PEN

inside

3 **As I See It:** Transition Time
4 **Inhibitor Insights:** Should Your Child Wear a Helmet?
5 **Richard's Review:** Finding Time to Read
6 **Project SHARE:** No Distance Too Far

New Factor Concentrates

The Future Is NOW!

Paul Clement

By year's end, as many as three new hemophilia products could be on the market. Next year? Expect at least another three products, and more to follow. The most new products ever released for hemophilia treatment so close together–now filling the "pipeline"–will present choices. Should you switch products? What features might make these new products better than what you currently use? Any risks associated with switching? Should you switch right away, or wait and see?

You'll make better choices about products when you know what to look for, what your needs are, and what questions to ask your physician. But first, it helps to know more about the bleeding disorder marketplace, and your role as a customer.

The US Bleeding Disorder Market

Who are the new products targeting? Let's look at the customers in the US bleeding disorder market–the people who use clotting factor concentrates ("factor"). Most factor is used by people with hemophilia, and because hemophilia is a rare disorder, this obviously limits the size of the market and the number of customers.

Currently about 20,000 people have hemophilia in the US; about 80% of them have hemophilia A, and 3,000 to 4,000 have hemophilia B. About 400 US babies with hemophilia are born each year.

But the actual US market for factor concentrates is even smaller than these 20,000 people. That's because only people with severe hemophilia tend to use factor regularly. This means only 8,000 to 14,000 people–a very small pool of customers.

Besides hemophilia A and B, the bleeding disorder market includes two additional groups: people with hemophilia who have inhibitors, and those with von Willebrand disease (VWD), which is sometimes treated with clotting factor.

Of the 20,000 Americans with hemophilia, about 1,200 have inhibitors–antibodies created by the body's immune system that neutralize or inactivate infused factor. In people who produce high levels of inhibitors, the factor is made useless within minutes. People with low levels of inhibitors may be able to control bleeds with large doses of standard factor concentrates. But people with high levels of inhibitors need special factor concentrates called *bypassing agents* to control bleeding. Because the number of people with inhibitors is so small, they represent a *niche* market.

Von Willebrand disease is the most common bleeding disorder, affecting about 1% of the population. Of the estimated 3 million Americans with VWD, few are diagnosed. Why? Because unfortunately, VWD isn't easy to diagnose. And for most people with VWD, the symptoms are mild, so they never seek medical help or even realize they have a bleeding disorder.

There are three VWD subtypes: type 1, type 2, and type 3. Type 1 is the mildest and most common form, accounting for about 75% of cases and only rarely requiring factor for treatment. Type 2 accounts for about 20% of VWD cases, with symptoms that are also generally mild and that usually don't require a factor infusion. Type 3 is the rarest and most severe, characterized by joint and muscle bleeds. Bleeds in people with VWD type 3 are usually treated with a special type of factor VIII concentrate that also contains von Willebrand factor (VWF). Of Americans with VWD, only about 8,000 have type 3 and need regular treatment with factor.

» *page 6*

welcome

Laurie Kelley

Progress is impossible without change, wrote Irish playwright George Bernard Shaw. The bleeding disorder community has had its share of change, but has seen no real product breakthrough in about ten years. Now, that era is ending. Within the coming year, we will see massive changes in product choice as new medications enter the market. Do you know what your choices will be?

Paul Clement, father of a son with hemophilia, does an exemplary job of describing the new products and your choices as a patient or parent. Not only will we have new products within the same classes (recombinant or plasma-derived) but we'll be able to select new types of products, such as long-lasting factor. What features do you look for in a product? How do you rate one over another?

Read Paul's article and learn about your new product choices. Welcome change, but be prepared: with insurance reforms happening weekly and our entire medical system in flux, don't be left on the sidelines while decisions are made that might affect your healthcare. Heed the words of Winston Churchill: "We must take change by the hand, or rest assuredly, change will take us by the throat." Sounds dramatic, but it may be appropriate for these revolutionary times.

inbox

"The App of Your Eye" (May 2013)

What wonderful apps. It's always good to know that our community is consistently being informed and educated. We are extremely fortunate to have so many people dedicated to education, information, and awareness.

We all need to know the importance of keeping complete, accurate, up-to-date records of our infusions and bleeds. Infusion logs are a profound instrument in receiving the best care from our doctors and HTCs.

Apps like these make it easier to track infusions and bleeds; easier means people will be more likely to keep complete, accurate records. Hooray for technology!

Keeping up-to-date records of our infusions and bleeds will also benefit us in satisfying requests from our health insurance companies.

Tom Albright
Arkansas

» *page 15*

CORRECTION: PEN regrets the following omissions in the May issue: Pfizer's HemMobile became available in Android in April. HemMobile allows the user control over the sharing of his or her information. Pfizer does not collect or retain any user information; the user decides to share the information with his or her healthcare professional through reports.

PARENT EMPOWERMENT NEWSLETTER
AUGUST 2013

Editor-in-Chief Laureen A. Kelley | Science Editor Paul Clement

Contributing Writers
Richard J. Atwood • Jo Schaffel • Imran Zia

Managing Editor Sara P. Evangelos

Layout Designer Tracy Brody

Director, Project SHARE Zoraida Rosado

LA KELLEY communications, inc.

37-39 West Main Street, #8
Georgetown, MA 01833 USA
978-352-7657 • fax: 978-352-6254
info@kelleycom.com • www.kelleycom.com

Angela Castaldo

Transition Time

"How did you get that red mark on your face?" I asked my nine-and-a-half-year-old son, Luke. He stared back at me. I continued, "Did you get a soccer ball in the face?"

These questions came as I was in my neighbor's backyard, holding my five-month-old daughter. Luke was sensitive about his hemophilia, so I tried to be as nonchalant as I could while looking at a huge red mark on his cheek. He finally answered, "I fell off my bike."

My eyes widened, but he quickly responded, "I'm okay. I don't need factor."

I realized that Luke had come home from a bike ride with his brother and dad an hour ago, and that his face must have hit the pavement then. My mind whirled.

I excused myself from my neighbor as politely as possible, not wanting to be rude.

Then, after interrogating my husband on the nature of the fall and remembering that Luke's last prophy dose was just a little more than 30 hours ago, I began to calm down. I called Luke over and looked at his face. The injury was over the cheekbone. I felt a large hematoma underneath, so I gave him an ice pack. "I really think we should infuse," I told Luke. "Daddy said that you hit the pavement hard."

"I'm fine!" Luke responded hotly.

I thought quickly. "Okay," I said, "it's not in a joint or too near something major on your head. Your cheek may swell up, but you have room there. So if you feel it getting bigger, we really need to infuse."

