February 2006 • Volume 16 • Issue 1

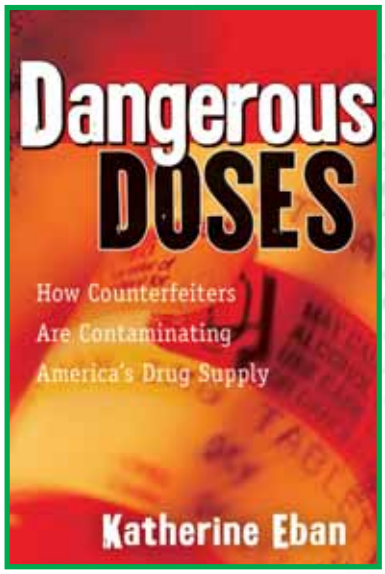
Parent Empowerment Newsletter

Hemophilia Thieves:

Where Does Your Factor Really Come From?

by Laurie Kelley

Anyone involved with hemophilia–patients, doctors or factor suppliers–will be intrigued by the opening page of Katherine Eban's new book *Dangerous Doses*.[1] A break-in at the Miami warehouse of BioMed Plus, a large pharmaceutical wholesaler, resulted in the theft of hundreds of thousands of units of the blood-clotting medicine NovoSeven®. Who did it? And why? Just days later, the same stolen NovoSeven was offered for sale by an unwitting vendor to a surprised BioMed Plus. The police set up a sting operation, recovered the stolen product and caught the hemophilia thieves. As the story unfolds, what appears to be an isolated case of local theft evolves into a gripping whodunit and a devastating indictment of our nation's distribution channels for prescription drugs. *Dangerous Doses* begs some tough questions: Where do our nation's medicines come from? Who has handled them? How is the safety and integrity of medicines preserved? As you will read in this issue, nothing is as it appears to be, or as it should be.



Could factor be next? *Dangerous Doses* warns of the risk of counterfeit and diverted medicine.

Eban's investigative journalism focuses on the weak national regulations that have allowed unethical business people–and some outright thieves–to infiltrate our nation's medicine distribution system and engage in *diversion*. Diversion is the repeated buying and selling of prescription drugs in a largely unregulated "gray market" where drugs change hands frequently, and sometimes illegally, before being delivered to the patient. Eban's book is the true story of patients who are deceived into thinking that their products come directly and safely from manufacturers. It's the story of insurance companies and government programs being swindled out of millions of dollars, and of manufacturers who must relinquish quality control once their products leave their doors.

"There is an epidemic of pharmaceutical theft in this country," Eban told *PEN* during a recent interview.[2] "Every day, every hour there is pharmaceutical theft, involving thieves–using guns, or through hijackings. That's dangerous for drugs like factor, which is fragile." While Eban's book focuses mainly on high-priced cancer drugs like Epogen® and Procrit®, how susceptible to theft are the equally expensive hemophilia products? As a consumer, what can you do to ensure that the factor you receive is safe?

New Standards to Define Safety

When we think of the word "safety" as applied to factor, we often think of the absence of blood-borne viruses. We think only in terms of the way our product is manufactured: Is it made from plasma or from genetic material? Is a viral-inactivation manufacturing process used that disables lipid-coated viruses like HIV and hepatitis C? All factor products on the US market today are considered safe–that is, free of HIV and hepatitis. And now, with third-generation products free of albumin in the manufacturing and finishing processes, US products have achieved a new level of perceived safety.

But safety should encompass a broader definition today. We can't apply the term "safety" only to the manufacturing process. A definition of safety should now encompass the distribution process as well. When factor leaves the manufacturing plants, what happens to it? It must be shipped, stored, handled, labeled and inventoried. It travels from truck to van

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[1] Eban, Katherine. *Dangerous Doses: How Counterfeiters Are Contaminating America's Drug Supply.* New York: Harcourt, 2005.
[2] Interview with author by Laurie Kelley, Dec. 21, 2005.

inside PEN

welcome

Sherrell Portrait Design

When you read this issue's feature article "Hemophilia Thieves" you'll understand one reason that US state governments and private insurance companies may be furious about the high cost of factor. Graft and corruption are found wherever there is money, and there's a lot of money in hemophilia. Sadly, the allure of money can corrupt even good people. The result? Medicaid fraud, insurance scams–illegal activities that dip into the liquid gold of factor.

At a party two years ago, I was stunned as I stood with a homecare rep I had known for a long time, listening to him brag of his wealth: motorcycles, cars, big home. I wondered how he came into such wealth when so many others in the factor distribution business were not at that income level. But what saddened me was the realization that his wealth had been squeezed out of insurance budgets that can no longer support many good, hardworking people in this country–like the mother who told me that she was again rejected by her insurance company because her son, who has an inhibitor, caused the company's premiums to skyrocket. Or the father who told me that he and his wife considered divorcing so that one of them could collect Medicaid to keep their medical benefits. They were forced into a lower income level to keep their child insured.

Hemophilia thieves live among us: unethical, immoral, and unsympathetic to the plight of so many in this community; indifferent to the effect of their greed on everyone, including the families with hemophilia that truly suffer when their insurance is on the line. But there are good people, too–and companies–who pump much-needed time and money into the community to ease the financial burden of living with chronic disorders. And there are wise people, like author Katherine Eban, who warn us of thieves and explain how we can protect ourselves and our products to ultimately reduce the spiraling cost of care.

