unwanted factor from US hemophilia treatment centers (HTCs), specialty pharmacies, and bleeding disorder patients, and redistributes it to under-privileged people with hemophilia and von Willebrand disease. Last year we shipped over 4 million IU to more than 30 countries. Despite these generous donations, our supply is chronically low and sometimes nonexistent.

"In a poor country like the Philippines, Project SHARE is truly heaven sent," Andrea attests. "The help it has been providing to patients like Kirby is not just life saving, it is also soul saving, in the sense that it gives renewed hope to people who had already given up on their conditions."

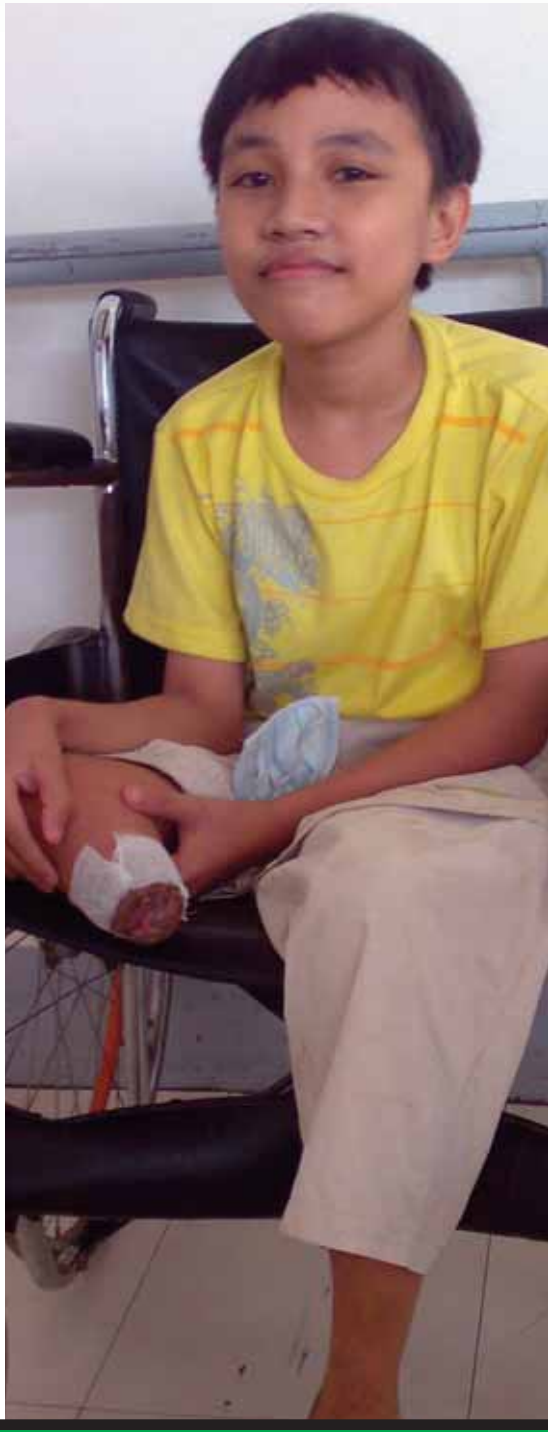
Kirby is one of the lucky ones. Although he lost his leg, Project SHARE was able to save his life. But things remain difficult for his family. To pay for expenses related to his disorder and his surgery, Kirby's parents had to sell their home and move to a more remote area of the Philippines where access to medical care is challenging. Kirby's family is even having trouble getting crutches or a wheelchair for him.

Like Kirby, about 75% of the world's estimated 400,000 people with hemophilia have little or no access to factor. Project SHARE's waiting list contains more than 80 unfulfilled requests for factor from people in 28 countries. We rely on patients, HTCs, and companies to assist us by donating factor and ancillaries.

How can you help? Just let us know when you have unwanted and unused factor. If you work in a pharmacy, check your inventory for product about to expire. When you switch product, send us the product you no longer need.

Or maybe you'll be the one to donate funding for a wheelchair for Kirby, so he can adjust to life with only one leg and enjoy the one thing he cherishes – attending school. With help from you and Project SHARE, we can improve Kirby's quality of life.

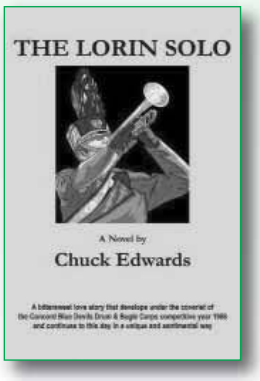
If you can donate funding for a wheelchair for Kirby, please contact Project SHARE at 978-352-7657 or share@kelleycom.com



Andrea H. Trinidad-Echavez

richard's review

Richard J. Atwood



The Lorin Solo

Chuck Edwards
Self-published, 2006

I was totally unfamiliar with the genre of romance novels until I started reviewing hemophilia literature. Several romance novels feature characters with bleeding disorders, but I favor *The Lorin Solo* as the best example of a young adult romance novel. Even so, this book needs a vivid warning label on its cover indicating the incorrect genetics. It demonstrates the importance of editors and fact checkers in the publishing process, and how the omission of their expertise can result in a flawed novel.

Lorin Lenki is a 20-year-old music student at San Francisco State University in 1985. He has mild hemophilia, which he treats with clotting factor. While waiting for a treatment in his doctor's office, Lorin meets nursing student Tracy Martin, and immediately falls in love. Tracy, who has severe hemophilia, writes a column for a hemophilia newsletter and plays bugle in a local drum and bugle corps, the Blue Devils. Lorin soon joins the Devils to play his bugle. Complicating this budding romance is Tracy's current boyfriend, as well as her Catholic faith. Tracy's identical twin sister, who also had hemophilia, died at age ten, and Tracy is concerned about having children. Unfortunately, tragedy strikes during the Devils' national competition in 1986.

Though it generously describes the world of competitive bugle corps, the novel contains several editing errors, a problem in many self-published books. Hemophilia plays an important role in the story. For example, the severity of Tracy's hemophilia is revealed when she has a nosebleed, is given a blood-clotting agent, and ends up in ICU. Some of the medical and product information is accurately presented, but most is not. Lorin mentions being shielded from sports as a child, then later learning the importance of exercise. But the main characters continually repeat the unsupported notion that having biological children is not possible for people with hemophilia, and they receive improper genetic counseling advising them not to have children due to the "consequences." Unfortunately, the genetics of hemophilia transmission presented for the two families is questionable.

Such incorrect information boggles my mind, because Edwards did some homework on understanding hemophilia – yet he got its genetics completely wrong. If only he had given Tracy the diagnosis of severe von Willebrand disease, his plot would have been more plausible, and could even have explained the fact that Tracy's father had a bleeding disorder.