"Okay, Mom."

I questioned if I was doing the right thing. But I also knew from other moms that it was normal for a child with hemophilia to push back. Luke needed to start taking ownership of his disorder–but was now the time, at age nine-and-a-half?

After putting more ice on the injury before bed, and reminding myself to note the size and monitor the hematoma, I went to sleep–only to be awakened at 5:00 a.m. by my infant daughter, who needed to be fed. After the feeding, as I fell asleep, it seemed like just seconds later that Luke was standing over me saying, "I did it!"

I groggily responded, "Did what?"

"My factor!"

I was fully awake then. "You did *what*?!"

Luke stood over me with a loose tourniquet on his arm. A big grin spread across his face. My face must have registered shock.

"It's okay, Mom. Philip helped me. You told me that if the bleed in my cheek got bigger, I would need to get factor. And it *is* getting bigger, so I gave myself factor."

All that he was saying began to sink in, and I couldn't help but smile. Luke had infused himself with the help of his little seven-year-old brother, Philip. We had been training Philip to change the lines for the saline flush. Little Philip's help was supposed to reassure me that everything was okay. Now, Philip came in to my bedroom and was grinning as he received praise from his older brother.

Later, after inspecting everything and reflecting on what had happened, I realized that a transition had taken place. We had started training Luke to self-infuse when he was six. He was able to self-infuse at seven, but he still needed assistance and confidence from Mom. Now, at age nine, he could do it without Mom.

Given the consistency of gravity, chances are that Luke will experience another fall or accident. When he does, I know that he will be able to treat himself. Luke is now eleven; and as I increasingly move to the sidelines, he is stepping up to the plate and taking responsibility for his hemophilia. It may not be on Mom's timetable, but Luke is learning to diagnose and treat himself–a huge milestone in his development.

Angela Castaldo and husband Chris have four children: Luke (11), Philip (9), Simeon (6), and Aliza (2). Luke has severe hemophilia A. The family lives in a suburb of Chicago.

"You did *what*?" Luke, co-conspirator Philip, and siblings Simeon and Aliza Catsaldo (*right to left*)

Castaldo family

Jo Schaffel

Should Your Child Wear a Helmet?

Ah, toddlers. Aren't they cute? We know that to develop mentally and emotionally, toddlers need to explore their environment and experience things for themselves. But their constant drive to test boundaries often gets them into trouble. Their brains aren't developed enough to plan ahead. Their balance is poor. Their heads are large and heavy compared to the rest of their bodies, so they often fall headfirst. You know there will be plenty of falls, bumps, and bruises along the way.

If your child has inhibitors, all these "normal" bumps and bruises have the potential to become quite serious. Some parents and healthcare professionals believe that helmets can help protect young children from head bleeds. It's a decision parents will need to make: should our child wear a helmet?

"At our clinic, we approach this on a case-by-case basis," says Peg Geary, clinical hemophilia social worker at New England Hemophilia Center in Worcester, Massachusetts. "Dr. Christopher Keuker, our pediatric hematologist, and our team could find no evidence-based data that shows general use of helmets in toddlers and young children decreases the occurrence of head bleeds. Of course, we advocate the use of helmets and other appropriate safety equipment when children with hemophilia–and all children–participate in certain sports and activities with higher risks of injury to the head." Peg explains, "We start where the parents are, and give them their options as they are ready. Every family is different."

Tips for Toddlers

Here are some basic tips for parents of newborns and toddlers with hemophilia, von Willebrand disease, or another bleeding disorder.

- Tape or glue foam pads to the sharp edges of counters and coffee tables, or remove coffee tables while your child is learning to walk.
- Use baby gates to block stairs and prevent falls.
- Use netted crib covers to prevent falls out of bed.
- Place nonskid strips on the floor of the shower or bathtub. Help your child in and out of the tub until the child is old enough to manage without falling.
- Consider getting your child a big-wheel tricycle, which is more stable and closer to the ground than regular tricycles.
- Make sure your child wears a helmet when skating, bicycling, and similar activities.

Source: National Hemophilia Foundation

Yes! Better safe than sorry!

All children should wear helmets while riding bicycles, and even when active on a hardtop playground. But should children with hemophilia and inhibitors wear helmets when they are not riding bikes or playing actively? Some parents believe that absolutely, helmets are needed for most of the day.

Cazandra is one of those parents. "When my son was about two years old and in daycare, I felt it was necessary for him to wear a helmet," she reports. "His inhibitor level was very high, and the slightest bump on the head was always an event."

Part of the decision depends on your child's personality and the severity of his inhibitor. Is he the type of kid who is always running around and getting into mischief? Compared to a more sedate toddler, he might need a helmet more often.

D'Rider Photography

ShaLinda Creer and children: "I wanted him to be as safe as possible"

Parents have to balance the value of preventing injuries with the benefits of allowing their child to explore and play. Some parents who decide to use helmets feel that this gives the child enough protection to be able to explore freely without too much fear, and to take part in more activities with other children.

ShaLinda felt that a helmet would protect her now four-year-old son, Josiah. He began wearing one about three years ago, as he started to toddle around. "I wanted him to be as safe as possible, and infants tend to be very curious," she explains. "I didn't want to take the risk of an accident happening that could result in a head bleed. Our HTC doctors recommended he wear the helmet long enough until he can understand that he has to be a bit more careful than his friends."

If your child has a low titer or has started prophylaxis, you may feel that he no longer needs a helmet all the time.

Some children wear helmets only when playing ouside or at a playground,

» *page 14*

richard's review

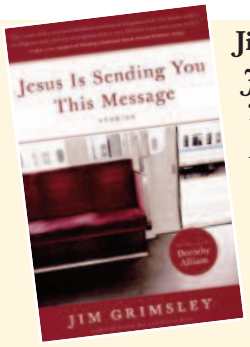
Richard J. Atwood

Finding Time to Read

It's summer! Don't we all wish we had more time to fit in some pleasure reading? Life is just too hectic.

One solution is short fiction. It's not as long as a novel, but still tells a complete story. Being compact, short fiction usually contains only the necessary ingredients to deliver its message. So it takes less time to read and can be fitted into those brief, peaceful summer interludes. But, like a potato chip, just one short story may not satisfy your reading appetite.