PARENT EMPOWERMENT NEWSLETTER FEBRUARY 2006

EDITOR-IN-CHIEF	Laureen A. Kelley
CONTRIBUTING EDITOR	Paul Clement
EDITOR	Sara P. Evangelos
LAYOUT DESIGNER	Tracy Brody
PROJECT SHARE℠ DIRECTOR	Julia Q. Long
EXECUTIVE ASSISTANT	Zoraida Rosado

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Funding provided through generous grants from our corporate sponsors (page 15)

LA Kelley Communications

LA Kelley Communications, Inc.
68 East Main Street, Suite 102 • Georgetown, Massachusetts 01833 USA
978-352-7657 • 800-249-7977 • fax: 978-352-6254
info@kelleycom.com • www.kelleycom.com

letters

Readers respond to "Journeys of Hope," *PEN*, November 2005

The narrative diary of your travels through the years gave readers not only a sense of the desperate political situations and needs of the third world countries, but also the compassion, humor and courage of the families and people you've met around the world. I laughed about your experience with Daisy's son, and your leaving your running shoes before entering the hotel. But most clearly I hear your plea for us to reach out across the globe. I hope your readers will respond with action, whether as groups, corporations or individuals. At this season of thanksgiving, I would like to thank you for what you have done for the bleeding community in this country as well as around the world. I also would like to thank your family for sharing you with us. There must be countless hours and sacrifices they have already made, and continue to make, without being acknowledged.

Elizabeth Fung, SW
Children's Memorial Hospital
CHICAGO, ILLINOIS

Recently we were in Mexico prior to the National Hemophilia Foundation meeting [San Diego, October 2005]. I had a thought as we ventured into a very rural part of Baja with our son Lynden: As we passed the military checkpoints, it dawned on me that they might not be able to read [our medical

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Becoming a Mover and Shaker

by Jeff Coelho

Jeffrey D. Coelho

Children love to move. It's the way they learn about themselves and their environment. Children who develop efficient movement skills early in life are more likely to continue moving and engaging in physical activity throughout their lives. Physically active children are healthier and happier. Conversely, inactivity among children is linked to obesity, diabetes, depression, and other diseases and health problems. Children with hemophilia are no different from those without hemophilia. The child with hemophilia who has developed effective movement skills and is physically active is less prone to injury. Research indicates that physically fit children experience fewer spontaneous bleeding episodes.

Physical activity through sports helps build self-confidence, social interaction skills and cooperation while developing muscular strength and coordination.

The treatment of hemophilia has advanced a great deal in the past ten years. Factor concentrate safety, prophylaxis, and the use of venous access devices such as a port allow children with hemophilia to engage in many types of physical activity and sports that were previously contraindicated. Yet despite medical advances in factor replacement therapy and treatment programs, adults have a tendency to overprotect children with hemophilia. Parents may not encourage their children to participate in the sports and activities that others enjoy.

While children with hemophilia do have some limitations, they are capable of participating in a variety of physical activities and should be encouraged to do so.

Motor Fitness

Motor fitness, the foundation of all physical activity, includes balance, coordination, agility and power. Children need a solid foundation in these fundamental motor skills:

1. *Locomotor skills:* moving the body from one place to another, as in running, leaping, hopping and jumping.
2. *Non-locomotor skills:* turning, twisting, swinging and balancing.
3. *Movement awareness:* cognitive abilities (special relations, measuring, risk assessment) needed to form an effective motor response to perform a motor task, such as estimating the length of a log before taking a leap over it.

When children have a rich repertoire of motor skills, it's easier for them to acquire sport skills, avoid injuries, and maintain active, healthy lifestyles. Children who are physically active from an early age and have positive, enjoyable and successful movement experiences will continue to engage in activity on a regular basis. On the other hand, children with inadequate motor skills often exclude themselves, or are excluded by others, from organized and free-play experiences. As a result, they are often consigned to a lifetime of inactivity. Children can build a solid foundation of motor skills by participating in basic gymnastics activities.

Educational Gymnastics for Children with Hemophilia

Appropriate basic gymnastic instruction for children with hemophilia is based on an *educational method.* Educational gymnastics allows for individual differences, focuses on problem solving, and develops body control. Children perform within their ability levels while developing body management skills. They progress at their own pace, exploring their own unique ways of completing a movement task. Educational gymnastics instruction helps children acquire the abilities and attributes needed to become confident and skillful movers. To introduce children to basic motor fitness, programs are developed around broad skill-themes: rolling, balancing, vaulting, traveling, hanging, climbing, landing, crawling and supporting. Children use these skills in their everyday lives and in many sports. The benefits of participating in an educational gymnastics program include improved body control, development of locomotive and manipulative skills, and the promotion of strength, power, flexibility, balance, agility and coordination.

All children, including those with hemophilia, can safely participate in a basic educational gymnastics program. They will enjoy improved body awareness, muscular fitness, flexibility and motor skill improvement. Along with these physical benefits, mental benefits include improved self-confidence, better

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by Paul Clement

Johnny! Drink your factor!

Wouldn't it be nice to do away with intravenous infusions of factor or the hassle of using a port? Instead, what if you could drink or eat your factor, or possibly even inhale it? Right now this isn't possible; however, research is currently underway that may make oral or inhaled therapy a reality. This research also holds the potential of bringing factor replacement therapy to people with hemophilia in some developing countries–people who presently have little or no access to clotting factor due to its high cost.