But despite its misinformation, I like this novel because it simplifies the story for a younger audience without talking down to them, and it is a tragic, mushy love story. The main character follows his passion for music, overcomes obstacles, falls in love, and just happens to have hemophilia, which he properly handles, as we would expect.

Chuck Edwards, a retired professor, has a passion for drum and bugle corps. *The Lorin Solo* began as an unproduced 1980 movie screenplay, was transformed into a staged musical in 1981, and eventually published as a novel. The Blue Devils Drum and Bugle Corps has existed in Concord, California since 1957, and has won many world championships.

New Treatments... from cover

VWD is hard to diagnose, it doesn't affect males as severely as females, and it results in mild symptoms for most patients. There are three VWD subtypes: type 1, type 2, and type 3. Types 1 and 2 are mild, characterized by bruising and mucosal (gastrointestinal, nasal) bleeding, and usually don't require a factor infusion. Type 3 is severe, not unlike severe hemophilia A, characterized by joint and muscle bleeds. Of those who have VWD, only about 1%, or 1,500 people, have type 3 and require regular treatment with factor VIII concentrate that also contains von Willebrand factor (VWF).

Of the 17,500 hemophilia patients, about 1,200 have inhibitors. Inhibitors are antibodies to infused factor; the body develops these antibodies when it doesn't recognize infused factor as belonging to the body. The antibodies neutralize the factor and, in high responders, make it useless. Because of this, inhibitor patients can't use the regular factor products used by people with hemophilia A or B without inhibitors. To stop bleeding, people with inhibitors need special factor concentrates called *bypassing agents*.

In the US, bleeding disorder patients treat their bleeds with injectible factor concentrates, produced by eight factor manufacturers. As far as chronic disorders go, our marketplace is small. With such a small market, and with excellent products available, why do so many companies race to introduce new products? Because as a community, we demand new products, and because the bleeding disorder market is highly profitable.

Treatment Types

Each time you or your child uses a vial of factor, you participate in a $3 billion market where factor is bought and sold. Factor is manufactured according to forecasts of how much factor will be consumed. It's not terribly hard to predict: relatively few consumers consistently use factor products, and every year, only about 400 new hemophilia patients are born in our nation.

Eight companies, whose factor products are registered in the US, currently split this $3 billion revenue:

Manufacturers licensed to sell factor in the United States

- Bayer HealthCare
- Baxter Healthcare
- CSL Behring
- Grifols
- Novo Nordisk
- Octapharma
- Pfizer
- Talecris Biotherapeutics

Baxter Healthcare, Bayer HealthCare, CSL Behring, Grifols, Novo Nordisk, Talecris, Pfizer (formerly Wyeth), and now Octapharma.

The factor products they manufacture fall into two main categories: *plasma-derived* and *recombinant*. Plasma-derived factor comes from human plasma. Recombinant factor is produced without plasma, through recombinant DNA technology. No matter which brand of factor you use, or which market you're in, your factor is either plasma-derived or recombinant.

Hemophilia A patients use either recombinant factor VIII or plasma-derived factor VIII products. Hemophilia B patients use either recombinant factor IX or plasma-derived factor IX products. VWD patients currently use only plasma-derived factor VIII products that also contain VWF, because there is no recombinant von Willebrand factor product yet available. There are two inhibitor products in the US market: a recombinant factor VIIa and a plasma-derived product.

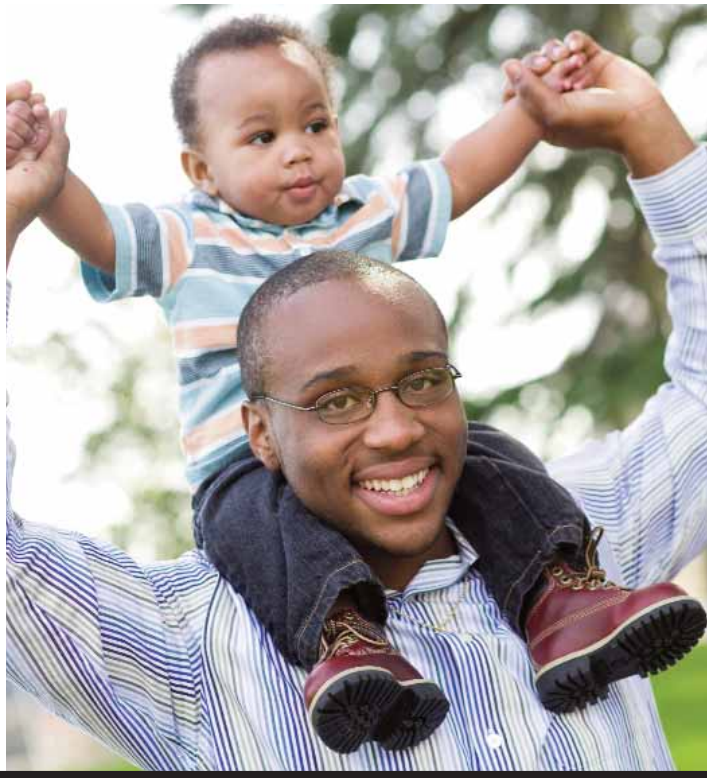
As a consumer, a good starting point is to know what kind of product you use, for yourself or your child: plasma-derived or recombinant? Regular factor or bypassing agent? Then, you need to know why.

Small Market, Many Products

Recombinant is the product of choice in the US, recommended by MASAC (National Hemophilia Foundation's Medical and Scientific Advisory Council). Although today's third-generation recombinant products are theoretically free of viral risk, it's important to note that all FDA-approved products are currently considered to have a very low risk of viral transmission. And though no blood-clotting product can be proved 100% safe, plasma-derived products now enjoy a 20-year history with no reports of transmission of serious viral diseases.

Recombinant products

About 90% of Americans with hemophilia A use one of five recombinant



products (see chart on p. 13). Baxter produces Recombinate and Advate. Bayer produces Kogenate® FS. CSL Behring distributes Helixate® FS, and Pfizer produces Xyntha™.

Baxter manufactures two different versions of recombinant factor VIII. Recombinate is classified as a *first-generation* recombinant product. Although the factor itself is not derived from human plasma, Baxter uses animal products in the cell culture medium and adds a human blood protein, *albumin*, during the finishing process to increase bulk and stabilize the factor protein. Advate is a *third-generation* recombinant product. Third-generation products use no human or animal protein in the production process or final product. Pfizer's Xyntha is also a third-generation recombinant product. Kogenate FS is a *second-generation* product, using animal-derived materials in the culture medium but no human albumin as a stabilizer. Instead, it uses sucrose as a stabilizer (FS means *formulated with sucrose*). Helixate FS is distributed by CSL Behring and is identical in formulation to Kogenate FS. That's because they are the same product: Bayer manufactures Kogenate FS, and then sells some to CSL Behring to be relabeled and sold as Helixate FS.

