PEN

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The Most Exciting Time in Hemophilia

Glenn Pierce, MD, PhD

The doctors told my mother when I was diagnosed in 1956, "This is a good time to be born with hemophilia. We'll have a cure in five years." That statement was pretty far from reality, but a cure may actually happen in 5–10 years. And, as new therapies with increasingly longer half-lives are appearing in clinical trials and the marketplace, a different concept of "functional cures" with repeated injections at long intervals is taking hold. Some of these therapies, if given once every two or four weeks, may temporarily suffice until gene therapy does become a reality.

This is the most exciting time in hemophilia research… ever! Today, research is occurring in three main areas.

Research Area 1: Prolonged half-life factor products

What exactly is half-life? Half-life is the amount of time it takes for factor to decrease its circulating concentration by half, or 50%. It's calculated by taking a series of blood samples over a specified time span after infusing clotting factor, and then measuring how much factor remains in each sample. When graphed, these measurements are called pharmacokinetic (PK) curves, and they show how rapidly your body eliminates factor. Half-life of factor may vary from product to product, and from person to person. So it's important to know how long a particular brand of factor lasts in your body, which may be significantly different from the average half-life of that brand. By knowing how quickly you eliminate factor from your blood, your HTC team can tailor a prophylactic dosing schedule specific to your needs.

For instance, immediately after 50 IU/kg of standard factor VIII is infused, the level of circulating factor VIII in the body is at 100%. If the product has a 12-hour half-life, then about 12 hours later, the factor VIII level will be at 50% (half has been eliminated). And 24 hours after the original injection, 25% is left. Two days after the initial injection, the factor VIII level is at 6.25%.

How does this work for a prolonged half-life product? If half-life is on average 50% longer than 12 hours, say 18 hours, then 36 hours after the original injection, factor VIII levels are reduced by two half-lives, so 25% is left. Three days after the initial dose, factor VIII is at 6.25%.

In other words, when using a prolonged half-life product with an 18-hour half-life, you may be able to go an extra day between infusions, as compared to a standard product with a 12-hour half-life.

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welcome

Laurie Kelley

Back in 1987, when my son with hemophilia was born, my HTC team recommended one factor product to use. I wasn't told I had a choice, even though I did. Probably, the team was trying to keep things simple for me. Come to think of it, I was pretty overwhelmed. In fact, I was so overwhelmed that when my nurse called to give me the diagnosis, I thought, I know just how to fix this. I hung up on her. Classic denial!

Time passed, and I came to grips with hemophilia. But when I learned that there were multiple products to choose from, I realized I wanted to be part of that decision-making process. When 1992 rolled around, our HTC team helped me decide to use the newly released recombinant product. But my insurance company denied me. Denial again! But I persisted, because I could now speak intelligently about factor. Once they heard me out–and it took a year–the company approved my choice.

I was able to advocate for the product I wanted because I'd read all about different products and spoken with our HTC team. I was prepared to advocate. Now, reading up on factor is more important than ever. As Glenn Pierce writes in the feature article, this is the most exciting time so far in bleeding disorders. The pipeline is stuffed with new products, advanced products, and even products that promise a cure–or the next best thing. You too might need to defend your choice of product to the payers who may try to limit access to so many factor brands. So be prepared: What types are there? How is factor made? Which product best meets your unique needs?

I urge you to bring this article to your clinic visit. Discuss current and new factor products with your HTC team. Learn the difference between plasma and recombinant, PEG and gen, hamster cells and endothelial cells. Unlike me in 1987, you now have Internet, Facebook, and lots of resources including PEN. You can participate in choosing a factor product, provided you do some homework. We've made it a little easier for you here, I hope!

inbox

THANK YOU FOR PEN. IT provides valuable information for those of us in the bleeding disorder community and those who care for us. Congratulations on 25 years.

Stephen Place
MASSACHUSETTS

I ENJOYED READING THE MOST recent issue in which Paul Clement eloquently asks, "Will Your HTC Be There When You Need It Most?" This is a great article because patients and their families will always need the guidance and expertise that a comprehensive HTC team can provide. We had this in mind in New York when I worked at the New York Blood Center. We helped set up a 340B purchasing consortium at HTCs in major university teaching hospitals, which became a model for the rest of the US and Puerto Rico. Your column *Inhibitor Insights* sponsored by Novo Nordisk was also near and dear to my heart, and an important read for patients with hemophilia A or B.

Michael Zeplin
NEW YORK

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PARENT EMPOWERMENT NEWSLETTER | MAY 2016

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A Letter to My Future Self

Ian Muir

Katie and Ian with Charlotte

Dear Ian of 2026,

How is 40 treating you? I have high hopes that it's going great in multiple respects (house, job, dog, wife, etc.). Of equal or greater importance, I hope that the next hemophilia treatment revolution is well under way. And I certainly hope that you're not taking anything resembling clotting factor concentrate, or for that matter any product that lasts less than four weeks to treat your hemophilia.

The years 2015 and 2016 were so hopeful, remember? You had been primed with knowledge, friends, and perspective from the Word Federation of Hemophilia Congress in Paris in 2012. Then, in 2015, you turned 30 and had a few mild health scares that reminded you of your own mortality. This set you off on a renewed quest of empathetic restlessness and searching. In 2015, novel approaches to treating hemophilia from some brilliant new players were being published, and the data looked promising. More accessible and effective treatment options were closer than the horizon for underserved people with inhibitors, and for some developing countries that lacked reliable access to any of the flavors of clotting factor. You felt excitement and hope every day (sometimes too much–do people still say you're too enthusiastic?), not only for you, but for your clotting-challenged friends and friends-to-be around the world.

What have you done with your new freedom to travel and be more "off the grid" when a single dose can last a month? I hope you've found time between stateside jobs to travel around the world and participate in preparing new markets that will do business with ambitious companies to expand access to hemophilia treatment. If all goes to plan, you should be far more concerned about what you're going to do with your now 12-year-old pit bull Charlotte for three months while hopping around the globe, rather than hassling with receiving $50,000 of clotting factor a month. I hope you only need a couple of doses of your current product. This should give you and your family some peace of mind to be abroad for several months at a time without needing to meet up with someone for a covert factor handoff or something. Just kidding.

I hope that your prediction has come true: that we have a new pace and standard for meaningful advances in improving quality of life for patients in developed and developing countries, with and without inhibitors. At the time, it seemed like a lot to ask, but I hope we were right about the capability of the bright minds in the companies that seemed almost ready to release–and community members that seemed almost ready to embrace–a revolutionary, game-changing product. Are you still as fond of analogies? Introduction of the iPhone, going to Mars, you couldn't quite decide which analogy would do justice, but I hope it has been all of those things and more.

Have we progressed, from only 20% of hemophilia patients treated globally to at least 50% now? I sure hope so. If not, please send word back to me in 2016 from your iPhone 16s, and I will rattle some extra cages for you.

Keep up the good fight,

Ian of 2016

Ian is a 31-year-old who has severe hemophilia A, and has thankfully been in remission for hepatitis C genotype 1A for the past 12 years. Ian graduated from California Polytechnic State University, San Luis Obispo, and currently works in Cambridge, Massachusetts, as an IT and informatics strategy consultant for early-stage biotechnology startups. He lives in Arlington, Massachusetts, with his fiancée Katie and their adorable mutt, Charlotte. Ian enjoys rock climbing, riding his road bike, and running outside on sunny days. He hopes to participate in bringing about the next era of hemophilia treatment for his friends with inhibitors and those with inadequate access to factor around the world.

The SIPPET Bombshell

Paul Clement

A bombshell was dropped at the Plenary Scientific Session of the 57th annual meeting of the American Society of Hematology (ASH) on December 6, 2015, in Orlando. Study coordinators of the SIPPET project (Study on Inhibitors in Plasma-Product Exposed Toddlers)[1] presented surprising preliminary findings: recombinant factor VIII products are associated with an 87% increased risk of inhibitor development compared to plasma-derived factor VIII products.[2]

In other words, for every 10 people treated with recombinant factor VIII as opposed to plasma-derived factor VIII, 1 patient can be expected to develop high-titer inhibitors.