Dr. William Velander, a chemical engineer at the University of Nebraska-Lincoln (UNL), in conjunction with more than a dozen scientists at three universities and two private companies, recently received a $9.98 million grant from the US National Institutes of Health (NIH) to develop a treatment for hemophilia B using factor IX proteins from pig milk.[1]

Pig milk, you say? Pigs produce human factor IX in their milk? Well, not normally, but Velander's *transgenic pigs* do. Velander has 17 years' experience working with these special pigs. A transgenic animal carries a foreign gene that has been deliberately inserted into the animal's genes through recombinant DNA technology. In the case of Velander's transgenic pigs, the gene for human factor IX was inserted into the animals' genes, along with a *promoter* gene that "turns on" the factor IX gene only in the mammary gland and only when milk is produced.

Why pig milk? Since the first transgenic sheep were announced in 1985, the hope has been that genetically modified animals would be capable of producing large amounts of human proteins, such as factors IX or VIII, in their milk or urine. The proteins could then be harvested and purified, yielding an abundant supply of rare proteins for human use. Previous efforts to produce blood-clotting proteins in the milk of transgenic animals have been disappointing. One of the reasons is that clotting factors are large and very complex proteins. Ruminants–sheep, cows and goats–were the focus of early research because of the large volume of milk they produce. But these animals proved to be incapable of producing any significant amount of "biologically active" (functional) factor IX or VIII in their milk. According to Velander, when compared to ruminants, pigs (non-ruminants) are biochemically closer to humans in the way they handle proteins. Pigs are also much more efficient than ruminants at "finishing" the proteins to make them biologically active.

Velander claims that the genetic engineering techniques used by his team have been successful in making pigs produce two to three grams of biologically active factor IX per liter of milk. That's about 70 to 140 units of factor IX per milliliter of milk, or about 100,000 units of factor IX in the volume of about a quart. This amount is almost a thousand times the amount of factor IX found in blood plasma (2.5-5 µg/ml). It's also estimated to be about 250 times the amount of factor IX produced in animal cell culture "bioreactors" that are currently used to make recombinant clotting factors. Velander estimates that the milk from his 60 existing transgenic pigs could supply enough factor IX for prophylactic treatment of the 3,000 hemophilia B patients in the US. In theory, several hundred transgenic pigs could satisfy the factor IX needs of hemophilia B patients worldwide. Velander also estimates that factor IX from pig milk could be produced for a fraction of the cost of current factor replacement therapy–possibly as low as $2,000 to $10,000 a year for the treatment of a single severe hemophilia B

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[1, 3] "NIH grant to UNL promises treatment for Hemophilia B": www.newswise.com/articles/view/514477.

by Julia Q. Long

Giving So Much, Asking So Little

The hemophilia patients of Belize have not received a Project SHARE℠ shipment since 2003, largely due to lack of requests from Belize's national hemophilia organization. But two days before Christmas 2005, factor VIII was shipped at last to three young boys living an hour north of the capital, Belize City. The success of this shipment indicates that the Belize Hemophilia Society may at last be developing a leadership role in accessing outside resources, and in communicating with local patients.

LA Kelley Communications President Laurie Kelley visited Belize in May 2001 to help hemophilia leaders establish their fledgling national society. During her visit, Laurie met George Dyck, a Mennonite farmer whose eight-year-old son Peter had just been diagnosed with factor VIII deficiency. Peter was suffering from a foot contracture that made it difficult for him to walk.

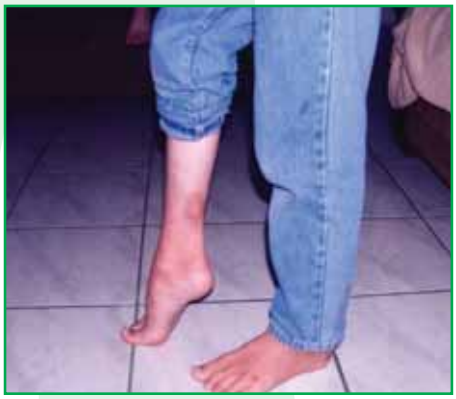
The Dyck family is part of the flourishing Mennonite community of Orange Walk Town. The Mennonites originated in the Netherlands more than 400 years ago, and the first Mennonites arrived in Belize in 1958 seeking freedom from religious persecution and the pressures of modern society. Currently more than 3,500 members live in agricultural communities throughout Belize, alongside Spanish, Indigenous Maya, East Indians and Chinese settlers. Mennonites have retained their language, which dates to the eighteenth century and resembles both Dutch and German.

Mennonites' farming methods utilize oxen rather than modern machinery, but are so efficient that they are the most successful farmers in Belize, supplying much of the country's produce. Mennonites practice a strict form of Protestantism, and carefully exercise proper moral behavior at all times. They refuse to bear arms, use contraception, pay certain taxes or support the military. For these reasons, they subsist without government-assisted welfare support, and in the Dycks' case, without government-sponsored factor.

No factor in Belize: Laurie Kelley meets the Dyck family in 2001.

The Belizean government signed a special agreement granting the Mennonite community exemption from military service and certain taxes, and guaranteeing them freedom to practice their religion. In addition, Mennonites can freely practice their own form of local government, and run their own schools, banks and businesses. Belize is considered the most peaceful country in Central America, and has been recognized worldwide for its commitment to preserving the cultures of its people, and for its unique environmental resources.

Since 2003, the Dyck family has added two more sons–Gerhard, age four, and Franz, age three–who also have factor VIII deficiency. These blond German farmers have been unable to access factor until now. With the national society and the Dyck's family doctor, Project SHARE plans to arrange a special surgery to correct Peter's foot contracture. Meanwhile, we hope that Gerhard and Franz will receive enough factor to avoid their brother's unfortunate condition. Project SHARE is pleased to help the Dyck family with factor, and to continue guiding the Belize Hemophilia Society toward making life easier for the patients who contribute so much to the economy and culture of Belize–and who ask for so very little in return.