For your reading pleasure, I propose the following collections of short stories written by three notable authors who also happen to have hemophilia:

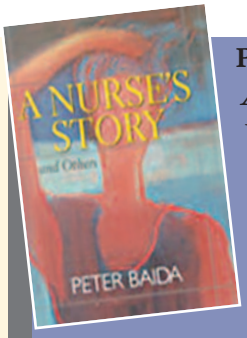


Jim Grimsley

Jesus Is Sending You This Message

Alyson Books 2008

This collection of 16 short stories is meant for mature readers. Set in locations such as Atlanta, New Orleans, and Chapel Hill, places familiar to the author, these stories take the perspectives of male and female narrators who are dealing with human experiences and hoping to find solutions. Jim Grimsley (1955–), an award-winning playwright and novelist, lives in Atlanta. Though his short stories do not mention hemophilia, Grimsley's novels *Winter Birds* (1984) and *Comfort and Joy* (1999) include protagonists who have hemophilia.

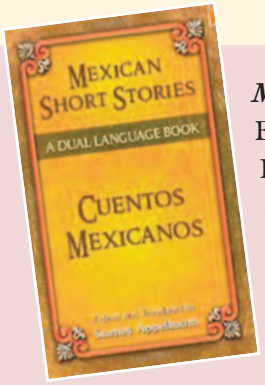


Peter Baida

A Nurse's Story and Others

University Press of Mississippi 2001

These nine short stories, all of which appeared previously in other publications, were collected and published posthumously for the author's first volume of fiction. The pleasant stories about ordinary people who confront ethical dilemmas during human experiences, with life-altering consequences, will linger with you. Peter Baida (1950–1999) worked for 20 years at Memorial Sloan-Kettering Cancer Center in New York City. His short story "A Nurse's Story" was rejected by 22 editors before being accepted for publication, and in 1999 it was awarded first place in the prestigious O. Henry Prize Stories. Regrettably, Baida was too ill due to complications from hemophilia to attend the award ceremony, and he died two months later.



Mexican Short Stories / Cuentos Mexicanos: A Dual-Language Book

Edited and translated by Stanley Appelbaum

Dover Publications 2008

Featuring stories by Manuel Guitiérrez Nájera

This anthology of eight Mexican authors contains nine short stories that were first published between 1843 and 1918. This is truly a dual-language book: the original Spanish versions and the English translations are published together. Born in Mexico City, Manuel Guitiérrez Nájera (1859–1895) worked as a journalist. For 20 years until his death, Nájera contributed over 1,500 articles, stories, and poems to 40 periodicals using 40 pseudonyms. He founded *Revista Azul* (*Blue Magazine*) in 1894 for the Spanish American school of writers stressing the genre of *modernismo*, which focused on local Mexican talent. The prolific work of Nájero is represented by two short stories in this dual-language anthology. The author died of a hemorrhage possibly induced by his hemophilia.

These three authors need to be recognized, not only because they have hemophilia, but also because their fiction is worth reading. Make some time to read their short stories this summer–or anytime!–and enjoy.

a project share story

Imran Zia

No Distance Too Far

Hemophilia Care of Pakistan

Above: A lifetime of savings to save brothers Izhar, Muneeb, Faheem, Daud, and Fazal, with Imran Zia (*second from right*). *Right*: Aquatherapy when facilities are lacking.

This is the story of five brothers, all with severe hemophilia A: Izhar, Muneeb, Faheem, Daud, and Fazal. They live in a small village called Tank, in Pakistan. Tank is about 310 miles from where I live, in Lahore, capital of the Sindh province. When I visited the brothers, it took me about eight hours to travel there by car.

All the brothers' major joints are damaged due to untreated bleeding, from the lack of factor concentrates and cryoprecipitate. When they bleed, they must travel several hours to get plasma from other cities. Our organization, Hemophilia Care of Pakistan, provides factor to the brothers in their homes for free, whenever we can find a donation.

We celebrated World Hemophilia Day on April 17 this year with these five brothers to raise awareness of the importance of physical therapy and hydrotherapy to reduce bleeding episodes. One brother, age 28, cut his leg and had a bone infection in his left knee joint. His father, a retired schoolteacher, spent his entire pension for four surgeries on his son's knees–$10,000 to purchase factor and to pay hospital expenses. A lifetime of savings!

Right now, his other son has a hematoma in his brain. We provided him with 40,000 IU of factor over ten days. Surgery is expected at any time, and he needs 40,000 IU more.*

Imran Zia has hemophilia, and is president of Hemophilia Care of Pakistan, an organization that provides medical care and social advocacy to patients with hemophilia in Pakistan.

**Project SHARE was able to donate factor for this patient's surgery.*

New Factor... from cover

Product Types

Products are bought and sold on a *market*. In the bleeding disorder market, "products" means factor. To understand what new factor products are coming to market, you first need to know what's currently available. Factor concentrates are classified in several ways. The most obvious is by factor type:

- Hemophilia A patients use factor VIII (FVIII)
- Hemophilia B patients use factor IX (FIX)
- Inhibitor patients use bypassing agents (factor VIIa [FVIIa] or FEIBA)
- VWD patients use factor VIII with VWF (VWF/FVIII complex)

All factor concentrates are also classified by the source of the factor:

- Plasma or
- Cell cultures (*recombinant* factor)

Plasma-derived factor (sometimes abbreviated *pd*) is extracted from human blood plasma collected and pooled from tens of thousands of donors.

Recombinant factor does not come from blood. It's produced by using recombinant DNA technology, in which the gene for a human clotting factor is spliced into another cell (usually a hamster cell). Large numbers of these genetically engineered cells are then grown in giant vats (bioreactors) containing a nutrient-enriched broth (growth medium). The cells secrete the factor into the growth medium, which is then harvested, and the factor is extracted. An *r* placed before the factor type indicates that it's recombinant: rFVIII, rFIX.

Recombinant FVIII is also classified as either *full length* or *B-domain deleted* (BDD). Full-length factor VIII consists of the entire factor VIII molecule. BDD factor VIII has the center section of the molecule (the B domain) removed; the B domain is not necessary for activity of the factor molecule. BDD factor is shorter than full-length factor and is easier for the genetically engineered cells being grown in the bioreactors to produce.

Finally, recombinant factors are classified into three *generations*, based on whether they contain extra human or animal proteins. First-generation recombinant factors contain added human and/or animal proteins in both the growth medium and the final product.[1] Second-generation recombinant factor concentrates contain no added human or animal proteins in the final product, but do use these proteins in the growth medium. Third-generation recombinant factor concentrates contain no added human or animal proteins in either the growth medium or the final product.

1. In most first-generation recombinant factor concentrates, such as Recombinate, human albumin from blood plasma is typically added to the final container to increase bulk and stabilize the factor.