As a parent of a toddler who does not have inhibitors, you may feel stunned, angry, or scared when you read these findings. Should you be? Before you rush to make a product change, learn how the study was conducted, what its potential shortfalls are, and why you should take a deep breath!

Shock and Awe

Understandably, many consumers are concerned. Some news releases describing the study results only heightened the alarm. Hemophilia Federation of America (HFA) issued a press release requesting that National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council (MASAC) "consider the temporary suspension of recommendations… that state any preference for recombinant factor products until the results of the full SIPPET study can be reviewed."[3]

Is this a reasonable reaction, or is this jumping the gun? It helps to examine how the study was conducted–and why.

Fighting Invaders

Why was the study looking to see if plasma-derived products are less immunogenic than recombinant products–that is, less likely to lead to developing inhibitors?

In the blood, factor VIII is normally tightly bound to another protein called von Willebrand factor (VWF). VWF has several functions, including protecting factor VIII from being digested and cleared from the bloodstream. Some researchers suggest that in doing this, VWF masks some of the sites on the factor VIII protein where antibodies attach, potentially making factor VIII with VWF less immunogenic. Note:

- Intermediate/high-purity plasma-derived factor VIII products are the only ones that contain VWF.
- Recombinant and ultra-high-purity (monoclonal purified) plasma-derived factor VIII products contain no VWF. Without the protection of its VWF "bodyguard," the immune system may recognize these factor VIII products as intruders and develop inhibitors to neutralize them.

The problem is, no one really knows for sure what causes inhibitors, and no one knows whether factor VIII with VWF is less immunogenic.

SIPPET Strategy

SIPPET set out to answer this question: Is plasma-derived factor VIII with VWF less immunogenic compared to recombinant factor VIII without VWF?

SIPPET researchers designed a study called a *prospective randomized controlled trial* (RCT). Prospective means looking forward, before the patient has developed an inhibitor (in contrast to *retrospective* studies, in which researchers look backward, after someone has developed an inhibitor). Controlled means that there are two groups: (1) an experimental group that will use factor VIII containing VWF, and (2) a control group that will use factor VIII without VWF. This second group is used as a standard of comparison against the

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1. https://ash.confex.com/ash/2015/webprogram/Paper82866.html (accessed Feb. 7, 2016). 2. Inhibitors are a major complication of hemophilia in which a person's immune system mistakenly recognizes infused factor as a foreign (and potentially dangerous) protein, and develops antibodies (inhibitors) to inactivate the factor, making factor infusions ineffective. 3. http://www.hemophiliafed.org/news-stories/2015/12/update-2-sippet-study-2/ (accessed Feb. 7, 2016).

Linda Weaver's Studio

Richard J. Atwood

Hemophilia and Poetry

To me, poetry specializes in the efficient expression of emotions and descriptions. It condenses writing into a purer form. You might compare poetry to the fractionation and purification of blood plasma to get the purest factor proteins, but I guess that metaphor would be a stretch.

Though I'm not an expert, I admire well-written poetry. Take time to read the exceptional works by the following poets who happen to have hemophilia.

Tom Andrews

Random Symmetries: The Collected Poems of Tom Andrews
Oberlin College Press, 2002

Tom Andrews (1961–2001) was born in Charleston, West Virginia. At age 11, freckled-faced Tom clapped his hands for 14 hours, 31 minutes so he could be listed in the *Guinness Book of World Records* (1974). As an accident-prone child, he had what he called "deep bruises" and multiple joint bleeds. At 15, Tom was diagnosed with factor VIII deficiency. He did not alter his risk-taking behaviors of motorcycle riding, skateboarding, and playing in a punk rock band.

In 1984, Tom was elected to Phi Beta Kappa fraternity at Oberlin College, and graduated from Oberlin summa cum laude in philosophy. He worked as a copy editor for the *Mathematical Review* before teaching writing at Ohio University and Purdue. He married and later divorced. In January 1989, Tom fell on ice, breaking his right ankle. He required hospitalization and codeine for pain relief.

Tom was a poetry fellow at the American Academy in Rome in 1999. In the summer of 2001, he became ill in Athens and subsequently died in London. His award-winning poetry, published in his books *The Brother's Country* (1990) and *The Hemophiliac's Motorcycle* (1994), was collected posthumously in *Random Symmetries* (2002). But he may be better known for his classic memoir *Codeine Diary* (1998). Tom's hemophilia was a catalyst, and writing about his hemophilia was cathartic at the beginning of his successful writing career–he taught and published poetry to earn his living. Tom had no close friends with hemophilia, and he found that each person needs to define what hemophilia means for himself, and to find his own strategies to negotiate hemophilia and be well. I became engrossed in the many styles of poetry that Tom employed.

Jerome Stephens

Read My Mind
Kildanore Press, 1990

Jerome Stephens (1955–1993) was born in Ireland with mild factor VIII deficiency. As he grew up, he was careful to avoid physical injuries and unnecessary knocks, and became a strong and robust young man who enjoyed outdoor activities. Living in Dublin, Jerome married and had children. In 1982, he underwent an appendix operation and was treated with contaminated factor concentrate imported from America. He was diagnosed with AIDS in 1987.

Jerome was an artist who expressed himself through sculpture and poetry. But he is better known for speaking out publicly–the first to do so openly for a television camera–about how AIDS had ravaged his life and family. With encouragement from his hemophilia nurse, Jerome published *Read My Mind*, a collection of 52 poems that includes photographs of six wooden sculptures carved by the poet. He does not mention hemophilia. Instead, his poems emphasize his struggles, and how his love and religion, along with his family and friends, strengthened him to fight.

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YOU

Baxalta

sponsored by Baxalta

Eeny, Meeny, Miny, Mo…
Choosing Factor? What Do You Know?

Laurie Kelley

Last year we invited patients via email to complete a survey. We asked specifically for people who used only plasma-derived factor. Lots of patients replied, but most used recombinant. Had we phrased the invitation correctly? One young guy with hemophilia even asked, "What's the difference?" I answered, "Yikes."

If you aren't sure what type and brand of factor you're using and why, how will you be able to successfully choose from the plethora of factor brands coming your way? As PEN's feature article reveals, we have many products to choose from now, and more in the pipeline.

The good news: lots of factor to choose from.

The bad news: lots of factor to choose from.

It's up to YOU to know what you are injecting into your (or your loved one's) veins. Sure, you can ask your hemophilia treatment center (HTC) hematologist, who is well versed in product choice, to help you decide what product to use. But if you're a parent or young person with hemophilia, don't you want to participate in making the decision? Use the talking points in this guide to review your choices with your HTC, and to prepare for choices in the future.

It Takes Two, Baby

If you remember nothing else, please remember that you can use only one of two types of factor products: (1) *plasma derived* or (2) *recombinant*. Choose one or the other. (Well, some people may use both, but that's probably an article for our *Insights* column).

What's the difference between the two? Plasma-derived factor comes from…plasma! It originates from the plasma of up to 60,000 blood donors, which is pooled together and then processed. Recombinant factor is made in the lab, from the human gene that produces factor, which is "recombined" or inserted into the DNA of a host cell (often a hamster cell) to produce human factor. That human factor-producing gene is spliced into the cell, and popped into a large tank called a bioreactor to keep it fed and alive. Then the cells grow to large numbers, and go to work producing factor–without ever having seen or touched blood.

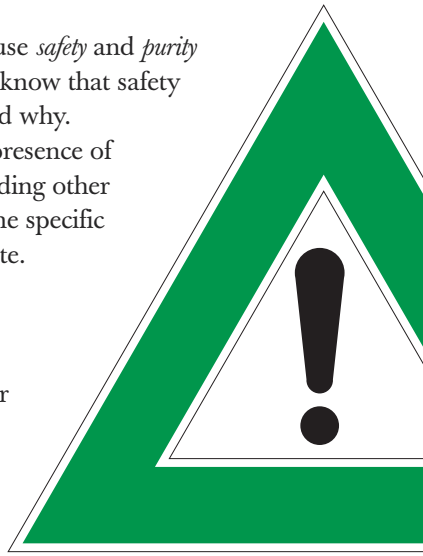
So one factor product type originates from blood, and the other from the lab. Blood versus lab. Which type is your product? And why are there two types, anyway?