Nerve damage from bleeding: Peter's foot.

PROJECT SHARE
It's time to give back

To make a donation of factor concentrate or money, or to obtain advice on donating factor internationally, please contact Julia Long at julia@kelleycom.com

or visit

www.kelleycom.com

With Access For All

by Ann E. Rogers

editorial

"Pennsylvania Introduces Legislation to Protect Choice: Who Will Benefit?" [*Storm Watch*, *PEN*, Nov. 2005] reports on the Delaware Valley Chapter's efforts to ensure access to all factor concentrates. I disagree with Mesfin Tegenu's [vice president, Keystone Mercy Health Plan] reported comments that the Pennsylvania Hemophilia Health Care Act, HB 1705, "seeks preferential consideration for patients with hemophilia versus patients with other chronic diseases," and that this bill "may encourage inappropriate utilization of medication and medical and financial resources for the benefit of special interest groups who stand to profit the most."

The intent of HB 1705 is misrepresented in the article, and Mr. Tegenu's comments are misinformed. Let me set the record straight on this bill.

In response to growing concerns about alarming practices of insurers, the Pennsylvania chapters of the National Hemophilia Foundation (NHF) introduced legislation in 2005 to protect access for patients with bleeding disorders to their life-sustaining factor therapies, treatment and home supportive services. The policies and practices of Keystone Mercy Health Plan and its affiliates are a clear and alarming example of what can happen to patients when insurance companies begin to limit patient access to medicine and care.

HB 1705 seeks only to benefit patients with hemophilia by protecting access to care. This legislation focuses on five key points:

1. Protecting patient access to all factor therapies. We believe that patients with hemophilia have the right to use the factor therapy that works best for them, not the one that an insurance company determines is the cheapest. We believe that all manufacturers of clotting factor agree with us.

We applaud clotting factor manufacturers for not participating in any system that would limit patient access to these specialized therapies, and for rejecting invitations by insurance companies to have a particular clotting manufacturer's product designated as a preferred product for the treatment of hemophilia. Patients with bleeding disorders need access to all factor therapies, understanding that each is unique. There are no therapeutic equivalents and no generics.

2. Protecting patient access to the eight state-recognized hemophilia programs in Pennsylvania. The Centers for Disease Control and Prevention (CDC), the NHF and every leading authority in the US on hemophilia and related bleeding disorders have documented the importance of patients being followed and treated at these centers of excellence. The CDC reports that patients treated at a hemophilia treatment center reduce their morbidity and mortality by 40%. Patients need their insurance companies to pay the bills for their care at these specialized treatment facilities, regardless of whether the hemophilia physician is on the approved provider list of the insurance company.

3. Protecting patient access to the coagulation laboratories associated with the eight state-recognized hemophilia programs in Pennsylvania, regardless of whether the coagulation laboratory is on the approved laboratory list of the insurance company. These specialized laboratories are able to perform specialized coagulation studies and have a faster "turn-around time" than labs contracted with an insurance company. Bleeding disorder patients can't always wait for the results.

4. Protecting patient access to home supportive services. You need only be the parent of a young child with hemophilia to understand the critical role of a good homecare company that can provide skilled nursing. A mail-order pharmacy can serve the needs of many patients with hemophilia, but for the ones that need homecare support, HB 1705 will allow a physician to write a prescription for that service and the insurance company will pay for it. Many insurance companies in Pennsylvania have now purchased their own specialty pharmacies. No wonder they oppose HB 1705.

5. Protecting women from unnecessary hysterectomies by mandating that insurance companies pay for a screening for von Willebrand Disease prior to authorizing a hysterectomy when a woman presents with excessive menstrual bleeding. The American College of Obstetricians and Gynecologists (ACOG) estimates that annually, more than 30,000 women have unnecessary hysterectomies. These women may have a manageable bleeding disorder. Diagnosis and management are always better than surgery.

HB 1705 is an access bill and will only protect what patients have had in the past in Pennsylvania: access to medicines and treatment. I suggest that everyone–especially all *PEN* readers–read this important legislation and decide for themselves.

The Pennsylvania chapters of the NHF were honored at the NHF Annual Meeting in San Diego for their advocacy efforts in the development of this important legislation. We hope that HB 1705 will be a model that all states can use to protect patient access. Many other chronic disease groups in Pennsylvania have congratulated us for our outstanding efforts. They, like us, are feeling the effects of insurance companies

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Hemophilia Thieves... continued from cover

to warehouse to refrigerator. It moves from refrigerator to box, and from van to truck to patient doorstep. There's plenty of room in this process for human error. And apparently, there's also room for human greed. Factor is expensive; the profits it generates can tempt some individuals, even companies, into behavior that could ultimately compromise factor's safety long after it has been manufactured to remove viruses. To understand this threat, you need to learn how the distribution system works to get factor into your hands–and learn what can go wrong.

How Factor is Normally Distributed

Treating hemophilia requires the injection of blood-clotting medicine, called factor, to stop uncontrolled bleeding. Factor is made by one of seven manufacturers in the US: Bayer, Baxter, Grifols, Novo Nordisk, Wyeth, ZLB Behring and Talecris. The manufacturers contract with many vendors that are licensed to buy factor. Factor is then shipped from the manufacturing plants to these vendors. Vendors include specialty pharmacies; homecare companies; hemophilia treatment centers (HTCs) that offer 340B programs[3]; and biological (injectibles) distributors and wholesalers.