The Manufacturers and the Current Market

The global bleeding disorder market generated $8.5 billion in sales in 2011. That's expected to grow to $11.4 billion by 2016, mainly due to increased use of prophylaxis in developed countries, as well as pharmaceutical companies' expansion of markets into underserved countries. The bleeding disorder market in the US is dominated by eight pharmaceutical companies.

Because the sale of clotting factor is profitable, the US bleeding disorder market supports a relatively large number of products, despite the small customer base. Table 1 lists factor concentrates currently available in the US. Although the majority of the products listed are plasma-derived, recombinant products account for the most sales. Recombinant products comprise almost 90% of US sales, with most patients under age 20 on recombinant products.

A Burst in New Product Development

Although many new products for bleeding disorders are coming to market in the next few years, most are being developed by current manufacturers. It's unlikely that we'll see more than two new manufacturers enter the market. Why? On average, it costs $1.2 billion to develop a new *biologic* drug (a drug made from living cells) such as a clotting factor–that's too expensive for most small companies.

Developing a new product is also risky: only 1 in 1,000 drugs in research and development ever makes it to market. It's even tough for big pharmaceutical companies with decades of experience in developing and manufacturing factor: Bayer, Baxter, Novo Nordisk, and Pfizer, all major players in the hemophilia market, each recently suspended work on one or more of their new products under development because of lack of efficacy (effectiveness) or because of increased immunogenicity (more-than-expected cases of inhibitors or allergic reactions).

Along with cost and risk, patents and FDA regulations can also be major hurdles.[2] Pharmaceutical companies can patent their new drugs and manufacturing processes, preventing other companies from copying their products for up to 20 years. Also, the FDA encourages the development of treatments for rare diseases by allowing a drug company to apply for *orphan drug* status. This status covers most clotting factors, allowing for tax breaks, fee waivers and reductions, and periods of data and marketing *exclusivity*–when the FDA will not approve a generic version of the drug for treating the same disease or condition. For biologic drugs, the period of exclusivity is seven years. These protections allow a company to recoup its investment in developing the drug, without fear of competition. The reasoning is that without such protections, most companies would be unwilling to take on the financial risk of developing a drug to treat a rare disorder if the company is unlikely to recoup its investment.[3]

So, with all these roadblocks and risks, why are almost 30 new treatments for bleeding disorders ready to enter the market in the next few years?

2. It can also be argued that treatments for many rare diseases and disorders would not exist without patents and favorable FDA regulations. 3. In June 2013, the US Supreme Court ruled that naturally occurring genes cannot be patented. This ruling immediately invalidated several thousand gene patents, but it does not apply to genetically engineered genes that have been modified by humans.

Trademarked Products

- ADVATE
- Alphanate®
- AlphaNine®
- Alprolix™
- Bebulin®
- BeneFIX®
- Corifact®
- FEIBA
- GreenGene™ F
- Helixate® FS Next Gen
- Hemofil M®
- Humate-P®
- Koate® DVI
- Kogenate® FS
- Monoclate-P®
- Mononine®
- NovoSeven® RT
- Novo Thirteen™
- Profilnine®
- RECOMBINATE
- RIXUBIS
- wilate®
- Xyntha®

New products are listed in green.

Table 1. Current US Factor Products on Market

MANUFACTURER / DISTRIBUTOR	PRODUCT: Recombinant – Factor VIII	Recombinant – Factor IX	Recombinant – Inhibitor	Recombinant – VWD	Plasma-Derived – Factor VIII	Plasma-Derived – Factor IX	Plasma-Derived – Inhibitor	Plasma-Derived – VWD
Baxter HealthCare	Advate				Recombinate Hemofil M	Bebulin VH	FEIBA VH	
Bayer Healthcare	Kogenate FS							
CSL Behring	Helixate FS Next Gen[1]				Monoclate-P	Mononine		Humate-P[5]
Grifols					Alphanate[3]	AlphaNine SD Profilnine SD		
Kedrion Biopharma US[2]					Koate DVI[4]			
Novo Nordisk Inc.			NovoSeven RT					
Octapharma								wilate
Pfizer Inc.	Xyntha	BeneFix						

1. Helixate FS Next Gen is exactly the same product as Kogenate FS. 2. Grifols manufacturers Koate DVI for Kedrion Biopharma. 3. Alphanate is FDA-indicated for treating VWD as well as hemophilia A. 4. Koate DVI is produced by Grifols and marketed by Kedrion Biopharma US. 5. FDA-indicated for treating VWD, Humate-P can also be used off label to treat hemophilia A. Note: Recombinate is a first-generation product. Kogenate FS, Helixate FS Next Gen, and NovoSeven RT are second-generation products. Advate, Xyntha, and BeneFix are third-generation products.

You've probably guessed: the patents and orphan drug periods of exclusivity on factor concentrates have expired or will soon expire. This has allowed for the development of generic forms of factor concentrates, called *biosimilars* or *follow-on biologics*. Biosimilars with improved properties, such as long-acting factor, are often referred to as "biobetters." With the loss of patents and manufacturer protections, and the introduction of biosimilars and biobetters, pharmaceutical companies will face increasing competition–potentially cutting into their market share and profits. To maintain competitiveness, most companies are developing additional products as well as "new and improved" products.

The New Products

As they lose the protection of patents and orphan drug periods of exclusivity, pharmaceutical companies are looking not only to retain their market share, but also to grab market share from their competitors by introducing new products–you've probably been hearing about some of these.

But getting people with hemophilia to switch products is notoriously difficult when patients view benefits as small or incremental. In fact, some have argued that the current rFVIII products are all essentially the same in terms of safety and efficacy, leading to a lack of motivation to switch between products. Pharmaceutical companies know this, and they don't expect to take the bleeding disorder market by storm. Instead, they hope to start by taking little bites out of their competitors' market share by introducing biobetters, and by building their own market share with new products slowly over time. The bleeding disorder market is expected to be able to support some new products, and it's expected to grow almost 6% yearly–about $500 million–over the next five to ten years.

So how can pharmaceutical companies maintain their market share or gain a toehold in a new niche market with increased competition? Most are using two approaches: (1) targeting segments of the market that have historically had little or no competition (FVII, FIX, FXIII) with new products; and (2) introducing "new and improved" biobetter versions of current products. For some products, "improved" means either being the only third-generation recombinant or being produced by a human cell line. But for most products, "improved" means longer acting.