Plasma-derived factor concentrate was developed first, in 1968. But as you may (and should) know, it was vulnerable to transmitting human viruses from the donors because it was not subjected to any method of viral inactivation. In 1985, in the wake of the HIV epidemic, new manufacturing processes were implemented to kill most blood-borne viruses, such as HIV. Then in 1992, in response to the bleeding disorder community's demand for greater safety, recombinant factor was developed and commercially released as a virus-free source of factor. It doesn't originate from blood.

Must know: Since 1987, no US FDA-approved factor product has transmitted hepatitis C or HIV. All factor distributed in the US is considered safe, whether it's plasma-derived or recombinant. For the record, National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council (MASAC) recommends using recombinant factor.

Safety versus Purity

Parents and patients often confuse *safety* and *purity* of factor products. You need to know that safety and purity are not the same, and why.



Purity is a measure of the presence of other proteins, sometimes including other clotting factors, in addition to the specific factor supplied in the concentrate.

Safety is the removal or inactivation of potentially harmful substances, including blood-borne viruses, from factor concentrate.

So purity refers to how much of your factor concentrate contains just factor, with no other proteins. Safety refers to reducing the risk of viral transmission.

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Prolonged half-life factor VIII

Two prolonged half-life factor VIII products on the US market are Eloctate (from Biogen) and Adynovate (from Baxalta). Eloctate has a half-life of 19 hours, while Adynovate has a half-life of 14.3 hours.

Why are the two half-lives so different? Each product is manufactured using a different technology to prolong the half-life. The different technologies–described next–create different half-lives.

One approach to prolonging the half-life of clotting factor involves harnessing one of the body's natural mechanisms for prolonging the half-life of certain proteins. Clotting factors are proteins, and each protein that circulates in the blood has a different half-life; some proteins last for a few hours, and others last for several weeks. Two proteins in particular, albumin and an immune antibody called IgG, both last for a long time–more than 21 days.[1] The question is, Why do these proteins last a long time and others not so long?

The answer to this question helps us understand how the longer half-lives of some proteins may be exploited to increase the half-lives of clotting factors. Many proteins in the blood are absorbed and broken down by endothelial cells–the cells that line the blood vessels. IgG usually manages to escape this process. Why? There's an area on the protein, called Fc, which allows the protein to bypass the breakdown process and causes the endothelial cell to eject the protein back into circulation. Scientists at Biogen took advantage of this fact and developed a recombinant form of factor VIII fused to an Fc molecule. With the Fc molecule attached to the factor, the endothelial cells treat the factor as if it were IgG, and eject the factor back into the bloodstream, extending its half-life. Eloctate is the brand name of Biogen's factor VIII Fc-fusion product, and it has a half-life about 50% longer than standard factor VIII products.

PRODUCTS THAT GIVE US HOPE

Prolonged Half-life Factor Products

	Brand or Clinical Name	**Engineered Protein**	**Company**	**Half-life (hours)**	**Status**
factor VIII	**Eloctate**	rFVIII-Fc	Biogen	19	Available June 2014
	Adynovate	PEG-FVIII	Baxalta	14.3	Available Dec. 2015
	N8-GP	GlycoPEG-FVIII	Novo Nordisk	18.4	Phase 3 (2017–18)
	BAY94-9027	PEG-FVIII	Bayer	19	Phase 3 (2018)
	rVIII-SingleChain	Single-chain FVIII	CSL Behring	14.5	FDA submitted
factor IX	**Alprolix**	rFIX-Fc	Biogen	82.1	Available Mar. 2014
	N9-GP	GlycoPEG-FIX	Novo Nordisk	93	Phase 3
	Idelvion	rIX-FP (albumin)	CSL Behring	101.7	Available Apr. 2016
factor VIIa (for inhibitors)	CSL689	rFVIIa-Albumin	CSL Behring	8.5@1mg/kg	Completed normal human volunteers; now phase 2/3
	MOD-5014	rFVIIa-CTP	Opko	No data yet	Preclinical in dogs; phase 1/2a open

Alternate Treatments for Inhibitors and Hemophilia A and B

Clinical Name	**Engineered Protein**	**Company**	**Dosing Frequency and Delivery**	**Status**
ALN-AT3SC	AT3 RNAi	Alnylam	Twice monthly subcutaneously	Phase 1
ACE910	Anti-FIX/FX (Bispecific MAb)	Genentech/ Roche/ Chugai	1–2 weeks subcutaneously	Phase 3 clinical trials now starting
Concizumab	Anti-TFPI	Novo Nordisk	IV or subcutaneously	Phase 1/2 clinical trials including hemophilia A/B
BAY 1093884	Anti-TFPI	Bayer	No data yet	Phase 1

1. Albumin (or human serum albumin) is the most common protein found in blood plasma and makes up about 50% of plasma proteins. One of its functions is to transport different compounds throughout the body. IgG, or immunoglobulin G, is a Y-shaped protein used by the immune system to fight infections by inactivating infectious agents such as viruses or marking them for removal or destruction by other immune system cells.

Adynovate uses a different technology to prolong its half-life: PEGylation. PEGylation is the process of attaching polyethylene glycol (PEG) to the factor VIII molecule. PEG is a petroleum derivative that is found in a variety of products, from cosmetics to food. Adynovate uses the random addition of PEG, which results in the protein being coated with PEG, protecting it from damage and destruction, and producing a longer half-life. Adynovate's half-life is 14.3 hours, 16% longer than that of standard factor VIII products.

Two other prolonged half-life factor VIII products use a different type of PEGylation, called *site-specific* PEGylation. In contrast to the random PEGylation process used by Adynovate, site-specific PEGylation is highly controlled and results in the attachment of only one PEG molecule on each factor VIII molecule. Bayer has accomplished this by changing one area on the factor VIII molecule to allow it to function as a PEG binding site. Novo Nordisk has taken a similar approach, using a technology called glycoPEGylation. In this process, a single PEG is attached to a sugar that is attached to a single site on the factor VIII molecule. The precise control in the placement of a single PEG on each factor VIII gives both the Bayer and the Novo Nordisk products an 18- to 19-hour half-life, comparable to Eloctate. Both these prolonged half-life PEG factor VIII products are still in clinical development, but their main clinical trials are completed.

Another approach to prolonging the half-life of factor VIII involves making a slight change in the structure of the factor VIII molecule. Normally, factor VIII is synthesized in the liver as a single long protein, called a *single-chain*. When secreted from the cell, the single-chain factor VIII molecule is broken into two parts, or two chains. Factor VIII travels in the bloodstream as a two-chain molecule. In the approach used by CSL Behring, the two chains of factor VIII are bonded back together to form the more stable single-chain molecule. Data from clinical trials sponsored by CSL Behring indicate the single-chain factor VIII has a half-life of 14.5 hours, similar to Baxalta's Adynovate, and marginally better than standard two-chain factor VIII products with half-lives of 12 hours.

With two prolonged half-life factor VIII products already on the market, and more coming, how will you decide which one to use?

Clinical trial results showed that Eloctate and Adynovate were as effective as standard factor VIII products in stopping bleeding episodes when used on demand. And like standard products, they can prevent nearly all bleeding episodes when administered prophylactically in a variety of dosing regimens. The new products were also shown to be safe–with no unusual adverse events, and no increased risk of inhibitor development. Prophylactic dosing regimens for standard factor VIII products are typically three times a week or every other day to ensure that factor VIII *trough levels* (the factor VIII level just before the next dose) are sufficient to prevent breakthrough bleeding. For prolonged half-life products like Eloctate, dosing once or twice per week is effective in preventing most breakthrough bleeding.

Because all prolonged half-life products were studied in different ways in their clinical trials, it's best to review the product inserts that come with each product (also available online) and then talk to your HTC team about which is best for you.