About 90% of hemophilia B patients use the only recombinant factor IX product available: BeneFIX®, made by Pfizer. Only one recombinant product is available for patients with inhibitors: NovoSeven® RT, recombinant factor VIIa, produced by Novo Nordisk.

Plasma-derived products

The 10% of American patients who use plasma-derived factor VIII products also have choices. Baxter produces Hemofil M, Grifols produces Alphanate, CLS Behring produces Monoclate-P®, and Talecris produces Koate®-DVI. For plasma-derived factor IX, hemophilia B patients can choose between CSL Behring's Mononine® and Grifols' AlphaNine® SD. Inhibitor patients can use FEIBA VH, made by Baxter.

Until recently, VWD patients had only one FDA-approved product: plasma-derived Humate-P, manufactured by CSL Behring. But last year Grifols' Alphanate, which contains VWF, was also FDA-indicated for treating congenital VWD during surgery or other invasive procedures. And of course, Octapharma's wilate, a new plasma-derived factor VIII/VWF concentrate, was just approved in America for VWD patients.

Considering the plethora of products, you'd think that any company would be crazy to enter the US market, or even to branch into another market by, for example, making an inhibitor product when we already have two. There are research costs, expensive production facilities, regulatory hurdles, and competition. And it's not easy to convince factor consumers to switch products unless the new product is seen as a major advancement or is a lot less expensive. We're usually reluctant to switch. Many of us take a "wait and see" approach.

But new products are coming: some from foreign companies, and others from companies already established here. And it appears that some companies are pushing into markets outside their established focus.

What's Driving New Product Creation?

Families and patients with bleeding disorders have long hoped for a cure. But with gene therapy progressing slowly, we wait for the next best thing: better or more convenient factor concentrates. In the past few years, we've seen products with an increased range of assays, from 250 IU up to 3,000 IU vials for convenient factor reconstitution.

Name Changes: From A(lpha) to Z(LB)

It's good to know the origins of the company that provides your factor. Some companies have merged, been acquired, or spun off since 1990, changing names along the way.

Armor Pharmaceutical → Centeon → Aventis Behring → ZLB Behring → **CLS Behring**

Cutter → Miles Laboratories → **Bayer**

Bayer (plasma division) → **Talecris**

Genetics Institute → Wyeth → **Pfizer**

Alpha → **Grifols**

And we've seen new third-generation recombinant products. Some new products feature tamper-resistant and anti-counterfeit packaging. Many offer lower infusion volumes and needleless reconstitution devices, and all offer room-temperature storage.

But one major concern has prompted a closer look at products: the formation of inhibitors. Some experts believe it's possible that recombinant products, which are ultrapure and contain no extraneous proteins, may not be readily recognized by the body, and may trigger inhibitor formation.[2] On the other hand, some studies have found no increased risk of inhibitors from recombinant products.[3]

Plasma-derived products that also contain VWF may have a positive role to play in immune tolerance induction (ITI), which attempts to overwhelm the inhibitor and desensitize the body so it stops producing inhibitors. Consequently, the demand for plasma-derived factor VIII with VWF has grown during the past few years, mainly because of its potential to help overcome inhibitors. Inhibitor eradication and VWD treatment continue to drive the demand for plasma-derived factor VIII.

Yet the bleeding disorder community has a long memory. Fear of viral infection keeps groups like Committee of Ten Thousand (COTT) and National Hemophilia Foundation (NHF) wary of the trend to expand support for plasma-derived products. But manufacturers of both recombinant and plasma-derived products are gambling on continued viral transmission safety, a growing market, and increasingly savvy consumers. They're preparing a wide array of bleeding disorder products for the new decade.

Most Likely New Product: Long-Acting Factor VIII

The next big breakthrough in hemophilia products? Long-acting factor is a probable candidate. Currently, the half-life of factor – the time in which half the amount of infused factor is used by the body – requires that factor be infused daily during an active bleed, and several times a week for prophylaxis. Factor VIII has a half-life of about 12 hours: after 12 hours, about half the factor is gone. After another 12 hours (24 hours after infusing) another half of the factor is gone, leaving only one-quarter active, and so on. Factor IX has a longer half-life, about 24 hours. Once factor IX is infused, the body begins to degrade the factor, so that half of its activity is consumed for each subsequent 24-hour time period until all the factor IX is used up. This means many infusions for severe or persistent bleeds.

With long-acting factor, a single infusion will last much longer than it does now, possibly even a week. The benefits? Fewer infusions and fewer needlesticks. And we hope that will mean reduced joint damage and a more normal life.

Currently, two companies are testing long-acting factor VIII. Baxter, which has the largest share of the recombinant factor VIII market, is studying multiple approaches to a longer-acting recombinant factor VIII product. One of the companies Baxter is partnering with is biopharmaceutical company Nektar Therapeutics, the leader in PEGylation technology (PEG stands for *polyethylene glycol*). This technology packages factor and protects it from being degraded in the bloodstream, so it survives longer and stays active. Baxter reports preclinical data showing that PEGylation gives

recombinant factor VIII a statistically significant longer half-life, about two to four times as long as regular recombinant factor VIII.[4]

PEGylation technology is used in many billion-dollar marketed drugs, but it isn't the only technology being researched for extending the half-life of factor. An alternative – and possibly better – technology to create long-acting factor is PolyXen. PolyXen technology uses one of the body's own natural materials, *polysialic acid*, a substance that coats most of the body's cells. PolyXen prolongs the life of an active drug in the bloodstream. Currently, Baxter is collaborating with Lipoxen, a British biotechnology company, to use its PolyXen technology in the development of another new long-acting factor VIII product.

Meanwhile, Bayer has been conducting clinical trials, called the Liplong Study, of its long-acting version of Kogenate FS. Bayer uses technology that encapuslates factor in tiny fat bubbles, called *liposomes*, to protect it from degrading in the bloodstream. Bayer is also applying PEGylation technology to develop another long-acting recombinant factor VIII molecule. This is now in preclinical studies.

Improved Cell Lines, Changing Markets

Novo Nordisk is best known for NovoSeven RT, a recombinant factor VIIa bypassing agent for inhibitor patients. But the company is now looking at other markets, particularly the non-inhibitor hemophilia A market. It's developing a recombinant factor VIII produced and formulated without animal or human-derived materials: a third-generation product. NovoEight is currently in a global phase III clinical trial. If all goes well, it might reach the market in 2012, becoming a direct competitor of Advate and Xyntha. And last year, Novo Nordisk also began developing long-acting factor VIII products.