What Long-Acting Factor Really Means

Much of the research into developing new products also involves making them longer acting–extending their *half-life*. Let's take a look at what half-life means. When factor is infused, some of it is used up in producing blood clots, but most of it is removed, or "cleared," from the bloodstream; the body does this through multiple processes that continually clear and recycle proteins from the blood. Different clotting factors, as well as other proteins, have a different life span in the blood; some are short, measured in hours, while others are longer and may last weeks. The term half-life is often used to describe how quickly a protein or drug is cleared from the blood: the half-life is the amount of time it takes for one-half of a drug to be cleared from the blood. The half-life varies with each clotting factor, and also varies from person to person. For FVIII, the half-life is 8–12 hours. For FIX, it's 18–24 hours. For FVII, the half-life is much shorter at a little over 2 hours. For patients with inhibitors, the half-life of factor may be very short–sometimes measured in minutes instead of hours.

Factor with a longer half-life would offer obvious benefits: fewer infusions, presumably fewer bleeds, lower lifetime cost, and better quality of life. Imagine having to infuse only once a week for prophylaxis instead of every other day!

Besides working on making factor longer acting, most pharmaceutical companies in the hemophilia business are also developing new products for market segments that have historically had little or no competition. These include FVII, FIX, and FXIII, explained in the following sections.

Recombinant factor VII, activated (rFVIIa); FEIBA

Since 1999, Novo Nordisk has cornered the factor VIIa market with its second-generation rFVIIa product, NovoSeven, which is used to treat inhibitors in hemophilia A or B, congenital FVII deficiency, and acquired hemophilia. NovoSeven has a very short half-life (2.3 hours) and often requires two or more doses in quick succession to control a bleed in people with inhibitors. This drug has been successful for Novo Nordisk, and it's no surprise that several of Novo Nordisk's competitors are bringing their own rFVIIa products to market.

Several new rFVIIa products may hit the market within the next few years. Baxter expects a new rFVIIa to be on the market within three years. CSL Behring has a long-acting version of rFVIIa under development. Pfizer/Catalyst Biosciences is working on a new rFVIIa. Finally, rEVO Biologics is developing a new rFVIIa produced by transgenic rabbits that contain the gene for human FVII and produce the factor in their milk.

Factor IX

BeneFIX, a third-generation rFIX product now sold by Pfizer, has held the market on rFIX since 1997. Now, five new rFIX products are poised to hit the market within the next few years (two in 2013). Three of the new longer-acting rFIX products–from Biogen Idec (a newcomer to the US hemophilia market), Novo Nordisk, and CSL Behring–have reported half-lives extended to 3.5–4 days, compared to 1 day for BeneFIX. These extended half-life products will represent a significant breakthrough in treating bleeds in hemophilia B, and would allow prophylaxis with infusions once a week to once every two weeks. Other, normal half-life products coming to market may make the hemophilia B market more competitive, and may be cheaper than BeneFIX.

Factor XIII

Only one FXIII product, Corifact (plasma-derived and produced by CSL Behring), is on the market. With the introduction of its product Novo Thirteen in 2014, Novo Nordisk will have the first and only recombinant FXIII on the market. This is truly a niche market: factor XIII deficiency is a very rare disorder, with only about 1,000 patients identified worldwide, 150 living in the US.

Will the New Factors Be Safe?

Yes, if they are approved. FDA approval for biologic drugs such as factor requires a complete series of clinical trials to check for safety, efficacy, and immunogenicity. This is because biosimilars and biobetters can never be made identical to the original drug. It's fortunate that the FDA requires these trials: more than six biobetters for treating bleeding disorders have had their development terminated during clinical trials because of lack of efficacy or increased immunogenicity.

Even though the FDA may certify a drug as safe to market, the bleeding disorder community has raised two concerns about switching to new or longer-acting products: (1) the use of PEGylation to enhance half-life, and (2) the risk of developing inhibitors.

PEGylation involves attaching long chains of polyethylene glycol (PEG) to the factor. PEG is used in many products, including prescription and over-the-counter drugs, and in many cosmetics and other products such as toothpaste. Most of us have some PEG in our bodies from products we use every day. PEGylation has been used successfully and safely in several drugs for short-term treatment since 1990. Although a few instances have been reported of children experiencing negative side effects from taking PEG-based laxatives, for example, PEG is considered a safe compound.

If PEG is safe, what are the concerns?

Most PEGylated drugs use small chains of PEG that can be removed from the blood by the kidneys and excreted through the urine. But PEGylation of factor uses very long chains of PEG, which cannot be eliminated like small chains of PEG because they are too large to be excreted by the kidney. This leaves the liver to do the work of removing PEG. The liver removes some PEG by concentrating it in the bile it generates and then dumps into the intestines, to be excreted with the feces. But removal of PEG by the liver is less effective than removal by the kidneys, and some PEG remains behind. So what happens to the remaining PEG? We all have an immune system that ingests foreign materials (such as PEG); if those materials can't be broken down, they remain in the cells of the immune system for a very long time.

We really don't know what happens to PEG: does it accumulate over many years? And what, if any, long-term consequences result? Some researchers have speculated that because hemophilia requires lifelong treatment, PEG might build up to toxic levels in the liver over time. But researchers developing PEGylated factor scoff at this idea, citing the long safety record of PEGylated drugs and the fact that the amount of PEG infused with factor is miniscule. Also, to date no toxic effects of PEG on humans have been reported in clinical trials of PEGylated factor.

So who is right? Because it's hard to track the passage of long chains of PEG through the human body, we don't know exactly how PEG is excreted or whether it builds up in the body over time. It may be decades before the safety of long-term use is validated. With no evidence to the contrary, the FDA considers PEG, as used in PEGylated drugs, to be safe.

For most consumers, the key concern about switching products is probably the risk if developing inhibitors. For decades, we've heard anecdotal accounts of people who switched products and developed inhibitors–the dreaded complication of hemophilia. This fear of inhibitors is a prime reason that many are

Long-acting factor: How do they do it?

Almost every manufacturer has a long-acting product coming to market (see Table 1). Several different techniques are being used to extend the half-life. The most common is **PEGylation**. PEGylation involves attaching long strands of the chemical compound polyethylene glycol (PEG) to the factor molecule. Researchers think that the constantly moving, long strands of PEG whip around the factor molecule–keeping away immune cells, antibodies, enzymes, and anything that might attach to the factor and mark it for removal from the blood. A subtype of PEGylation, called glyco-PEGylation, involves attaching the PEG to a sugar, which is then attached to the factor. It's believed that this method is less likely to interfere with the factor activity.

Another technique being used to make long-acting factor is **fusion**: genetically linking a half-life-enhancing molecule to the factor, so that both the half-life-enhancing molecule and the factor are produced as a unit by the recombinant cell line. Several products are using **albumin fusion**. Albumin is the most common blood plasma protein; it has low immunogenicity and a long half-life of about 20 days. One of albumin's jobs is to ferry smaller molecules through the circulatory system. Attaching this long-lasting protein to factor may help protect the factor and extend its half-life. Indeed, CSL Behring has two albumin-fusion products in clinical trials that have demonstrated an increase in half-life.