A safety concern that has been discussed since research into PEGylated factor VIII started more than 10 years ago deserves mention: How does PEG get removed from the body? The body does not

FACTOR BRANDS AVAILABLE IN US BY MANUFACTURER AND TYPE

	Recombinant			Plasma Derived		
	FVIII	**FIX**	**Inhibitor**	**FVIII**	**FIX**	**Inhibitor**
Baxalta	Advate Recombinate Adynovate	Rixubis		Hemofil M	Proplex T Bebulin VH	FEIBA VH
Bayer HealthCare	Kogenate FS Kovaltry					
Biogen	Eloctate	Alprolix				
CSL Behring	Helixate FS	Idelvion		Monoclate-P	Mononine	
Emergent Biosolutions		Ixinity				
Grifols				Alphanate	AlphaNine SD Profilnine	
Kedrion				Koate DVI		
Novo Nordisk	Novoeight		NovoSeven RT			
Octapharma	Nuwiq					
Pfizer	Xyntha	BeneFIX				

First-generation: Recombinate. Second-generation: Kogenate FS, Helixate FS. These are the same product; CSL Behring is licensed to sell Kogenate FS as Helixate FS. Third-generation: Advate, BeneFix, Rixubus, Xyntha, Novoeight, Ixinity, Kovaltry, Nuwiq. Prolonged half-life: Eloctate, Alprolix, Adynovate, Idelvion. Kedrion distributes Koate-DVI in the US for Grifols, the manufacturer.

metabolize or break down PEG into smaller units, as it does with natural compounds such as proteins and carbohydrates. Small PEGs are more easily excreted than large PEGs. Small PEGs are removed from the blood mainly by the kidneys and then excreted through the urine. Larger PEGs do not easily pass through the kidneys, and it's believed that most are excreted through the liver to the intestine, and then eliminated in the feces. PEGylated factor VIII products use some of the largest PEGs. Because it's not possible to eliminate every molecule of PEG, and because PEG is not broken down, some PEG remains in the body. Research has shown that the impact of PEG remaining in the body seems minimal, but the long-term safety of PEGylated factor VIII products has not been conclusively established: most other PEGylated drugs are used in other diseases for short periods of time and use smaller PEGs. Hemophilia is one of the first instances where PEG will be administered over many years, even decades. So it will be important to understand the safety risks versus benefits when considering a PEGylated factor.

Prolonged half-life factor IX

Three technologies have been used to prolong the half-life of factor IX.

1. Fc fusion is being used in Alprolix, Biogen's Fc fusion factor IX product. Alprolix uses the same Fc technology as Eloctate, but in this case, Fc is fused to factor IX instead of factor VIII. This technology significantly increases the half-life of factor IX over standard factor IX products, from about 19–24 hours for standard products to an average of 86 hours for Alprolix. Most important, this product reduces the number of infusions required to prevent bleeding. Standard half-life factor IX products typically require twice-a-week dosing to maintain good coverage and prevent bleeding. By contrast, prolonged half-life products like Alprolix can be used weekly, and in the clinical trials, about half the patients had good results with every-two-week dosing.
2. Albumin fusion technology is being used in Idelvion, CSL Behring's factor IX albumin fusion product. Idelvion uses the same recycling pathway as Fc; but instead of using Fc, the factor IX molecule is fused to albumin. Because albumin circulates for at least 21 days, it can also be used to extend half-life when fused to other proteins. The latest prolonged half-life product to hit the market, Idelvion was approved by the FDA on March 4, 2016. Idelvion has a very prolonged half-life of 104 hours and can be used once weekly or up to once every two weeks for patients over age 12. In the clinical trials for FDA licensure of Idelvion, breakthrough bleeding was very low for patients treated every one to two weeks.
3. GlycoPEGylation is the same technology Novo Nordisk uses for its prolonged half-life factor VIII product. In this case, Novo Nordisk is using glycoPEGylation to attach PEG to one of two sugars on the factor IX molecule. The clinical trial reports good results and a prolonged half-life of 92 hours. The glycoPEGylated factor IX product, currently named N9-GP, completed a successful phase III clinical trial in 2013 but has not yet been filed for licensure with the FDA.

All three of these prolonged half-life factor IX products are effective and safe. They each stopped bleeding episodes and prevented almost all breakthrough bleeding when used prophylactically. No increased incidence of inhibitors was detected, and no other unusual adverse events were seen in clinical trials. Dosing regimens are currently every 7–10 days for Alprolix, with half the patients in the clinical trial achieving every-two-week dosing. Idelvion dosing is every 1–2 weeks, and although N9-GP is not yet approved, its clinical trial tested weekly and longer dosing intervals with excellent results.

Research Area 2: Bypassing agents

Developing and managing inhibitors is the greatest unsolved problem in hemophilia today. Bypassing agents like NovoSeven (rFVIIa) and FEIBA offer some control of bleeding in inhibitor patients by skipping the need for factor VIII or factor IX in the clotting cascade. But these agents don't always work when administered prophylactically, and don't control bleeding as well as standard factor VIII and IX in people without inhibitors. Three widely differing scientific approaches are being researched to address the urgent need for better therapies for inhibitor patients.

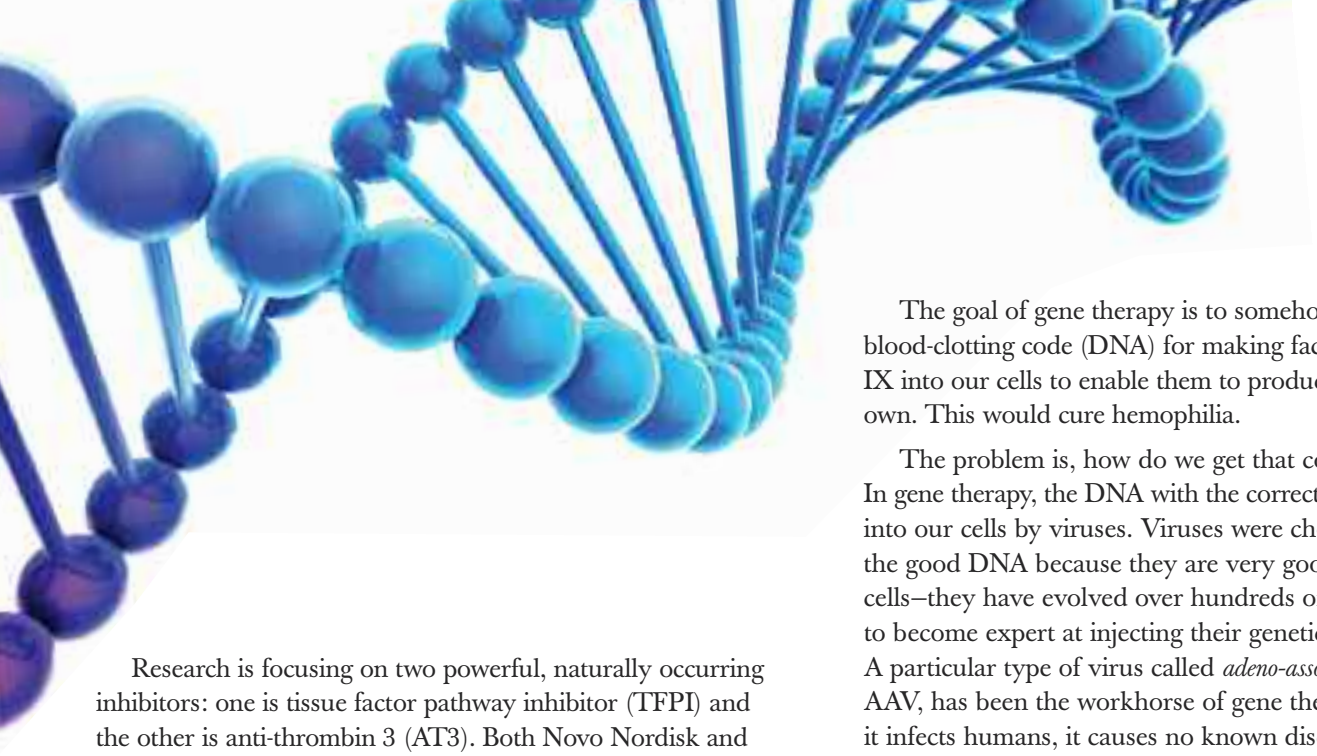
1. Extending the half-life. One technology involves prolonging the half-life of factor VIIa. Factor VIIa has a very short half-life, about 2.5 hours, and may require several infusions every few hours to bring a bleed under control. CSL Behring is developing a recombinant factor VIIa-albumin fusion product that, in early clinical trials, demonstrated a half-life of 8.5 hours–more than *three times* as long as standard factor VIIa. No data are available yet on factor VIIa-albumin's effectiveness.