Octapharma is known for its plasma-derived products and recently entered the American VWD market. The company is now pursuing the first recombinant factor VIII therapy produced from a *human* cell line – something never done before. A product could be available in three to five years. Currently, recombinant products are made from hamster cell lines. Octapharma believes that proteins of human origin may be recognized by a patient's immune system better than proteins from cell lines of other mammals. The reasoning is that products made from human cell lines may lower the chance of inhibitors, though this has yet to be clinically proved.

Talecris, maker of the plasma-derived factor VIII product Koate-DVI, is staying within its market, hemophilia A. But it's also looking to expand into recombinants, and, like Octapharma, wants to develop purely human recombinant products. Talecris has licensed a cell line – PER.C6®, derived from a single human retina cell – from Dutch biotech company Crucell.

Clinical Trial Phases

Most clinical trials, or studies, are designated as phase I, II, III, or IV, based on the questions the study seeks to answer.

Phase I: Researchers test a new drug or treatment in a small group of people (20–80) for the first time to evaluate safety, determine a safe dosage range, and identify side effects.

Phase II: Researchers give the drug or treatment to a larger group of people (100–300) to see if it can demonstrate effectiveness in patients, and to further evaluate safety.

Phase III: Researchers give the drug or treatment to an even larger group of people (1,000–3,000) to confirm effectiveness over a broad range of patients, monitor side effects, compare to commonly used treatments, and collect information to promote safe use.

Phase IV: Post-marketing studies provide more information, including the drug or treatment's risks, benefits, and best use.

These phases are defined by the US Food and Drug Administration in the Code of Federal Regulations.

For more information: clinicaltrials.gov

Recoly N.V., a Netherlands Antilles biotechnology company, has new a technology called NecLip (*non-encapsulating liposomes*), which could change the economics of the entire factor VIII market. Why? Because NecLip is designed to create a long-acting factor from either recombinant or plasma-derived products. NecLip has already been licensed to Bayer for Kogenate FS. But also in Recoly's pipeline are two products: plasma-derived LongAte for factor VIII deficient patients, and recombinant factor VIIa LongSeven for inhibitor patients.

Pipeline: Factor IX

A long-acting factor IX product could soon be a reality. Pfizer has signed deals with Nautilus Biotech and MediVas to develop long-acting factor IX proteins, possibly delivered subcutaneously (under the skin) or orally.[5]

Biogen Idec purchased Syntonix Pharmaceuticals to use Syntonix's technologies for long-acting factor, possibly even administered through the lungs. Biogen Idec's major product is rFIXFc, a long-acting factor IX product. rFIXFc is currently in phase II clinical trials.[6]

CSL Behring is developing a recombinant factor IX product, and recently announced that it has established the manufacturing cell line. The new product, still in a preclinical stage, will be made through albumin-fusion technology. This technology creates a long-acting factor through *genetic fusion*, or joining the DNA of two genes: in this case, the gene that expresses, or secretes, human albumin is fused to the gene that expresses factor IX. The newly created, long recombinant protein has recombinant albumin at one end and recombinant factor IX at the other. The half-life of this new protein in the bloodstream is days long, like albumin, rather than hours long, like factor IX. When this protein is activated for clotting, the albumin portion breaks off and the activated factor IX portion works like any other activated factor IX. No modifications, like PEGylation, to this new molecule are needed to achieve the longer half-life after it is purified.

Inspiration Biopharmaceuticals is a fairly new company with a low profile – until recently. It was founded in 2004 by John Taylor of New York and Scott Martin of Texas, two fathers of children with hemophilia B. Taylor and Scott are tackling the factor IX market, with a recombinant factor IX product for hemophilia B called IB1001, now in phase III clinical trials. IB1001 is manufactured in a way that increases cell-line productivity and so decreases cost of production – possibly translating to a lower price per unit for consumers. Inspiration is also applying its lower-cost technology to recombinant factor VIII, with a product that is currently in preclinical trials.

Pipeline: Recombinant VWD Products

The only US market currently without a recombinant product is VWD. People with VWD currently use Humate-P or Alphanate, and now wilate. All three are plasma-derived factor VIII products containing VWF.[7]

Although Baxter currently markets only factor VIII products for hemophilia patients, it is exploring the VWD market. The company has initiated a clinical trial, now in phase I, of its recombinant VWF product for patients with type 3 VWD and other VWD patients who don't respond to or can't receive *desmopressin*, a synthetic hormone that promotes the release of natural stores of VWF.

Pipeline: Inhibitors

Long-acting factor for inhibitor patients is also in the works. Novo Nordisk has begun a phase I clinical trial of glycoPEGylated factor VIIa, a long-acting version of NovoSeven RT. This is especially welcome: currently, the dosage recommendation for NovoSeven RT is every two hours.

CSL Behring is partnering with Novozymes, a Danish biotech company, to apply a new technology to create a long-acting factor VIIa. The new product albufuse™ extends the half-life through genetic fusion of factor VIIa to recombinant human albumin. Pre-clinical data[8] suggests that the half-life of the factor VIIa was increased six to nine times over the half-life of infused recombinant factor VIIa.

Pfizer and Catalyst Biosciences are planning a worldwide collaboration, with a goal of discovering and developing recombinant factor VIIa products for patients with hemophilia and inhibitors, and other bleeding conditions.

And finally, Inspiration has teamed up with Ipsen, a French biotech company, to develop the first recombinant porcine (pig) factor VIII product, called OBI-1. Until 2004, inhibitor patients could use Hyate:C®, a porcine factor VIII made by Ipsen from pooled porcine plasma, to treat acute bleeding on a limited basis. The product was eventually discontinued. Recombinant porcine factor VIII could present an effective alternative to bypassing agents for treating inhibitor patients with acute bleeds.

Pipeline: Transgenic Animals

Manufacturing factor is expensive. Recombinant factor is produced in genetically engineered Chinese hamster ovary cells or baby hamster kidney cells into which the human gene for a clotting factor has been inserted. The cells with the recombinant DNA are then grown in big stainless steel vats called *bioreactors*. A cell-culture factory like this can cost hundreds of millions to build.

Pipeline or Pipe Dreams?