Another fusion technique, being pioneered by Biogen Idec, involves **Fc fusion**: linking factor to an Fc protein fragment found on plasma immunoglobulin G (IgG). Proteins with Fc attached to them tend to be recycled instead of removed from the blood. Here's how it works: circulating proteins, including factor, are continually being cleared from the bloodstream by various mechanisms. One clearance process involves endothelial cells, which line the inside of blood vessels. These cells randomly latch onto proteins–such as factor–circulating in the blood, and then pull the proteins into the cell, where they are digested by enzymes. The body sees the older proteins as trash and metabolizes them, allowing "fresh" proteins to be synthesized. When proteins attached to Fc are drawn into an endothelial cell, the cell does not digest them; instead, it "spits" them back out into the bloodstream, thus recycling the proteins. Clinical trials of factor fused to Fc have shown that this recycling process increases the half-life of the factor.

Table 2. New Products Under Development or Recently Approved

MARKET SEGMENT

Manufacturer or Partner	Product Name*	Type or Indication	Feature
FVIII			
Baxter	BAX 855	PEGylated rFVIII	Long acting
Bayer	BAY 81-8973	BDD rFVIII	Third-generation rFVIII; normal half-life
Bayer	BAY 94-9027	PEGylated rFVIII	Long acting
Biogen Idec	BIIB 031	BDD rFVIII-Fc fusion	Long acting
CSL Behring	CSL627	Single-chain rFVIII	Improved stability during manufacturing; greater affinity for VWF
Green Cross Corporation	GreenGene F	rFVIII	Not a new recombinant FVIII, but applying for a license to sell in US
Novo Nordisk	NN7008 (N8) Turoctocog alfa	BDD rFVIII	BDD rFVIII; normal half-life
Novo Nordisk	NN7088 (N8-GP)	Glyco-PEGylated rFVIII	Long acting
Octapharma	Human-cl rhFVIII	Hemophilia A	First factor concentrate to be produced from a human cell rFVIII; normal half-life
Recoly NV	NecLip-pdFVIII (LongAte)	Plasma-derived FVIII formulated with NecLip	Long acting
FIX			
Baxter	BAX 326 (brand name Rixubis)	rFIX	Normal half-life
Biogen Idec / Swedish Orphan Biovitrum	BIIB 029 (brand name Alprolix)	rFIX-Fc fusion	Long acting
Cangene Corporation	IB1001	rFIX	
CSL Behring	CSL654	rFIX albumin fusion	Long acting
Novo Nordisk	NN7999, (N9-GP)	Glyco-PEGylated rFIX	Long acting
Inhibitors or FVIIa			
Baxter	BAX 817	Hemophilia with inhibitors rFVIIa	Normal half-life
Baxter	OBI-1	Hemophilia A with inhibitors or acquired hemophilia A	rFVIII (porcine [pig])
CSL Behring	CSL689	Hemophilia with inhibitors rFVIIa-albumin fusion	Long acting
Pfizer/Catalyst Biosciences	PF-05280602	Hemophilia with inhibitors Human rFVIIa	Normal half-life
Recoly NV	NecLip-rFVIIa (LongSeven)	Hemophilia with inhibitors rFVIIa formulated with NecLip	Long acting
rEVO Biologics/LFB Biotechnologies	LR769	Hemophilia with inhibitors Transgenic rhFVIIa	Factor produced in rabbit milk
VWD, Rare, or Novel Treatments			
Baxter	BAX 111	rVWF	First recombinant VWF
Baxter	BAX 513	Fucoidan, a natural substance extracted from a brown algae	Enhances platelet activation to improve clotting
Novo Nordisk	NN7415	Hemophilia A and B	Anti-TFPI (tissue factor pathway inhibitor)
Novo Nordisk	NN1841 (brand name Novo Thirteen)	rFXIII-A subunit	Will be first rFXIII product on market

*Most of these are code names of the products used during development and have no resemblance to the final name of the product used in marketing. Note: For more details on the techniques used to make long-acting factor, see "Hemophilia Renaissance: New Treatments and Gene Therapy" by Paul Clement (PEN, May 2012, www.kelleycom.com).
BDD: B-domain deleted. BLA: Biologics License Application.

	Status	Launch Estimate
	Phase II/III	2015
	Phase III completed 3/2013	2014
	Phase III	2015
	Phase III completion 3/2014	2013
	Phase II/III	2016
	Phase III	2016
	Phase III	2014
	Phase III	2016
	Phase III	2014
	Approved for marketing in Russia	
	Phase III completed 7/2012; BLA filed 9/2012	6/2013
	Phase III initiated 2/2012; completion 2/2015	2013
	BLA submitted 4/2012; drug approval on hold pending more data requested by FDA	
	Phase II/III	
	Phase III	2015
	Phase III	2016
	Phase III for acquired hemophilia	
	Phase I	
	Phase I	
	Phase I/II completed	
	Phase II	
	Phase III	2016
	Phase I completed	
	Phase I	
	BLA submitted	

reluctant to switch products.

But this fear has finally been put to rest, as least in most cases!

A study published in January 2013 tracked inhibitor development in 574 children with severe hemophilia between 2000 and 2010.[5] It found that 32.4% of the children developed inhibitors, with 22.4% of these being high-titer inhibitors (the more serious form). The study also found that the inhibitor risk was similar for plasma-derived and recombinant factor; that the VWF content had no effect on incidence of inhibitors; and, perhaps most important, that *switching between products had no effect on the incidence of inhibitors.* The one exception was that second-generation recombinant products carried a significantly higher risk of inhibitor development than third-generation full-length recombinant products. So far, there is no explanation for this difference.

Numerous other studies have come out in the past year that confirm that switching does not increase the risk of inhibitors: most older patients in the US have switched products several times, and in some countries, much of the hemophilic population has switched multiple times when the country purchases a different product every several years. The bottom line: switching products is not a risk.

Should I Switch?

That's the looming question that you and your hematologist must answer. But some people may have more incentive than others to switch.

If you have hemophilia B, you'll soon have the option of switching to one of several products that are significantly longer acting than the current rFIX product, BeneFIX. A significantly longer-acting rFIX product would allow for prophylaxis once every one to two weeks–for many, that's a powerful incentive to switch. Also, one or two new third-generation rFIX products with a normal half-life will also come to market. It's hoped that the added competition from these newer third-generation products will lower the cost of these products.