These next two novel approaches being researched by several companies don't involve the infusion of *any* clotting factors or bypassing agents!

2. Using a *bispecific antibody*. You may know that factor VIII works in the clotting cascade by bringing factor IX and factor X together and activating them. These activated factors in turn activate other clotting factors, eventually resulting in the formation of fibrin fibers, the stringy protein necessary for a strong clot. In the absence of factor VIII or IX, little fibrin is formed. This results in weak clots that easily break down, causing prolonged bleeding–hemophilia. Roche and its subsidiary Genentech are developing a new antibody drug (ACE910) to replace factor VIII. Antibodies are Y-shaped proteins produced by the immune system; they have two arms that usually bind or stick to one target, such as an infectious agent like a virus, to eliminate it from the body. Through the process of recombinant DNA technology and genetic engineering, scientists have been able to develop a bispecific antibody that binds to two different molecules. In this case, one arm of the genetically engineered bispecific antibody binds to factor IX, and the other arm binds to factor X. So the antibody latches onto factor IX and factor X in the bloodstream and brings them together–essentially, the bispecific antibody is doing the job of factor VIII.

   In early clinical testing, this bispecific antibody was effective in preventing bleeding in factor VIII-deficient patients with and without inhibitors. That's right, this antibody isn't just for inhibitor patients. It may be used by all patients with hemophilia A. And it doesn't require venipuncture–it's administered as a weekly subcutaneous injection. In these trials, patients were protected from most bleeding episodes with ACE910 alone, without the need for prophylactic factor VIII. ACE910 has generated much interest in the hemophilia community and larger-scale clinical trials are under way now.

3. Stopping naturally occurring inhibitors. Another approach that doesn't involve the infusion of factor targets the part of the clotting cascade that shuts down the clotting process. How do we stop bleeding by stopping part of the clotting process? In addition to clotting factors like VIII and IX that participate in forming a blood clot, our bodies also have *naturally occurring inhibitors* that keep the clotting cascade in check by shutting it down. This is necessary to prevent unwanted clotting, possibly resulting in a stroke or heart attack. Think about it: people with hemophilia have enough trouble making clots without their own coagulation inhibitors trying to shut down the process! Perhaps these naturally occurring inhibitors could be neutralized to allow the clotting process to proceed with little or no factor?



Research is focusing on two powerful, naturally occurring inhibitors: one is tissue factor pathway inhibitor (TFPI) and the other is anti-thrombin 3 (AT3). Both Novo Nordisk and Bayer have made antibodies that can bind to and eliminate TFPI in the bloodstream. These are being tested now in early human clinical trials to see if they can improve clot formation in patients with hemophilia and hemophilia with inhibitors by reducing the negative effect of TFPI on clot formation. No data on effectiveness are available yet.

Alnylam Pharmaceuticals has made a completely different type of molecule to inhibit production of AT3. It's called an RNA interference therapeutic (RNAi). RNA is normally the message that DNA (genes) uses to make proteins in the cell. The RNAi binds to and eliminates AT3 RNA, preventing the liver from making AT3 protein. Clinical trial data on humans suggest that RNAi is effective in preventing bleeding when patients are given a subcutaneous dose sufficient to block the production of most AT3 protein. Bleeding was prevented in patients without the use of any clotting factor. This RNAi—the anti-AT3 molecule (ALN-AT3)—will be tested in larger studies in hemophilia A, hemophilia B, and all inhibitor patients.

The early clinical data for the bispecific antibody (ACE910) and the RNAi (ALN-AT3) are very encouraging when used in both inhibitor and non-inhibitor patients. Larger-scale clinical trials are under way or will start soon to confirm and extend these data. If confirmed, both drugs may offer a meaningful advance for inhibitor patients, and may be used by non-inhibitor patients instead of factor VIII or IX.

Research Area 3: Cell and gene therapy

Our community dreamed of a cure for hemophilia long before my family doctor's 1956 conversation with my mother. Since human gene therapy clinical trials began in earnest in 1990, hemophilia has been touted as an ideal disorder to research and cure. But it's now 2016—are we much further along?

The goal of gene therapy is to somehow put the correct blood-clotting code (DNA) for making factor VIII or factor IX into our cells to enable them to produce factor on their own. This would cure hemophilia.

The problem is, how do we get that code into our cells? In gene therapy, the DNA with the correct code is transported into our cells by viruses. Viruses were chosen to transport the good DNA because they are very good at infecting cells—they have evolved over hundreds of millions of years to become expert at injecting their genetic material into cells. A particular type of virus called *adeno-associated virus*, or AAV, has been the workhorse of gene therapy because when it infects humans, it causes no known disease and typically produces only a mild immune response. These AAV vectors (DNA transporters) have been genetically engineered for gene therapy. To prepare the viral vector for use in gene therapy, the viral genes are removed, and the DNA that makes factor VIII or factor IX is inserted into the viral vector. The virus is then grown to very high quantities and injected into patients. Much of the virus goes to the liver, the normal site of factor VIII and IX production, where it enters the liver cells and delivers the instructions for making factor VIII or IX.

Gene therapy has many challenges. What's the best vector, or transporter, to use without causing an immune response that would destroy it? What vectors could we use that we're not already immune to? What vectors are capable of carrying a large gene such as the factor VIII gene? What vectors can place the gene into a cell's DNA where we want it? The answers to these and many other questions are technically challenging, and that's why it has taken researchers so long to get to this point of some early successes.

Over the past five or six years, a small number of severe hemophilia B patients in a successful clinical trial at University College London (UCL) and the Royal Free Hospital London have been "cured" with gene therapy using a viral vector developed with St. Jude Children's Research Hospital in Memphis. Their factor IX activity is 1% to 6%, and they have few to no bleeding episodes.

Currently, multiple hemophilia B clinical trials are being conducted. They are variations on a theme, testing improvements in all stages of the process, from construction of the vector to the type of factor IX gene to improvements in manufacturing. Results reported to date are cautiously encouraging, with a few more patients making a small amount of normal factor IX. UniQure, a Netherlands-based gene therapy company, has licensed the St. Jude's/UCL technology and has enrolled five people with hemophilia B in a gene

therapy clinical trial that started in 2015. Two of the five patients produced 4.5% and 5.5% levels of factor IX, based on a press release recently published by UniQure.

In other hemophilia B gene therapy studies, researchers are using a super-active form of factor IX, called factor IX Padua, that was first discovered in 1998 and identified in 2009 in a man in Italy who was experiencing excessive clotting. This factor IX variant is being evaluated for gene therapy by several groups because it might solve one of the current problems with gene therapy–low "expression" rates; in other words, low factor levels produced as a result of gene therapy. The factor IX Padua variant might solve this problem because it has about seven times the activity of normal factor IX. So an expression of 2% using a normal factor IX gene would be equivalent to an expression of 14% using factor IX Padua–truly resulting in a cure for hemophilia B, even if not much factor IX protein is made. Recently Baxalta, Spark, and Dimension have taken this factor IX variant into clinical trials. Baxalta has reported some variable but, in some cases, positive data.

And what about factor VIII? Factor VIII is much more difficult to work with than factor IX because of its large size. The viral vector used by almost every gene therapy trial is adeno-associated virus (AAV). Viruses have evolved to carry their own genetic material and not much else. To be used for gene therapy, most of the viral DNA has to be removed and our human DNA "payload" inserted. Some viral vectors can carry larger genetic payloads than others. Unfortunately, AAV can carry only a relatively small payload, and the factor VIII gene overstuffs this virus, making production and manufacturing difficult. Still, BioMarin has an AAV-factor VIII product in clinical studies, and other gene therapy companies are actively pursuing this method too.