Better Blood-Clotting Products In Research

Manufacturer	Product	Feature	Partner	Status
Factor VIII				
Baxter	rFVIII	long acting	Nektar Therapeutics	preclinical
Bayer	rFVIII	long acting	none	preclinical
Biogen Idec	rFVIII	long acting	Swedish Orphan Biovitrum	phase I/II
Novo Nordisk	rFVIII	no animal/human derived materials	none	phase III
Talecris	rFVIII	human cell line	Crucell	preclinical
Octapharma	rFVIII	human cell line	none	phase I/II
Recoly	pdFVIII	long acting	Bayer	phase I/II
Pfizer	rFVIII	long acting	none	preclinical
Inspiration	rFVIII	low cost	Ipsen	preclinical
Genavia Therapeutics	rFVIII	low cost, transgenic	Origen Therapeutics	preclinical
Factor IX				
Pfizer	rFIX	long acting	Nautilus Biotech/ MediVas	preclinical
Biogen Idec	rFIX	long acting	Swedish Orphan Biovitrum	preclinical
CSL Behring	rFIX	long acting	none	preclinical
Novo Nordisk	rFIX	long acting	none	phase I
Inspiration	rFIX	low cost	Ipsen	phase III
GTC Biotherapeutics	rFIX	low cost, transgenic	LFB Biotechnologies	preclinical
VWD				
Baxter	rVWF	recombinant	none	phase I
Inhibitors				
Novo Nordisk	rFVIIa	long acting	Neose Technologies	phase II
CSL Behring	rFVIIa	long acting	Novozymes	preclinical
Pfizer	rFVIIa	long acting	Catalyst Biosciences	preclinical
Inspiration	rFVIIIa	low cost	Ipsen	preclinical
Inspiration	rFVIII	recombinant porcine	Ipsen	phase III
GTC Biotherapeutics	rFVIIa	low cost, transgenic	LFB Biotechnologies	preclinical
Recoly	rFVIIa	long acting	none	phase I/II

The cost of factor production eventually translates into huge insurance costs: the average American hemophilia patient spends from $60,000 to $150,000 on factor annually.[9] We all want a less expensive brand of factor. One way to lower costs is to increase production without increasing production cost. The result? More factor for the same money, and lower per-unit prices. This has led to a new area of development: transgenic animals. Cows, mice, sheep, rabbits, pigs and chickens bred especially to express factor through their milk or in their eggs.

How does it work? Transgenic animals are bred to carry genetic material containing human DNA that will produce a certain human therapeutic protein, such as factor. Because they have the genetic information, the animals can express these proteins in their milk. Once the proteins are produced, they can be purified from the milk and used in drugs.[10] The transgenic-animal-based technology could allow biotech companies to produce drugs more economically, perhaps reducing costs to 20% of the current market price.

Transgenic animals are already being commercialized. In February 2009, the FDA approved ATryn®, an anticoagulant therapy produced in the milk of genetically engineered goats. The product prevents blood clots in people with hereditary antithrombin deficiency, a rare coagulation disorder. ATryn, produced by GTC Biotherapeutics, Inc., of Massachusetts, is the first approved drug using genetically engineered animals.

Is hemophilia next? GTC is experimenting with transgenic goats, rabbits and pigs that may eventually express factor in the animal's milk. The company is partnering with LFB Biotechnologies of France to develop a transgenic human recombinant factor VIIa and a human recombinant factor IX excreted in the milk of transgenic pigs. Although these transgenic recombinant factors are produced by animals, after purification they are analyzed for structure, purity and activity, and are held to the same standards as any other recombinant protein.

Mammals aren't the only transgenic animals involved in hemophilia. Last year two biotech companies, Origen Therapeutics and Genavia Therapeutics, teamed up to develop therapies via transgenic animals for disorders such as hemophilia. Origen's technology uses transgenic chickens that synthesize human proteins in egg white. One of the proteins slated for development by Origen is factor VIII.

Pipeline or Pipe Dreams?

It's an exciting time for the bleeding disorder community. Research and exploration could give us products that require fewer infusions, last longer in the bloodstream, are safer and less likely to cause inhibitors, and possibly are even cheaper. Yet this happens at a time when insurers are trying to lower healthcare costs, sometimes even attempting to limit product choice. So far it's unclear how products in the pipeline will affect remibursement. Will new products lower costs through competition, or raise costs to recoup research dollars?

We know that new products benefit our community. We have demanded

newer, better, safer products. And we've enjoyed the results. Not all of the products we've discussed here will pan out: some might fail their clinical trials, some might not survive commercially. In fact, as PEN went to press, the global LipLong study by Bayer was terminated because of unsuccessful results. But the race is on for better products, and in time, we can expect more product choices to improve our health and brighten our community's future.

Laurie Kelley is president of LA Kelley Communications. Chris Lamb is president and CEO of BioSolutions Consulting Services.
The authors wish to thank Paul Clement for his research, and for his scientific and editorial input.

1. *Indication* means that a product is approved by the US FDA for a specific purpose. Using a drug for a "non-indicated" purpose is often referred to as *off-label* use, and is done at the discretion of the treating physician. 2. Goudemand and colleagues (Blood 2006 107:46) found a 2.4-fold greater risk in patients treated with recombinant factor VIII than in those treated with a VWF-containing plasma factor VIII concentrate. Chalmers and colleagues (*Haemophilia* 2007 13:149) found a 1.8-fold greater risk in patients treated with recombinant factor VIII than in those treated with VWF-containing plasma concentrates. 3. These studies suggest that the apparent higher rate of inhibitors for patients using recombinant products is due to *transient* inhibitors that would not have been detected during the less-frequent testing in clinical trials of plasma-derived products. Transient inhibitors are low-responding inhibitors that sometimes disappear spontaneously after weeks or months. In "Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study" (*Blood* 2007 109:4693–97) Samantha C. Gou and colleagues reported finding no difference in immunogenicity between these two types of factor VIII products. 4. Metzner, H. J., T. Weimer, U. Kronthaler, Lang, W., and Schulte, S. 2009. Genetic fusion to albumin improves the pharmacokinetic properties of factor IX. *Journal of Thrombosis and Haemostasis* 102/4:634–644. 5. Subcutaneous injection of a factor molecule is not an option for factor VIII because factor VIII is a much larger protein than factor IX. 6. Syntonix is pursuing other early-stage programs, including a long-acting factor VIII, with the potential to improve the treatment of hemophilia A. 7. Wilate is a higher purity product; the others are intermediate purity, manufactured originally to treat hemophilia A. Wilate is manufactured specifically to treat VWD, and contains fewer (almost no) unwanted proteins, giving it a higher specific activity. *Specific activity* is the term used to measure how active factor is in the blood. 8. "CSL Behring study in animal models shows feasibility of developing a half-life extended recombinant FVIIa that retains biologic activity." Paper presented at American Society of Hematologists, 49th Annual Meeting, Atlanta, GA, December 5, 2007. CSL Behring press release. 9. www.hemophilia.org 10. Purifying factor VIII and factor IX from milk has been a challenge. Milk contains more than 30 proteases (enzymes that break down proteins) that immediately start degrading the factor (especially factor VIII). And it's difficult to purify factor from the multitude of other proteins in milk.

headlines

manufacturer

Baxter's New Scholarship Program

Baxter Healthcare Corporation recently launched Education Advantage, an innovative scholarship program to promote career development and to encourage proactive health management and community involvement among people with hemophilia A. Teenagers and adults with hemophilia A, including those with inhibitors, are eligible for the program regardless of which brand of factor VIII therapy they use. Deadline for applications: April 1. Why this matters: Encourage your teen or young adult with hemophilia to apply for financial support.