The same goes for people with factor VII deficiency, acquired hemophilia, or hemophilia A or B with inhibitors. Many currently use the rFVIIa product NovoSeven, which has a short half-life and often requires multiple successive infusions to control a bleed. A long-acting rFVIIa product that allows a bleed to be controlled with fewer infusions–that's also a powerful incentive to switch. Although the development of three long-acting rFVIIa products was terminated during clinical trials due to development of inhibitors to the products, one long-acting product is still in clinical trials, and two normal half-life products are under development. It's hoped that, because of increased competition, these products will come to market at a significantly lower price than the current NovoSeven, helping to

» page 14

5. "Factor VIII Products and Inhibitor Development in Severe Hemophilia A," Samantha Gouw, Johanna van der Bom, Rolf Ljung, et al. *New England Journal of Medicine* 368 (Jan. 17, 2013), 231–39. The study was funded by Bayer HealthCare and Baxter BioScience.

headlines

PHARMA

Joining the FIX Club

The US FDA has approved Baxter Healthcare's new blood clotting drug, Rixubis, a recombinant factor IX (rFIX). This is the first new rFIX approved for hemophilia B in more than 15 years, and the first FIX product in Baxter's US portfolio of hemophilia drugs. Rixubis is the only rFIX indicated for both routine prophylaxis and the control of bleeding episodes in adults with hemophilia B. Why this matters: Rixubis is only the second third-generation rFIX product in the US market.

For info: www.baxter.com

Seeking More Effective Immune Tolerance Induction

Kedrion Biopharma will provide financial backing for RESIST (Rescue Immune Tolerance Study), a prospective clinical trial designed to evaluate whether a concentrate containing both human factor VIII and von Willebrand factor, and given at a high dose, will induce immune tolerance. Why this matters: Recent evidence from studies in Italy and Spain suggest that highly purified factor VIII/VWF complex concentrates can be effective in immune tolerance induction (ITI), even in patients at high risk of failing ITI.

Source: *IBPN*, Apr. 2013

First Long-Lasting Factor Becoming a Reality

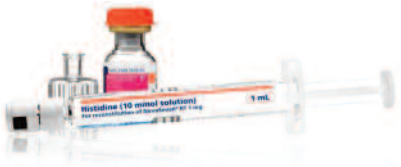
The US FDA has accepted Biogen Idec's Biologics License Application (BLA) for the marketing approval of Elocate (recombinant factor VIII Fc fusion protein) for treating hemophilia A. Why this matters: Elocate is the first hemophilia A product candidate in a new class of long-lasting clotting factor therapies being developed to provide long-lasting protection and reduce the burden of treatment for patients.

For info: www.biogenidec.com

Mix It Up!

Novo Nordisk has a new reconstitution device for NovoSeven RT. The device, MixPro™, is available to congenital hemophilia A or B patients with inhibitors, acquired hemophilia, and congenital factor VII deficiency. Why this matters: The kit includes a syringe prefilled with diluent and a vial adaptor to reduce the number of steps needed to prepare NovoSeven RT for infusion.

For info: www.novosevenrt.com



WORLD

Fast and Furious Wins

Last summer, cyclist Barry Haarde became the first person with hemophilia and HIV to cycle 3,667 miles across the US. Barry completed his second cross-country bike tour, "Wheels for the World 2013: Fast and Furious," in May to raise funds for Save One Life. This year, Barry again dedicated each day of his ride to someone with hemophilia who died from hepatitis or AIDS, and posted the photos and names on Facebook. Barry averaged 110 miles a day, and completed his 3,456-mile ride, traveling mainly through 15 southern states, in just 30 days, raising over $35,000. Sponsored by Baxter Healthcare Corporation, Alliance Pharmacy, and Matrix Specialty Pharmacy. Why this matters: Unique physical activities like this ride help to shatter the misconception that people with hemophilia are fragile, while at the same time raising public awareness and much-needed funds.

For info: www.saveonelife.net

Europa, Europa

A recent report shows that the European factor market was $3.59 billion in 2011, of which $2.7 billion was for recombinant factor. Why this matters: Europe is a huge market for factor, consuming about as much recombinant factor as the US.

Source: Marketing Research Bureau

NONPROFIT

California, Here I Come!

NHF Annual Meeting
Oct. 3–5, 2013
Anaheim, California

National Hemophilia Foundation looks forward to seeing you at its 65th annual meeting, United in Progress. Why this matters: This is the largest single gathering of bleeding disorder families in the world.

For info: Sonia Roger, sroger@hemophilia.org

When Hemophilia Is a Laughing Matter

Learn a little about hemophilia via YouTube while laughing a lot. *Stop the Bleeding!* is a series of YouTube videos by Patrick Lynch, a young man with hemophilia, who is an actor, writer, and producer. STB! videos were sponsored through an unrestricted charitable donation from Baxter. Go to YouTube.com and search "Stop the Bleeding!" Why this matters: Some people learn about topics best through visuals or humor.

For info: patrickjameslynch.com

LA KELLEY COMMUNICATIONS

Pulse *on the Road* to Visit Six States

Pulse on the Road (POTR) is a comprehensive, hands-on insurance symposium and workshop. So far in 2013, POTR has traveled to four states–New York, Colorado, Alabama, Pennsylvania–and will visit Oregon in September. POTR offers an overview of the Affordable Care Act and the importance of being able to choose your own insurance, and provides a practical workshop on choosing the best insurance policy. Funded by Baxter Healthcare Corporation and run in cooperation with NHF. Why this matters: POTR provides hands-on workshop that allows participants to compare actual healthcare plans.

For info: Zoraida Rosado, 978-352-7657

SCIENCE

Prophylaxis with Factor VIII Reduces Inhibitor Risks

Prophylactic use of factor VIII appeared to decrease inhibitor risk in children with severe hemophilia A, according to one study's results. The findings suggest that in previously untreated patients with severe hemophilia A, high-dosed intensive factor VIII treatment increases the inhibitor risk and prophylactic factor VIII treatment decreases the inhibitor risk. Why this matters: If these results prove true, starting young children with hemophilia on prophy doses may prevent inhibitor formation.

Source: *Blood*, June 2013

New Factor... from page 11

reduce the cost of this very expensive therapy.

And of course, people with factor XIII deficiency will now have a second product to use: a third-generation rFXIII product from Novo Nordisk called Novo Thirteen. Another powerful incentive to switch.