Hemophilia patients are most familiar with specialty pharmacies, homecare companies and HTCs. These factor providers are licensed to sell factor directly to patients. In addition to specialty pharmacies, homecare companies and HTCs, there are biological distributors and pharmaceutical wholesalers. These providers act as middlemen, purchasing large amounts of factor from the manufacturers and selling it not to patients, but to other providers, including other pharmaceutical wholesalers and biological distributors. The three biggest pharmaceutical wholesalers in the US–McKesson, AmeriSource Bergen and Cardinal Health–own about 90% of the pharmaceutical distribution market. They normally sell pharmaceuticals (noninjectibles) to hospitals, but are now also providing factor and other biological products. Along with these three major wholesalers, about 15 regional biological distributors–like BioMed Plus–sell factor and other biological products to US hospitals and small homecare companies. It's clear that once any drug, including factor, leaves the manufacturing plant, it enters a complex, interwoven market of buyers and sellers competing for profits.

The hemophilia marketplace is somewhat unique when compared to other chronic disorders: It's a small market in terms of patients, but with huge per capita revenues. With only an estimated 17,000 US hemophilia patients, industry revenues are well over $2 billion per year for factor sales alone. We've witnessed an explosion of providers, pharmaceutical wholesalers and biological distributors all competing for the hemophilia business. Why? Large profits can be made, due in part to the special requirements of providing factor to the bleeding disorders community. For example, it takes a huge amount of money to become a manufacturer-authorized provider or distributor of factor–some factor manufacturers require a $1 million dollar secure credit line before selling to a licensed provider or distributor. You might expect that any company buying factor and selling it to patients would be responsible, established, licensed and well-run. But the vast amounts of money involved in the hemophilia marketplace can attract unsavory and unethical people who attempt to make large profits by taking advantage of loopholes in a weakly regulated distribution system.

Welcome to the Gray Market

These were the unsavory people who broke into BioMed Plus's warehouse to steal NovoSeven in January 2002. Hired by unethical secondary wholesalers, these thieves delivered the stolen medicine, which then changed hands from wholesaler to wholesaler. By the end of its journey, this batch of NovoSeven had changed hands at least six times. The good news was that this factor never reached the patients. The bad news? The changing of hands was all too easy and entirely unregulated. There was no assurance of quality control of a fragile medicine that might have reached patients. Welcome to the gray market.

Operation Stone Cold

Beginning with the investigation into the 2001 BioMed Plus break-in and theft of NovoSeven, prosecutor Stephanie Feldman, drug inspectors Gary Venema, Cesar Arias and Gene Odin, and Miami-Dade investigators Randy Jones and John Petri formed a special task force. "Operation Stone Cold" aimed to uncover the way that drugs were stolen, diverted and possibly counterfeited in South Florida from 2001 to 2003. The five male members of the team called themselves "Horsemen of the Apocalypse." Knowing that patients' lives were threatened by ruthless wholesalers and by the thieves who worked for them, Feldman and the Horsemen worked relentlessly to track down the criminals running an elaborate network of drug distribution through licensed wholesale companies. The team also worked to change weak and ineffective Florida drug laws. What the Horsemen uncovered is not only astonishing but frightening: Patients have doubtless lost their lives to counterfeit drugs sold to them by hospitals. Operation Stone Cold revealed that fraud accounted for about 20% of the $1.8 billion that the Florida Medicaid program spent on medicine, paying for drugs that had been dispensed more than once and resold into a gray market. The team's report showed that many Florida wholesalers are uneducated and inexperienced, often holding criminal records.

The tenacious work of the Horsemen has made Florida the state with the strongest prescription drug distribution laws, and has put other states and the FDA on alert. Read about the "stone cold" killers hunted by the Horsemen, and learn the unsettling truth about our nation's drug distribution system in Katherine Eban's provocative and timely book *Dangerous Doses*.

Dangerous Doses is available at www.dangerousdoses.com or any Barnes and Noble, or through Amazon.com.

[3] 340B programs allow HTCs to sell and distribute factor concentrates purchased at discounted rates.

"Every day, every hour there is pharmaceutical theft, involving thieves. That's dangerous for drugs like factor, which is fragile."

KATHERINE EBAN

From manufacturer to provider or distributor, and finally to patient, all US medicines move through many channels. This is legal, and should be safe as long as medicine is protected, refrigerated, documented and handled by licensed entities. But in the gray market, buyers and sellers, both licensed and unlicensed, look for discounted pharmaceuticals. In the frenzy of buying, few ask questions about the origin of a drug: Who previously purchased it? How was safety maintained? Has it been stolen? How many times has it changed hands? By law, all medicine should come with a "pedigree," or documentation tracking the previous buyers all the way back to the original manufacturer. Yet many licensed distributors don't demand that a pedigree accompany the drug they are buying. Even if they do demand it, they don't check to ensure that the pedigree is valid.[4]

"What most consumers do not realize," Eban writes, "is that while the FDA oversees drug manufacturers, the regulation of drug wholesalers is left to each state and a patchwork of regulations." In other words, once a drug leaves its manufacturer, there is very little regulation and inspection as it gets passed hand-to-hand. Some drugs, such as factor or Epogen (which stimulates red blood cell growth so needed by cancer patients), require a constant temperature and gentle handling. The responsibility for ensuring quality control and safety rests solely with the homecare company, specialty pharmacy, HTC, distributor or wholesaler. Where the distribution chain is short–from manufacturer to specialty pharmacy to patient–quality control is usually rigorous. But what if the medicine passes first from manufacturer to distributor, then from wholesaler to wholesaler, and eventually to the homecare company or HTC before finally arriving to the patient? So many purchasers have been involved that quality control may not be guaranteed. Most serious of all, without the necessary regulations and inspections, the buyers and sellers in the chain may be tempted into illegal acts such as diversion–entering the gray market–or worse, counterfeiting.