For information: www.myeducationadvantage.com

Pfizer Aquires Wyeth

On October 15, 2009, Pfizer, the largest pharmaceutical company in the world, acquired Wyeth, including its hemophilia products division. Why this matters: Patients who use BeneFIX and Xyntha should see no change in services or products. Eventually, product vials will carry the Pfizer name.

For information: www.pfizer.com

New Drug Treats Heavy Bleeding

The FDA has approved tranexamic acid, under the brand name Lysteda™, to be used for treating heavy menstrual bleeding (menorrhagia). Produced by Xanodyne Pharmaceuticals, Inc., Lysteda slows the breakdown of clots, reducing bleeding. Previously used as an injectable, Lysteda is now available in tablet form. Why this matters: Lysteda may be helpful in treating VWD.

For information: contact your gynecologist and HTC

New VWD Product from Swiss Company Octapharma

wilate®

The US FDA has approved wilate® for the treatment of spontaneous and trauma-induced bleeding episodes in patients with all types of von Willebrand disease (VWD). Wilate is a high-purity, double virally inactivated factor concentrate. No albumin is added as a stabilizer. Wilate is exclusively derived from large pools of human plasma collected in FDA-approved plasma donation centers. Why this matters: A higher-purity VWD product may mean lower infusion volumes or fewer adverse reactions.

For information: contact your HTC

nonprofit

HFA Annual Symposium

Hemophilia Federation of America will hold its annual symposium April 23–25, 2010, in Kansas City, Missouri. Community members and industry reps meet for education, networking and advocacy. Why this matters: It's a great venue for getting educated and involved in the bleeding disorder community.

For information: 800-230-9797

science

Ataluren Trial in Hemophilia Patients with Nonsense Mutations

PTC Therapeutics, Inc. announced a phase IIa clinical trial of Ataluren PTC124®, an investigational new oral drug, in patients with hemophilia who have a type of genetic mutation known as a *nonsense mutation*, in which formation of the factor molecule stops prematurely, resulting in a shortened and nonfunctional protein. Ataluren is designed to allow the ribosome to ignore this premature stop signal and continue forming a functional protein. The trial consists of two 14-day treatments at two different dose levels. The primary goal is to determine whether Ataluren can safely improve factor VIII and IX functioning. As an oral therapy, Ataluren has potential as a noninvasive treatment option. Why this matters: Ataluren could be a viable future treatment for some people with hemophilia.

For information: www.ptcbio.com

global

Pfizer Donates 40 million IU to WFH

Pfizer has pledged more than 40 million IU of factor concentrates to the World Federation of Hemophilia (WFH). This is the largest donation ever made to the WFH Humanitarian Aid Program. Why this matters: The donation will bring lifesaving treatment to many people with hemophilia around the world who don't have adequate treatment.

Project SHARE Ships $4 Million in Factor

Project SHARE (Supplying Hemophilia Aid and Relief), a humanitarian program of LA Kelley Communications, donated over 4 million IU of factor to more than 30 countries in 2009. Why this matters: If you have unused or unwanted factor, your donation can help save a life. (See Project SHARE, p. 6.)

For information: share@kelleycom.com

Chinese Hemophilic Petitioners Hospitalized

On December 29, 2009, at least 20 people with hemophilia and their relatives protested at Sinopharm, the state pharmaceutical group, in Beijing. They were petitioning for a compensation package that provides each patient infected with HIV from Sinopharm's products $146 and six units of factor VIII to get them through the next four months. At least three people were hospitalized in clashes with police. Petitioners asked Sinopharm to develop a new compensation package by April 2010. Sinopharm rejected the requests, offering each patient $732 in "consolation" money. The patients rejected this, claiming that it looks like charity and not a compensation. Why this matters: Developing countries must still struggle for compensation from their governments over contaminated blood products.

advocacy

CSL Behring's LEAD Gives $87,000 for Advocacy

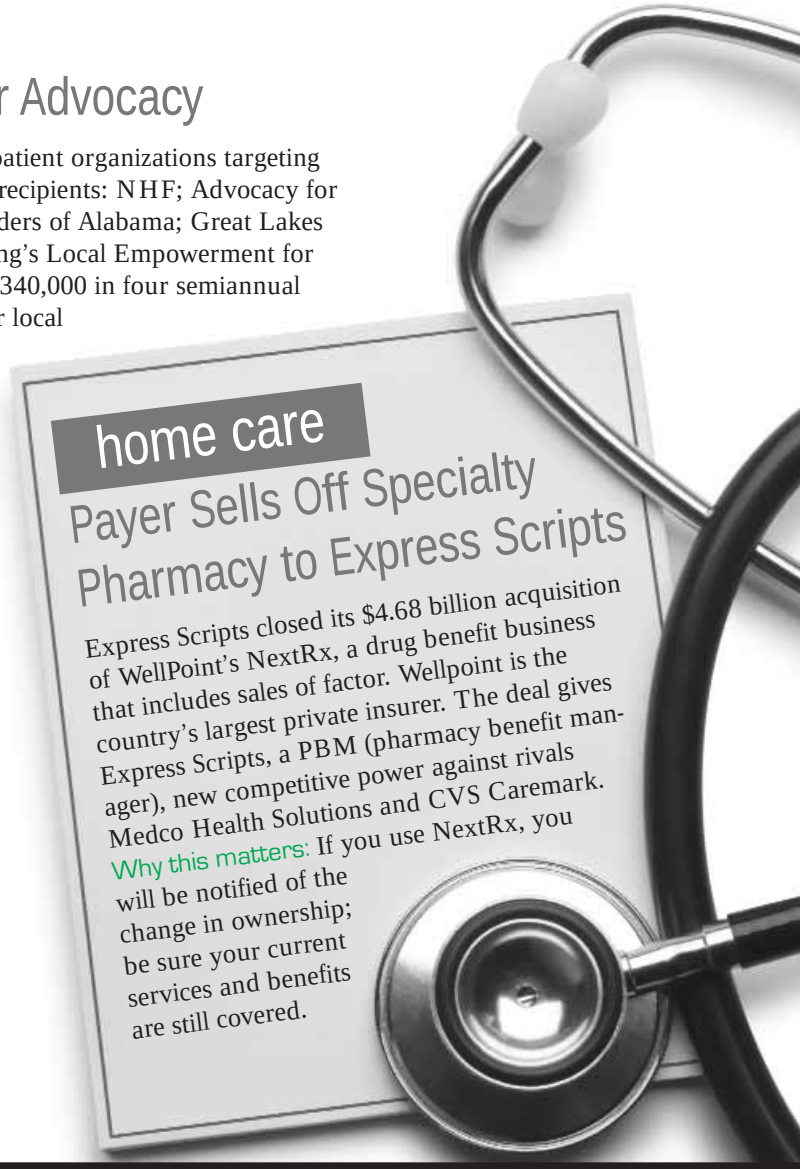
CSL Behring has awarded $87,000 in advocacy grants to four US patient organizations targeting people with bleeding, immune, and other chronic disorders. Grant recipients: NHF; Advocacy for Patients with Chronic Illness, Inc.; Hemophilia and Bleeding Disorders of Alabama; Great Lakes Hemophilia Foundation. Grants were awarded through CSL Behring's Local Empowerment for Advocacy Development program. LEAD has awarded more than $340,000 in four semiannual grant cycles. Next deadline: April 30, 2010. Why this matters: Your local hemophilia nonprofit can benefit from a grant, which may help safeguard your insurance.