What about the rest of the 80% of people with hemophilia, who have hemophilia A without inhibitors? A handful of longer-acting rFVIII products are in clinical trials, as well as two normal half-life products. The long-acting rFVIII products in the pipeline have shown a modest 20%–60% increase in half-life; and although this is nowhere near the increase in half-life seen for biobetter rFIX products, it's still nothing to ignore. Biogen Idec, the only company so far to have released phase III clinical trial data, has demonstrated that prophylaxis with its long-acting product can be achieved with only one to two infusions per week, as opposed to the commonly used regimen of three infusions per week.[6] This translates into 50 to 100 or fewer infusions per year!

Given that switching products is not a risk for inhibitors, the big question is this: what *is* enough incentive to motivate people to switch products? Consumers usually compare benefits to cost. The benefit of long-acting factor, for example, would be fewer infusions for prophylaxis. Will consumers be willing to pay more per unit for this? A price close to that of current products, or the prospect of cost savings realized through fewer infusions, might entice healthcare professionals and consumers to switch to save money. Cost is the big unknown: will new normal half-life products come to market at a cheaper price in order to gain a market share? Will the longer-acting products cost significantly more? Or will pharmaceutical companies price them competitively to maintain or gain market share? We'll see.

The Pipeline Starts Delivering

The bleeding disorder community has anticipated the arrival of new products for several years–and it's finally time! As new products come to market, starting in 2013 and continuing for the next several years, we can expect more product choices and improved products. For some, the decision to switch will be easy–the new products will offer significant advantages over current products and may greatly improve quality of life.

For others, the improvements may be incremental and the decision to switch will be tougher. But whether you switch or not, the increased competition among factor manufacturers can only benefit our community. Get ready. New products are coming: the prospects are bright and the future is now!

6. Biogen Idec press release, May 13, 2013, www.biogenidec.com.

Inhibitor Insights... from p. 4

daycare, or sitter's. When at home, or doing something quietly like watching TV, parents feel the child can be without the helmet. Sheryl's family handled it this way: "My son is now eight. He wore a helmet only when he was outside playing from about age one-and-a-half until age three. I was afraid of him falling and hitting his head. We stopped the helmet when he was more steady on his feet and we became more comfortable with treating his hemophilia."

No! Let kids be kids!

Some parents believe that helmets make children feel "different" and can interfere with making friends–particularly if other adults treat the child differently. The issue of feeling different is important. Will your child feel inhibited by his helmet? Will he get teased?

"We decided not to have Lee wear a helmet because mainly, we believed that it would affect his self-esteem and that he would consider himself different than other children," recalls Eleth, whose son is now an adult.

Do helmets give a false sense of security? Peg Geary reports hearing from some parents who worry that they or their child might be less cautious if a helmet is worn. And some believe that helmets may not protect against brain bleeds anyway, but may protect only against bleeding in the soft tissue on the head. It's important to remember that head bleeds can occur spontaneously, without any trauma.

Peg has also noticed a trend of fewer children using helmets. For example, she notes, "There seemed to be very few children with helmets at the consumer conferences where I've attended or presented in recent years."

Are helmets accepted?

Either way you decide, Peg stresses, there's a lot of support among parents. "Inhibitor parents tend to be good researchers and networkers. They all support one another's decisions."

If you choose to use a helmet, different types are available. And you can be creative in making a helmet appeal to

your young child.

Sheryl's son started wearing a helmet outside when he was so young that he accepted it. "He decorated it with stickers," she adds. "He saw the other children in the neighborhood wearing a helmet when they rode their bikes, so he didn't think anything of it."

ShaLinda says her son Josiah accepts the helmet as part of his daily life, like his medical ID bracelet. "He will remind you that we can't leave the house or go out to play without it."

We do seem to be more accepting of differences in appearance these days. Helmets may elicit some odd looks, but they may not provoke as much reaction as they might have a generation ago.

Your healthcare provider can explore with you what's best for your child and your family. And you can always change your mind. You may decide to use a helmet while your child is very young, and then decrease its use as your child matures.

Cazandra has one son with inhibitors who wears a helmet, and one who doesn't. "I don't like to see children with helmets because it makes them stand out," she says. "But when a child needs that extra protection, then it is necessary. The bottom line is that as a parent, I have to get over what makes my child 'look' different–whether he wears a helmet, uses a wheelchair, or has lots of bruises–and know that what I am doing [when I have my child wear a helmet] is in the best interest of my child."

Peg Geary agrees. "We really want to reassure parents that there is no one right or wrong answer to the helmet question. We counsel the parents to do what seems right for them and their child."

Inbox... from p. 2

I FOUND YOUR ARTICLE INTERESTING FOR many reasons, but especially because my 13-year-old son just started to use a factor-tracking app for his iPhone. He is participating in a study at our HTC that involves an app, very similar to the apps you featured, but different in that it keeps track of the patient's fluctuating factor activity level. This requires the patient to have had a factor survival study at some point. My son's factor VIII half-life is short, at four hours, thanks to an inhibitor that was successfully [tolerized] a decade ago. He is very athletic and participates in many sports, so it gives us peace of mind knowing what his factor VIII level is at any given time. Using this app has helped my newly teenaged son take control of his hemophilia, and has increased his feeling of ownership of his bleeding disorder.

Thanks for another interesting and useful article!

Allison Pohl
TEXAS

Project SHARE

THANKS, MUCH LOVE, AND RESPECT. I received the meds for my son. May the good Lord bless all of you. Keep up the good work.

Milton Tomlinson
Gang Intervention Specialist
JAMAICA

Medical ID

I WANT TO COMMENT ON THE ARTICLE about medical identification jewelry [Richard's Review, May 2013]. I published an article about Emergency Medical Identification (EMI) in *Haemophilia* in 2011; it was the result of a survey of hemophilia nurses across the US. I found that many children did not wear [medical ID], and instead placed it in their wallet, car visor, or car seat. This created issues because EMS staff typically do not check outside the body. In addition, I interviewed several EMS and ER doctors who confirmed that treatment is well underway before they get to check a wallet for [medical ID]. Ultimately I worked with the National Hemophilia Foundation board and the Nursing Working Group, and we developed guidelines for the use of EMI. The medical board of NHF accepted these as the official guidelines, which include the recommendation that EMI should be worn on the child (MASAC Recommendation 201).

Jocelyn Besette-Gorlin, RN
MINNESOTA

Ed. note: Find MASAC Recommendation 201 online at www.hemophilia.org

LA KELLEY
communications, inc.
37–39 West Main Street, #8
Georgetown, MA 01833 USA
www.kelleycom.com

WE'VE MOVED!
Please update your records.

Visit Your HTC Annually!

Parenting Moment

I have always imagined that Paradise will be a kind of library.
–Jorge Luis

There is more treasure in books than in all the pirate's loot on Treasure Island. –Walt Disney