Gene therapy for hemophilia may benefit from using a vector other than AAV–one that can carry a larger payload and is more easily developed into a therapeutic product. Research is ongoing on at least one additional viral vector system, lentiviruses, which have been successfully used for gene therapy on bone marrow stem cells. Diseases such as sickle cell disease and some immunodeficiency diseases have been cured by using gene therapy to introduce corrected genes into bone marrow cells removed from the patient. The cells are then grown to large quantities outside the body and reinjected into the patient, curing or partially curing the disease.

Speaking of stem cells, these are the cells in the body that have the ability to produce any type of cell, including those cells that make up our tissues and organs. If cells from a hemophilic patient's liver could be removed via biopsy, cultured, and turned into stem cells in the laboratory, then the gene for factor VIII or IX could be placed into the stem cells, which could be grown in the lab to large quantities.

These stem cells could then be changed into liver cells, and reinjected into the same patient. The new liver cells would make and secrete factor VIII or IX into the blood and cure hemophilia. Is this science fiction? Maybe not. This kind of research worked in mice in two different laboratories, in Korea and the Netherlands.

It's the most exciting time in hemophilia. Many technically cutting-edge research groups have been attracted to hemophilia because it seems an easy target for gene and cell therapy. Hemophilia is an attractive disorder for researchers to work with because the protein involved–factor VIII or factor IX–does not have to be produced within strict limits like, say, insulin: too much insulin could kill you, but almost any level of factor will have a therapeutic effect. Though hitting the target hasn't been easy, given the number of failures over the past 15 or more years, the incremental progress made by scientists brings our community closer to the goal of a permanent cure.

Dr. Glenn Pierce was responsible for the development and approval of Eloctate and Alprolix, the first prolonged half-life products, when he was senior vice president of hematology, cell and gene therapy and chief medical officer for the hemophilia program at Biogen. Before that, Glenn was vice president of US Research at Bayer HealthCare, responsible for the preclinical testing of Bayer's PEGylated FVIII. Glenn retired from Biogen in 2014, and is a consultant to BioMarin and Genentech/Roche, and an advisor to Alnylam. He lives in California, and travels frequently for hemophilia causes, especially the World Federation of Hemophilia's Expanded Humanitarian Aid program. He is on the board of directors of WFH and serves on NHF's Medical and Scientific Advisory Council (MASAC). Glenn had hemophilia until a liver transplant in 2008.

experimental group. Randomized means that no one involved in the study influenced which group a patient was assigned to. Randomization is often done by a computer.

RCT studies are often considered the gold standard, thought to produce more reliable data than other types of studies. Although an RCT can show relationships between variables being studied, it cannot prove causality. So the RCT used for SIPPET can't prove that the presence or absence of VWF in factor VIII *caused* the observed results.

SIPPET was conducted between 2010 and 2015, and data was collected on 251 patients from 42 participating sites in 14 countries from Africa, the Americas, Asia, and Europe. The patients were younger than six years old, had severe hemophilia A, were previously untreated with factor, and had minimal exposure (less than five times) to blood components. Of the 251 patients, 125 were treated with one of the plasma-derived factor VIII products containing VWF. The remaining 126 patients were treated with a VWF-free recombinant factor VIII product.[4] The patients were followed to see if they developed an inhibitor, for 50 exposure days (days they received factor infusions) or three years, whichever came first.

It's important to note that only *one* of the plasma-derived products used in this study is available in the US, and that the study was funded by manufacturers of plasma-derived products. Is this a conflict of interest? Does it influence the findings?

SIPPET Shortcomings?

The preliminary findings were startling: of the 251 patients, 76 developed an inhibitor, and 50 of those were high-titer inhibitors. And 90% of these inhibitors developed in the first 20 days of treatment. Most important: recombinant factor VIII products were associated with an 87% increased risk of developing an inhibitor compared to plasma-derived factor VIII products containing VWF.

Remember, *these are not final results and have not yet been reviewed by researchers outside of the study*. Before you decide whether to switch your toddler to a plasma-derived factor VIII containing VWF, know that many other variables affect inhibitor formation. In any experiment, variables not directly being tested, but which could have an effect on the outcome, are called *confounding variables*.

For example, the single greatest risk factor for developing inhibitors is the type of genetic mutation that caused your child's hemophilia. If the mutation in the factor VIII gene resulted in *no* factor VIII being produced in his body, then he is already at significantly higher risk of developing an inhibitor. This is one of many confounding variables in the SIPPET study.

One way to reduce the effects of confounding variables on the data is to use a large study sample. If the sample size is large enough and patients are randomly assigned to two groups, then each group should have about the same number of patients with the same confounding variable, so its effect will be canceled. The problem is that the more confounding variables you have, the larger your study sample size must be–perhaps several thousand patients. And many variables affect inhibitor development.

Another way to account for the effects of confounding variables is to identify and measure them, and then to separately compare and analyze the data from patients who share the same confounding variable. This process is called *stratification* (meaning to separate into layers) and was used by SIPPET along with other statistical analysis methods. But the study identified and measured only six confounding variables: (1) age at first treatment, (2) intensity of treatment, (3) type of factor VIII gene mutation, (4) family history, (5) ethnicity, and (6) country site. What about the effects of the other confounding variables that were not measured? If the study sample size was too small to reduce the effects of other, unmeasured, confounding variables, then the study's conclusions are questionable and might be explained in other ways.

Don't Jump Ship Yet

At the time of this writing, SIPPET has not been published in a medical journal. That means researchers–outside of those conducting the study–don't know much more about the study than you do after reading this article. Only a short synopsis of the SIPPET study was presented at the ASH annual meeting–just enough to cause a stir and raise many questions. You can be sure that as soon as the journal article is released, it will be examined by bleeding disorder experts worldwide. Questions will undoubtedly be asked about the handling of confounding variables and whether the study sample size was large enough.

And experts will have another question, too: Why didn't the study include any of the new prolonged half-life products, several of which appear to have a lower immunogenicity than other recombinant factor VIII products?

Should you switch your toddler from a recombinant to a plasma-derived factor VIII product containing VWF based on the preliminary SIPPET results, in the hope that it will reduce the risk of developing an inhibitor? This is a question for you and your hematologist, but if you were a betting person, the answer would be no. To bleeding disorder experts, the results of SIPPET are not a bombshell, but merely a piece of the puzzle that is inhibitors.[5] The conclusions of this study contradict those of several other studies. It may take years, and several additional studies, to sort everything out. MASAC is on top of this, and as the data becomes available, you can be assured that NHF will share its expert opinion. So keep calm and carry on!

4. The VWF-rich plasma-derived factor VIII concentrates used by SIPPET: Alphanate (Grifols), Fandhi (Grifols), Emoclot (Kedrion), or Factane (LFB). The VWF-free recombinant factor VIII products used: Recombinate (Baxalta), Advate (Baxalta), Kogenate SF (Bayer), or Refacto AF (Pfizer). 5. Visit the Believe Limited website for an excellent interview by Patrick James Lynch of bleeding disorder expert Dr. Steven Pipe about the SIPPET findings: http://believeltd.com/inhibitors-sippet-and-the-double-edged-internet/ (accessed Feb. 7, 2016).

YOU... from page 6

I sometimes think of it like a choice of drinking water source. US tap water is generally safe to drink (unless, sadly, you live in Flint, Michigan). But it isn't that pure: it contains minerals, metals, and possibly chlorine and fluoride. Bottled water is safe and of higher purity: it still contains minerals, but other compounds such as chlorine and fluorine are removed. Distilled water is both safe and pure: it contains no minerals or other compounds.

Because of varying production methods and based on the source of the factor, the relative purity of the final products–whether plasma-derived or recombinant–varies. Plasma-derived products are classified as intermediate purity, high purity, and ultrapure or monoclonal. The intermediate purity products are still pure (and all are safe), but some are more pure than others. Recombinant products are the purest of the factor concentrates.