What is a Counterfeit Drug?

In *Dangerous Doses*, Eban investigates what happens behind the scenes in America's distribution market for pharmaceutical drugs–and her revelations are shocking. Each year, more than three billion prescriptions are filled in the US. But since 2000, writes Eban, an increasing number of Americans who think they are picking up legitimate prescription drugs get counterfeit medicine instead.

What is a counterfeit drug? Eban defines it as any drug that has been tampered with–for example, by substituting a fake pill or water for a legitimate pharmaceutical. Counterfeits are also created by changing units on the prescription labels to make the dose appear higher than it really is, an illegal process known as "uplabeling."

Eban claims that counterfeit drugs are a consequence of America's flawed drug distribution system. The wholesale market trades constantly and eagerly at all hours, to take advantage of discount prices for brand-name drugs. In their haste to make deals and gain greater profits, traders and wholesalers may obscure a medicine's origin, making its purity impossible to guarantee. Pedigree papers are not requested; and products change hands so quickly that some buyers appear not to notice that they have been tampered with, uplabeled or otherwise adulterated.

Compounding the problem is the infestation of criminals in the wholesaler market. These criminals, claims Eban, are drawn away from the illegal narcotics trade to the wholesale pharmaceutical market because it is less regulated, more profitable, and easier to enter. "Investigators realized by 2002," she writes, "that felons including narcotics traffickers and those with ties to organized crime had infiltrated America's drug supply." Michael Carlow, president of one wholesale company and a prominent character in *Dangerous Doses*, had an extensive criminal record. He was later implicated in the NovoSeven heist. And he is not alone. Graduating from grand theft and narcotics trading in the late 1990s, by 2002 these thieves were prescription drug distributors. They did–and still do–anything for profit, including adulterating prescription drugs that are eventually used to treat critically-ill cancer patients.

While no counterfeit hemophilia product has been documented to date, and while the FDA reports that only a small percentage–less than 1%–of US drugs are counterfeit, even this conservative estimate means that almost 30 million prescriptions are at risk. For the past two years, politicians have warned us about foreign imports of counterfeit drugs; yet Eban stresses that we have much more to fear from our own US suppliers. Eban notes that in 2003 the US experienced 54 counterfeiting incidents, more than reported by any other country. Counterfeiting has become a grave problem. It's been fostered by criminal entry into the distribution system, skyrocketing biological prices, and a weak federal regulatory system.

Diversion: The Greatest Threat

Diversion is the illegal practice of obtaining discounted prescription medicine through fraud, misrepresentation or outright theft, and then reselling it. "Pass any Medicaid clinic in South Florida," writes Eban about drug distribution in 2002, "and you'd see Hummers and BMWs idling outside, their occupants waiting [for patients] to exit with government paid medicine,

[4] In 1988, Congress passed the Prescription Drug Marketing Act (PDMA), aimed at creating transparency and ending the recycling of drugs through distribution channels. PDMA prohibits the sale of drug samples and restricts the resale of pharmaceuticals by hospitals, pharmacies and other end users. It prohibits the reimportation of American-made drugs sold overseas. It requires wholesalers to disclose the source of the drugs they purchase. Above all, it requires each drug to have a pedigree identifying previous buyers and sellers. The law has been largely ignored and not enforced in many states. Source: *Dangerous Doses*.

which patients were often ready to sell for cash." Prescription drugs, explains Eban, were bought from patients by thieves like those in the Hummers, then sold to distributors, and then recycled into the system, with Medicaid paying each time. Some of the thieves befriended patients at rehabilitation programs, built personal relationships, and then bought their medicine. This soon became a way of life for some: Patients regularly ordered extra medicine, kept what they needed, and sold the rest to the middlemen for cash.

In 2000, diversion was a thriving practice in some states and sectors.[5] "By 2002, the FDA's criminal investigators realized that a huge volume of the nation's medicine no longer flowed directly from drug makers to one of the big three distributors to a pharmacy or hospital," Eban writes. "Instead, the medicine was sold and resold in a swelling gray market of middlemen, passing through numerous hands, as each company took a wedge of the profits. These sales often were unrecorded or were accompanied by phony pedigrees that obscured the origin and left no way to ensure its safety." Diversion had become a multi-billion-dollar illicit business in America.

Besides the obvious problem of insurance fraud, the greater problem with diversion is that medicine can change hands several times illegally with no assurance of quality control. Eban notes that sensitive medicine has been left in car trunks for hours, baking in the Florida heat, before exchanging hands. Fragile medicine has been stored without refrigeration for days or months in warehouses full of trash, water damage and mold. Factor is a sensitive medicine, and all patients are trained to refrigerate it whenever possible. Dramatic temperature changes can cause the rubber stopper, designed to protect the product from bacteria, to shrink and swell. This can create micro-gaps between the stopper and the glass vial, increasing the risk of bacterial contamination.