For information: www.cslbehring.com/leadgrants

Visit the Capitol and Make a Difference

NHF Washington Days will be held February 24–25, 2010, in our nation's capitol. Families and individuals play a key role during the two-day gathering, meeting with their state senators and representatives to discuss issues such as access to care and treatment and eliminating lifetime caps in insurance policies. Why this matters: If you've ever wondered how you can make a difference, here's your chance. By telling your story in your own words, you put a face on real issues that affect everyone dealing with bleeding disorders.

For information: contact your local hemophilia chapter and www.hemophilia.org



home care

Payer Sells Off Specialty Pharmacy to Express Scripts

Express Scripts closed its $4.68 billion acquisition of WellPoint's NextRx, a drug benefit business that includes sales of factor. Wellpoint is the country's largest private insurer. The deal gives Express Scripts, a PBM (pharmacy benefit manager), new competitive power against rivals Medco Health Solutions and CVS Caremark. Why this matters: If you use NextRx, you will be notified of the change in ownership; be sure your current services and benefits are still covered.

Insights... from p. 4

bleeds stop faster when they use *both* products – alternately infusing one product and the other product. This practice is considered off-label, is not endorsed by Baxter or Novo Nordisk, and may increase the risk of unwanted blood clots.

The vapor-heat viral inactivation process used on FEIBA does an excellent job of inactivating lipid-enveloped viruses such as HIV and HCV. But despite FEIBA's 30-year safety record, some people worry about the small risk that the product might transmit some new, still undiscovered, non-enveloped virus that is less affected by viral inactivation processes. For some high responders (whose inhibitor titer is above 5 BU and rises several days after a factor infusion) the factor VIII or IX in FEIBA can stimulate the immune system, producing an *anamnestic response*, causing the inhibitor level to spike several days after the infusion – not good if you are on immune tolerance induction (ITI) or preparing to start ITI. Other people with inhibitors have allergic reactions to FEIBA. About half of hemophilia B patients with inhibitors also develop allergies to factor IX at the same time they develop the inhibitor. Some of these allergic reactions are severe, and it's not uncommon for some people to experience anaphylactic shock, a life-threatening allergic reaction, when exposed to factor IX. These people can't use FEIBA because it contains factor IX, which triggers the allergic reaction.

Both FEIBA and NovoSeven RT also carry the low but potential risk of a dangerous, sometimes fatal side effect, *disseminated intravascular coagulation* (DIC), in which unwanted clotting occurs throughout the body. This is believed to be a risk mainly if the products are infused more often than recommended, at higher than recommended doses, for a prolonged time, or when the patient has suffered certain types of injuries, such as a crush injury.

Treating bleeding episodes in people with inhibitors is always a challenge. For patients who are high responders and have not successfully completed ITI, bypassing agents are the mainstay for treating bleeds.[2] And patients should continue to use FEIBA or NovoSeven RT with confidence, as recommended by their hemophilia treatment center (HTC) hematologist. The future of inhibitor treatment looks bright: as you'll read in this issue of PEN, research into the cause and treatment of inhibitors is at an unsurpassed level, and new, more effective products are in the pipeline.

1. Lipid-enveloped viruses have a fatty outer layer and include all the blood-borne viruses that cause serious diseases such as HIV and HCV. 2. People with inhibitors should always be seen at an HTC, where physicians have the expertise to properly treat bleeds in the presence of inhibitors.

Transitions... from p. 5

Greg also encourages patients to attend hemophilia meetings and events, both for their educational value and for the chance to network. He believes that some of the best resources available are other members of the community. "There's nothing like talking with people who have experienced the same anxieties you have, in order to learn how they dealt with them."

For instance, when Michael had resigned himself to the fact that he might never get married or have a family, he happened to read an article by Shawn Decker that changed everything.

Shawn, like Michael, has hemophilia and HIV, and the article was about Shawn and his wife. Inspired by what he'd read, Michael contacted Shawn. Their conversation boosted Michael's confidence and self-esteem and gave him a better perspective on his health conditions.

Shortly after, Michael met a young woman named Sandy. Armed with renewed confidence, Michael pursued the relationship. Three years later they were married.

Keeping It All in Perspective

If you're not dating, and hemophilia is the reason, it's time to remedy the situation by building your confidence.

The best place to start is within the hemophilia community. Talk to guys you know from summer camp or the HTC. Ask open, honest questions: How did hemophilia impact their dating lives? How did girls react when they brought up hemophilia? If you'd rather not talk with your peers, consider sitting down with your HTC's social worker to come up with a game plan.

However you choose to go about it, gather advice and information from all the resources available. You'll grow more comfortable with your hemophilia and improve your perspective on where it fits in your life. Sure, at times hemophilia might be an overwhelming part of your life, but it is simply that – a *part* of your life.

Both Michael and his wife Sandy keep his hemophilia and HIV in perspective. Sandy acknowledges that his health sometimes affects decisions they make, but she stresses, "Michael's health is not the defining aspect of our relationship."

Once you've achieved a level of self-esteem where you don't let hemophilia define you – or determine how others define you – you're better prepared to take that first step across the room to talk to that interesting girl.

But keep in mind that you may never get the chance to talk about your hemophilia. She might take one look at your clothes and turn the other way.

Inbox... from p. 2

THANK YOU FOR THE IN-DEPTH REVIEW of home care, 340Bs and insurers. We join you in your plea for people with hemophilia and their families to have a united voice of advocacy.