Talking 'Bout My Generation

Recombinant products are all über pure. Beyond purity, they're further classified by *generation*. Generation refers to when the products were first commercially available, but also to the presence of animal or human proteins used in the production process or the final product. Yeah, even though I just said that recombinants are produced in a lab, and they don't come from human blood…a blood product may be put into the finished product to stabilize the factor and add bulk. Generation, then, relates to how the product is manufactured.

First-generation recombinant products were introduced in 1992 (points if you know which product was first!). They use human or animal proteins in the growth medium–the serum used to feed the host cells that produce the factor. These products also contain human albumin[1] added at the final production stage to help stabilize and bulk up the product. So they don't come from human blood, but they do contain a human blood product added in the manufacturing process.

Second-generation recombinant products, introduced in 2000, contain no human albumin added to the final product, but like first-generation products, they still use human or animal proteins in the growth medium.

Third-generation recombinant products, first available in 2003, contain no human or animal proteins in the growth medium or added to the final product. Because they are not exposed to any animal or human proteins outside of the manufacturing process, they have no risk of transmitting blood-borne viruses.

So if you use a recombinant product, which "gen" is it?

New Kids on the Block: Prolonged Half-life

Finally, we have what so many families were waiting for: prolonged half-life products. Because they last longer in the bloodstream, they should require fewer infusions per week or possibly only a single infusion to treat a bleed. But read up: some prolonged half-life factor VIII products have only a marginally longer half-life, and may require the same dosing schedule you are currently using. One prolonged factor IX product has a significantly longer half-life, allowing you to infuse less often.

Prolonged half-life products are recombinant. They are still subject to all the criteria of purity and safety. They are exciting. They might be more expensive. Be sure to check your insurance coverage before switching to any product. Your HTC team should always be involved in any product choice discussion, for medical, safety, and insurance considerations.

There you have it in a nutshell. The Hitchhiker's Guide to the Galaxy of Factor Products. Please know your product: What's its name? Why do you use it? Who selected it? Might another product better meet your needs? What are your personal needs, anyway? Which products does your health insurance cover, and what's your copay?

So many choices. But there's only one *you*, and you'll want to decide on the right factor for you. We've only scratched the surface here, but remember, you're injecting this factor into your own or your child's vein. Know what you're putting in there. Bring this article to your HTC for a good, long chat about products…and about product choice.

Ask this (with your HTC team):

- Do I want a plasma-derived or recombinant product?
- If recombinant, what generation is the product?
- Which product does my (or my child's) doctor recommend? Why?
- What is the viral inactivation process for the product?
- What is the purification process for the product?
- Does the product have a prolonged half-life?
- Is my child (or am I) at risk of an inhibitor?
- Do I need an intermediate or high-purity product?
- Does the assay size range meet my (or my child's) needs?
- Is the product covered by my insurance policy?
- How will the price per unit affect my out-of-pocket costs?

Know this (with or without your HTC team):

- All US FDA-approved factor concentrates are considered safe.
- No plasma-derived US factor concentrate has transmitted hepatitis C or HIV since 1986.
- Recombinant factor products are generally more expensive than plasma-derived products.
- NHF's MASAC recommends recombinant factor concentrate for hemophilia treatment.

1. Albumin (or human serum albumin) is a protein found in blood plasma that makes up about 50% of plasma proteins. In some brands of recombinant factor concentrate, albumin is added to the final product as a stabilizer or used in the production process.

Richard's Review... from page 5

Jerome wanted to speak on behalf of all Irish people with hemophilia and AIDS. His poems still capture that desire. After he died, his daughter spoke on his behalf in 2000, giving emotional testimony at the Lindsay Tribunal, after which those infected with HIV or their families received a financial settlement.

Carlos Fuentes Lemus
4:56: Poems
Dalkey Archive Press, 2012

Carlos Fuentes Lemus (1973–1999) was born to a literary family: his father, Carlos Fuentes, was a Spanish-language Mexican novelist and ambassador to France; his mother, Silvia Lemus, was a journalist. Carlos was a Mexican citizen who grew up mostly in Princeton, New Jersey, with short stays in various American cities where his father taught.

Carlos was factor VIII deficient and was infected with HIV by 1985. Carlos was a bright student, but never finished high school. He immersed himself in literature (mainly English) and in music. His interest in pop culture and the arts led him to become a writer, poet, photographer, painter, and movie director.

Carlos wanted to publish his first book of poetry after E. Shaken Bumas solicited several of his poems for the *Minnesota Review* in 1999. Bumas helped to record over 50 of Carlos's poems that were to be used as the soundtrack for Carlos's unfinished movie *Gallo de Pelea*. Unfortunately, Carlos died before completing those projects. Instead, his poems were posthumously published in *4:56: Poems*. Written in English with some Spanish words and syntax, the poems delve into imaginative interpretations of youthful experiences. There is no mention of hemophilia in these lively poems that seem almost experimental or unfinished. Carlos also collaborated with his father on the book *Retratos en el Tiempo* (1998), in which his father wrote profiles of famous people he knew and Carlos took their photographs.

Poetry is an international genre that appears in many forms. These three poets with hemophilia did not have to include their bleeding disorder in what they wrote, but having it possibly sparked their passion to write. Maybe you'd like to express yourself in a poem? Go ahead! Dream, compose, write.

headlines

nonprofit

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A.C.C.E.S.S.® is a Patient Services, Inc. program dedicated to finding solutions to social and economic problems that confront families with chronic medical conditions. A.C.C.E.S.S. helps families navigate the complex maze of state and federal entitlement programs, understand eligibility for health insurance coverage under the Affordable Care Act, and learn about group health insurance continuation under federal law (COBRA and HIPAA). **Why this matters:** PSI services are free, and can help reduce the time and effort required to obtain healthcare benefits.

For info: www.patientservicesinc.org

Row, Row, Row Your Boat

Two University of Georgia students, Jacob Pope and Chris Lee, are planning to compete in the Great Pacific Race in June 2016. Jacob has moderate hemophilia B. The students plan to complete the 2,400-mile journey in 45 days. They're currently raising $150,000, with about two-thirds to be donated to Hemophilia of Georgia. **Why this matters:** If successful, Jacob will become the first hemophilia patient to complete this race, and possibly any ocean row.

For info: www.hog.org

NHF 68th Annual Meeting

July 21–23
Gaylord Palms Resort & Convention Center
Orlando, Florida

National Hemophilia Foundation's annual meeting is the largest educational and networking event in the US, drawing thousands of bleeding disorder community members to share information, learn new treatment, and build support. This year, following the meeting and in cooperation with NHF, World Federation of Hemophilia will host its biannual congress in Orlando. **Why this matters:** Holding the two meetings back-to-back may create the largest bleeding disorder meeting in history.

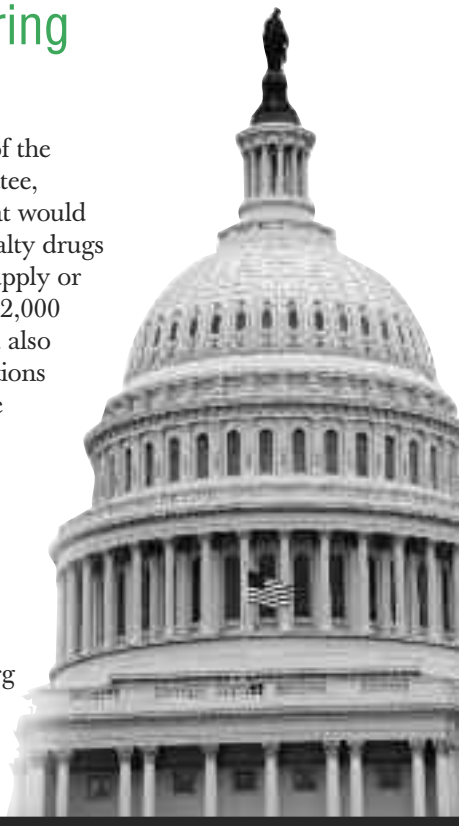
For info: www.hemophilia.org

payer

Limiting Cost-Sharing for Factor

Rep. Lee Hawkins (R), vice chair of the Health & Human Services Committee, introduced legislation (HB 875) that would limit cost sharing for covered specialty drugs (like factor) to $200 for a 30-day supply or $1,000 per insured per plan year ($2,000 per insured family). The bill would also force insurers to standardize definitions of drug tiers and post on applicable websites all drug formularies, drug costs, and prior authorization requirements. **Why this matters:** The bill would help ease the financial burden of factor copays on families with bleeding disorders.