"Diversion is rampant in this country," Eban told *PEN*. "Federal investigators estimate that half of the nation's drugs are routinely diverted from their intended path." And the greatest threat is that diversion can lead to counterfeiting. "There's never been a counterfeit drug entered into the US market that didn't come from an illicit diversion network," explains Eban. And while counterfeiting has never been documented with factor products, diversion of factor has.

Wolves in Sheep's Clothing

In September 2005, the hemophilia community was shocked to hear allegations that two prominent homecare representatives admitted in Los Angeles federal district court to diversion of hemophilia products. One defendant is a former homecare representative who served the hemophilia community in Southern California for years, and then became vice president of hemophilia operations at a large specialty pharmacy. The other was president of a homecare company.[6]

While the details of the case are not yet clear, this breach of trust within the hemophilia community is shocking. According to online sources[7], both men admitted in court to buying factor from patients who had purchased it legally from homecare companies or HTCs, and then allegedly reselling the factor to a wholesaler in Miami. The wholesaler is alleged to be none other than BioMed Plus, the company from which NovoSeven was stolen, as described in the opening pages of *Dangerous Doses*. An arraignment is scheduled in March 2006 for both men, who may face jail sentences. There is a 288-count Department of Justice indictment against the president of BioMed Plus and several of his colleagues for their alleged role in this scandal.[8]

Action Steps to Avoid Counterfeit or Diverted Product

WATCH WHAT YOU TAKE.

- Know your factor brand, name, manufacturer and assay size.
- Know the typical shape, color and size of the box and vial.
- Examine the factor-filled syringe under a strong light before infusing.
- Look for altered packaging or changes in design.
- Make sure the box and vials are clean, with no sticky residue on labels.
- Inspect all vials for thin cracks.

OBSERVE YOUR REACTIONS TO INFUSED FACTOR.

- Be aware of new or unusual side effects.
- Notice if your factor is no longer effective.
- Be suspicious if your factor stings or causes a rash when infused.

LOOK FOR THE LATEST WARNINGS.

- Sign up with PNS for any recalls or warnings. Call (800) UPDATE U to sign up.
- Get information regularly from your manufacturer or homecare company.

IF YOU THINK YOUR FACTOR IS DIVERTED OR COUNTERFEITED…

- Do not use it.
- Tell your doctor, manufacturer and supplier immediately.
- Submit a report with your doctor to the FDA at www.fda.gov/medwatch/report/consumer/cosumer.htm.
- Keep a sample of your medicine as evidence even if the manufacturer asks you to send it all back.

GENERAL ADVICE:

- Buy only from a reputable seller.
- Inform your doctor, homecare company, local hemophilia organization and police if someone offers to buy factor from you directly.
- Ask for a factor pedigree from your homecare company or HTC.
- Read *Dangerous Doses*.

[5] Eban writes that in 2000, a task force for the National Association of Boards of Papacy estimated that up to four-fifths of the closed-door pharmacies that received discounted medicine resold at least a portion illegally to outside buyers. [6] www.LawFuel.com, Sept. 7, 2005; www.nashuatelegraph.com, Sept. 22, 2005; www.curative.com, company press release, Sept. 21, 2005. [7] http://lawfuel.com/index.php?page=press_releases&handler=focus&pressreleaseid=4201&category=&return=list-publications&sortby=timestamp&screen=5. [8] For more information, see www.usdoj.gov/usao/gas/pr/2005/09_05_BioMedPlus1.pdf and http://myfloridalegal.com/newsrel.nsf/newsreleases/BF8B24770B3086DC85256FCE0050DEC2.

Selling Factor to Russia: Is This Illegal?

by Laurie Kelley

A few years ago, a young Russian man with hemophilia I know emailed to ask my advice before buying factor from someone in the US. I'd been to Russia twice on hemophilia-related work, and I knew that the situation there can be difficult for people with hemophilia. Factor is purchased by the government in small amounts, and usually only in four major cities. If you live in a small city or rural area–and remember that Russia is the largest country on earth–you must either travel great distances to reach Moscow, for example, in the hope of obtaining factor concentrate, or you must settle for cryo or fresh frozen plasma administered locally. Traveling long distances to treat a bleed with concentrate means joint damage (or worse) en route; being treated locally and quickly often means accepting the viral risks inherent in cryo or plasma. Many Russians with hemophilia are desperate to obtain factor concentrates–by any means. And because of a thriving Russian black market, which often includes corrupt customs officials, shipping factor to Russia is almost impossible for anyone except a licensed exporter.

I asked my friend to tell me about the American who offered to sell him the factor. Was it a pharmaceutical representative? A homecare rep? A licensed distributor? No, said my friend, this man was a patient, like himself, who had extra factor that was not expired. When my friend sent me this man's email contact information, I immediately recognized the American seller, and emailed him some tough questions: Did he realize that he was breaking international law? Shipping pharmaceuticals and biological without a license, for profit, is illegal. Did he realize he was breaking US federal law by committing insurance fraud? This man's insurance company had paid for his factor, and now he sought to sell it. He knew that this was illegal, but didn't realize how serious. He also didn't think he'd even get caught. I asked, *Why would you do such a thing?* He replied simply, *I have a lot of bills to pay off.* Ultimately, he was unable to sell the factor to my friend. When he understood the situation, my Russian friend didn't want to get involved in such a scheme.

The moral? Be forewarned if you ever think of selling the factor paid for by your insurance company or government: You'll be committing a serious crime, punishable by fines and/or imprisonment.