Barbara Chang
California

YOUR ARTICLE APPEARS TO POINT A finger at insurance companies as "profit takers" in the hemophilia market. I am a CPA and want to point out that there is no way insurance companies can be making a profit on hemophilia patients. *Profit* is strictly defined as an excess of revenue over expenses. For an insurance company to make a profit on hemophilia care, the company would have to bring in more revenue than it expends on each patient. In any chronic illness, and especially in hemophilia treatment, that is virtually impossible, as there is no way individual patients are able to pay in premiums more than the cost of their care. Even if insurers enter the pharmacy market and retain a percentage of the cost of the medications, that is more of a cost savings for the insurer, not a profit generator. To say that insurers should be passing on the profits from supplying factor is misleading, as there are no profits being made by insurers on hemophilia treatment. Insurers generate profit by taking in more premiums than they pay out for care. Insurance generally works because *risk* (defined as the potential to have to pay more than you take in) is spread over a diverse group of individuals. The insurer "bets" that some individuals will pay more in premiums than they require in care, and those profits can be used to offset the losses generated by the individuals who require more treatment costs than they can pay in premiums. Hemophilia is certainly a loss generator for any insurer. Any way that an insurer can offset the losses without raising premiums for everyone should not be viewed as inherently bad. If saving money on providing factor products is one way for this to happen, then the hemophilia community should understand why this is necessary and try to address the underlying causes of the high cost of care.

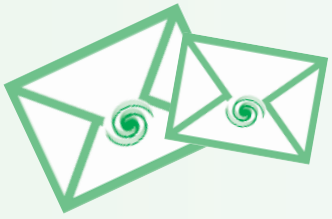
As a CPA, I believe the community needs to look at the complete factor supply picture to understand how profits and losses are generated in this industry. This would start with the development and manufacture of the factor products themselves. One thing you fail to examine in your [feature] article is the profits generated by the factor manufacturers. The manufacturer prices are setting the baseline for all of the additional costs (or cost savings) that eventually are generated. You correctly state that hemophilia treatment is a business. The hemophilia community needs to understand how that business operates and determine how to best position the community to work within those constraints.

As a community, we have been very lucky to have almost unlimited access to almost any factor products we desire. We have seen vast improvements in the past 20 years in the quality and safety of these products. Maybe we all need to be a little less selfish at this point and start figuring out how our community can start cooperating with the rest of society to address how to make this more affordable for everyone.

Debbie Porter
California

I HAVE TRIED TO BE A GOOD INSURANCE advocate. My husband is a retired marine and the benefits have just been restricted. I am trying to contact patients with bleeding disorders who are active duty or retired and on the Tricare [military insurance] benefit. We are such a small number, to both the Tricare and hemophilia community, and I fear that future restrictions to access may occur. I enjoy your spirit, and you are my inspiration for advocacy.

Colleen Pascua
California



Project SHARE

I CANNOT THANK YOU ENOUGH, together with the people behind Project SHARE, for the assistance you have given my son. May God continue to bless you!

Joane Marianito
Philippines

THERE ARE SIX IN my family. My elder brother Jagat Lal (Monsoon) and I both have severe hemophilia A. Thanks to you all for saving my life. I was close to death with a high-titer inhibitor (38.4 BU). Thank you so much for donating NovoSeven for me. Though I lost my leg, collective effort has given me a new life, and I thank you all for the valuable contribution from every sector.

Jagat Man Rajbahak
Nepal

PROJECT SHARE IS THE LARGEST SOURCE of factor for people with hemophilia in Kenya. For this, we are forever grateful to all the institutions that donate factor. Help us add life to the lives of our children. Thank you Project SHARE.

Maureen Miruka
Kenya

thank you

I'M VERY GLAD THAT PROJECT SHARE is now on Facebook so we could freely post our pictures with my son smiling because Project SHARE helped him with his lifetime journey.

Myra Acosta
Philippines

MAY GOD BLESS YOU AND YOUR organization and show you a way to continue impacting the lives of less fortunate people in the wonderful way that you do.

Gerald Monize
Guyana

PETRU SIMONEAC PHONED ME TO SAY that he received the donation safely. He is very glad for the nine vials of 596 IU. He wants to thank you for making this Christmas a special one to him.

Sorin Jorg
Romania

I WANT TO JOIN THE BOUSSAD FELLAG family to wish Happy New Year to you and all loved ones. Thank you for all the support you provided to Boussad.

Hamid Haddou
Algeria

I AM VERY GRATEFUL TO THE ALMIGHTY for bringing people like you into my life. Thank you for your contribution, without which I can't imagine where I would be now. May the good Lord grant you peace, love and all your wishes in this new year.

Emmanuel Agyekum Fofie
Ghana

I'VE BEEN SUFFERING FROM HEMATURIA for six days already; I don't want to be admitted in the hospital; I don't want to spend my Christmas once again there.

Randolf Apnay
Philippines

Ed. note: Factor was sent so that Randolf could spend Christmas at home.

THE FIRST TIME THAT I'M ACQUAINTED about this disorder was when I met the one who showed me what "real love" is. My boyfriend Kevin Nico Marzoña, age 22, is suffering from this disorder and is discriminated against because he is deprived of good education that could help him improve his life. Every now and then, bleeding and swelling of joints causes him to stop studying. At this moment, only our prayers can help him survive. His family cannot support blood and platelet transfusions because they don't have enough resources to do so. Also, three of his siblings suffer from this disease. I beg you, from your kindest heart, to help them with what they are suffering now. I hope that you will consider this message. I pray that you can help us – any help will be appreciated. Please pray for the survival of all those who suffer from this disorder. Thank you and God bless you all.

Charito Gavadan
Philippines

HemaBlog

SOY UN JOVEN CON HEMOFILIA DE Republica Dominicana. Pertenesco a la Fundación de Apoyo al Hemofílico (FAHEM). Siempre visito su blog para enterarme de muchas informaciones importantes. Muchas gracias por este medio. Pasaba por aquí a dejarle un caluroso saludo desde la DR. Queria darle las gracias por todas las cosas que usted a hecho por nosotros los hemofiliocs.

I'm a young man who registered with FAHEM, the Dominican foundation for hemophilia. I visit your blog often to learn important information. Thanks so much for this media. And thank you for everything you've written for those of us with hemophilia.

Isaias Lora Vargas
Dominican Republic

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the hemophilia newsletter by families & for families

Inside: New Treatments in the New Decade: Longer Acting, Purely Human, and Possibly Cheaper

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Parenting Moment

If you want your children to improve,
let them overhear the nice things you say about them to others.
Dr. Haim Ginott

If a child is to keep his inborn sense of wonder, he needs the companionship of at least one adult who can share it, rediscovering with him the joy, excitement and mystery of the world we live in.
Rachel Carson

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