For info: www.patientservicesinc.org



world

A Taxing Decision

India's government tried to end a customs duty exemption for import of 76 lifesaving drugs including hemophilia treatments. The government said Indian manufacturers are already selling most of these imported drugs at cheaper prices, and expected only marginal price increases due to exemption withdrawal. Treatment for hemophilia patients is paid through state and federal budgets. Thanks to persistent lobbying and press releases by Hemophilia Federation (India) chapters, the government backed down and will not repeal the exemption. **Why this matters:** Though the government purchases factor, many patients still buy factor themselves because not enough is purchased for all; a customs duty would have made costs skyrocket.

For info: www.financialexpress.com

soundbites

- **ACA Marketplace** enrollment increased by 15% over last year's open enrollment period, with more than 12.7 million signups.
- Florida and California lead the nation in Marketplace enrollments, as they did last year. Oregon and Nevada, which scrapped their state-based Marketplaces in favor of the **federal web portal**, are among the states showing the greatest enrollment growth for 2016.
- Find an **HTC near you** fast with the CDC's website listing: https://www2a.cdc.gov/ncbddd/htcweb/Dir_Report/Dir_Search.asp
- NHF will schedule 2016 **Inhibitor Summits** soon. For more info, email inhibitorsummits@hemophilia.org
- The **Colburn-Kennan Foundation** provides financial assistance programs to individuals and families living with chronic conditions. Call 800-966-2431.
- The Greek economic crisis has had little effect on hemophilia treatment for **children in Greece**: the number of patients on prophylaxis aged 8–10 between 2008 and 2014 increased by 21%.

manufacturer

New Prolonged Half-life Factor IX Product!

In March, CSL Behring announced FDA approval of its new prolonged half-life recombinant factor IX albumin fusion product, Idelvion®. By combining factor IX with albumin, a naturally long-lasting plasma protein, CSL Behring produced a factor IX product with a half-life of 104 hours, as compared to 18–24 hours for standard factor IX. **Why this matters:** Idelvion will allow patients with hemophilia B and under age 12 to infuse prophylactically once a week, and patients over 12 to infuse once every two weeks, reducing the number of infusions needed to protect against bleeding.

For info: www.idelvion.com

New Products Keep Coming

The US FDA has approved Kovaltry®, the latest hemophilia product on the market. Bayer's new recombinant factor product is an unmodified, full-length factor VIII compound for treating hemophilia A in children and adults. The approval is based on results from the LEOPOLD (Long-Term Efficacy Open-Label Program in Severe Hemophilia A Disease) clinical trials, which supported Kovaltry's approval for routine prophylaxis. **Why this matters:** NHF has expressed support for new products to create greater choice for US consumers.

For info: www.bayer.com

science

From Denied to Deferred to Decreed

The US FDA has amended a longstanding recommendation on blood donations: donations from men who have sex with men (MSM) should now be deferred 12 months–rather than indefinitely–from the last sexual contact with another man. The FDA examined recent studies, epidemiologic data, and shared experiences from other countries that have made recent MSM deferral policy changes. But the FDA continues to defer people with bleeding disorders, not because of the increased risk of HIV transmission to potential recipients, but for their own protection from large needles used during the donation process that might cause bleeding. **Why this matters:** The FDA noted that Australia's well-conducted study evaluated over 8 million units of donated blood and observed no change in risk to the blood supply with use of the 12-month deferral.

For info: www.fda.gov

patient resources

I Am Iron Max

Max Levy, a boy with hemophilia, has become the latest Marvel comics superhero. In 2014, Max received a port in his chest as part of his treatment, and to help him cope and better understand his condition, Max's father told him the port was like character Tony Stark's Arc Reactor (which gives him Iron Man's power). Max's nickname became Iron Max. The creators of Iron Man caught wind of Max's story and contacted Levy. Marvel then featured Iron Max in an Iron Man comic book. **Why this matters:** Iron Max helps spread awareness of hemophilia through a vast public network via the hugely successful Avengers franchise, helping children identify with a hemophilia superhero.

For info: #ironmax

For Families Newly Diagnosed with an Inhibitor

September 9–11

Families newly diagnosed with an inhibitor can attend a special program in New York City, hosted by Comprehensive Health Education Services. Free for qualifying participants; supported by a grant from Grifols. **Why this matters:** Inhibitor families need a tailored program, often missing at larger hemophilia events, directed at their unique needs.

For info: www.comphealthed.com

Got Factor VII Deficiency? Take a Break!

Factor Seven Retreat
June 17–19
Denver, Colorado

Factor VII deficiency is 100 times rarer than factor VIII deficiency, making it hard for people with this bleeding disorder to network and learn more about the condition. Enter the Factor Seven Retreat. Now in its fifth year, this weekend family retreat is a unique opportunity for people with factor VII deficiency to get together. This year's retreat is free for qualifying participants. It offers medical and treatment updates with separate sessions for men and women, and psychosocial and stress management sessions. Childcare is provided onsite for children through age 12, with a separate teen track for ages 13–18. Run by Comprehensive Health Education Services and the LadyBugs Foundation, supported by an educational grant from Novo Nordisk. **Why this matters:** This is the only national retreat and gathering for factor VII deficient families.

For info: www.comphealthed.com

X-Men!

Leading X is a weeklong backcountry adventure for young people with hemophilia that takes place in a tandem sea kayak or the hull of a canoe. Learning the fundamentals of navigating and traveling for a week by boat, and camping along the way, will challenge participants physically, emotionally, and mentally. Programs in May, August, September, December. **Why this matters:** The program teaches leadership skills and personal responsibility development, and promotes community bonds.

For info: info@gutmonkey.com

from
LA Kelley Comunications

Color Your Toddler's World

My First Factor Coloring Book is back in print! With selected illustrations from the popular series My First Factor, this book helps your child understand hemophilia while coloring in the pictures. Free to families; postage may apply.

Also available as a free download: www.kelleycom.com

For info: info@kelleycom.com

Inbox... from page 2

PROJECT SHARE
It's time to give back

In 2015, Project SHARE saved lives! We donated over $4.8 million of factor VIII and IX, and over $1.5 million of recombinant factor VII to more than 35 developing countries.

JEREMI IS A NINE-YEAR-OLD BOY with hemophilia B who had a brain bleed. His initial treatment came from the factor provided by Project SHARE. But we requested additional factor IX for his subsequent treatments. When Jeremi's mother called me last Christmas, his condition was deteriorating. He was then in another government hospital. Thankfully, his parents followed our advice to have him transferred to the Philippine Children's Medical Center, the only place where factor IX is available.

The close monitoring of doctors and your quick assistance once again helped save a precious life.
Andrea Trinidad Echaverrez
THE PHILIPPINES

I WOULD LIKE TO DISCONTINUE my Save One Life sponsorship and give it to another person with hemophilia who needs it most, because I am now working. I would also like to say thank you to Save One Life and Project SHARE for the opportunity and help you have given to me.

I am currently working in Capital One as a senior representative, and because I am already employed, I think it would be fair if I shared the blessings with another hemophilic patient, hoping someday he could finish his studies and find a job, too.

To my sponsor, I always pray that God will continue to bless you. Your unconditional love is amazing, and you're an example to us that you don't need to be rich to help others.
Jeffrey Rodriquez
THE PHILIPPINES

I RECEIVED YOUR FACTOR this afternoon. I'm very happy; it's a huge amount. Thank you, thank you so much.
Hung Lee
VIETNAM

THANKS A LOT FOR HELPING my little nephew. We are very grateful.
Afrin Akther
BANGLADESH

inbox

Hung Lee

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