"Diversion is a violation of consumers' trust," says Patrick Schmidt, CEO of FFF Enterprises and president of NuFACTOR, a hemophilia specialty pharmacy. "And it's an abuse of the system. There's a lot of money to be made in selling factor. Some homecare reps are told they can make up to $600,000 a year. Think of the river of wealth that has been created. And yet it could have gone to helping out HTCs instead of making select individuals wealthier."

Diversion is more likely to occur during times of shortage, notes Ken Trader, vice president of sales and marketing for Hemophilia Health Services (HHS). "During the shortage of plasma-derived product in the mid-1990s and the recombinant factor VIII, albumin and IgIV shortage from 1999–2003, product moved quickly through the distribution channels, and distributors not normally involved with factor now were looking to make spot deals," Trader recalls. "This increases costs, but also increases the possibility of a product not being handled properly."

To those skilled in finding loopholes in the pharmaceutical distribution marketplace, or those desperate to buy factor, diversion is tempting. Some industry experts believe that temptation may lure smaller distributors–those without the hemophilia patient base to carry enough contract 'clout' to purchase factor directly from manufacturers. These distributors may be more susceptible to using secondary wholesalers to obtain their factor, perhaps running a higher risk of accepting diverted product. "One businessman I know who owned a smaller homecare company wanted to buy from a wholesaler," says one homecare manager. "Why? The wholesaler didn't require a million-dollar line of credit to buy product, like the manufacturers do. He didn't have the credit to buy from the manufacturers."

The only answer to ensuring safety of product lies in closing the various loopholes that allow diversion.

What is Industry Doing to Preserve Safety?

Obviously, the US drug distribution system needs to be tightened. Great strides have been made in Florida, where efforts by the "Horsemen of the Apocalypse" (see page 7) have brought much-needed change: rigorous regulations for anyone hoping to become a drug wholesaler, stiffer penalties for diversion or counterfeiting, and pedigrees for all drugs. Who else is acting to protect hemophilia products from diversion and even counterfeiting?

Some specialty pharmacies and distributors publicly declare strict quality control and an avoidance of any gray market for diverted drugs. FFF Enterprises is one of the industry leaders pushing to eliminate the gray market, and proudly advertises itself as being free of any market for diverted drugs. Hemophilia Health Services, currently the country's largest hemophilia specialty pharmacy, also avoids the gray market and buys solely from manufacturers. "One of our tasks is to match correct assay sizes to the prescriptions given to us," explains Ken Trader of HHS. "We once asked a manufacturer for a certain assay size, which they did not have. They suggested we purchase their product in the correct size from a biological distributor, so we would be able to fulfill our assay sizes. We refused. We want to reinforce to the manufacturer the need to limit the distribution channels to those providers who supply product directly to the hemophilia patient, and who support their company's image and product integrity in the community."

Manufacturers are also getting wiser. They can choose to sell only to specific factor providers. According to Terry Tenbrunsel, vice president of sales and marketing for Kogenate® FS, "Bayer

Ask Your Factor Provider These Tough Questions to Prove Safety

1. Do you purchase directly from the manufacturers?
2. Do you ever purchase from secondary wholesalers? How often? Under what circumstances?
3. What is your purchasing policy when there is a factor shortage?
4. Do you require pedigrees from your suppliers?
5. Can I see the product's pedigree on demand? If not, why not?
6. Do you perform criminal checks on your employees?
7. Has any employee, including company owners, ever been accused, indicted or convicted of fraud, embezzlement, diversion or counterfeiting?
8. Have you ever had been cited for code violations?
9. When was your last pharmacy inspection?
10. What is the average salary of your homecare reps?

has a multi-faceted commitment to product safety and integrity, which encompasses the entire supply chain, including manufacturing, packaging and distribution. Bayer only sells and ships Kogenate FS directly to licensed distributors, homecare companies, specialty pharmacies and 340B HTCs. In the US, our distribution policy places restrictions on these entities' ability to sell product to other organizations."

In addition to eliminating the gray market, manufacturers can create tamper-evident packaging. Bayer is the first recombinant factor VIII manufacturer to offer tamper-evident devices to the hemophilia A community. Beginning in January 2006, each package of Kogenate FS released will be equipped with a top-glued flap with the product logo that cannot be resealed.

Product labels can also be made with embedded features that can be detected only through special inventory equipment designed to detect counterfeit labels. Since mid-January 2006, the labeling on Kogenate FS with BIO-SET® contains several anti-counterfeit features that help identify forged labels.

Security measures for manufacturing will need to be continuously updated. Eban warns that within 18 months, counterfeiters can copy almost any packaging. Our best hope lies in ensuring that all factor distributors eliminate the use of a gray market, and deal directly–and exclusively–with the manufacturers. Manufacturers can help by limiting sales to wholesalers and distributors. There is also a role for patients to play, and there are many steps you can take to ensure that your hemophilia products come from reliable and safe sources.

What Can You Do?

Patients can be on alert for counterfeits and diverted product. Eban suggests starting with your own product:

Know your factor brand, manufacturer, typical box shape and color. Examine the factor-filled syringe under a strong light before each infusion. Look for altered packaging or changes in design, and make sure that box and vials are clean, with no sticky residue on labels. Record each infusion, including the lot number.

Observe your reactions after each infusion. Do you experience any new or unusual side effects? Is your factor no longer effective? Does an infusion sting or cause a rash? Of course we are taught that these are signs of anaphylactic shock, but we should also consider the possibility of impure products, however unlikely.

Stay informed. Sign up with the Patient Notification System[9] for immediate news of product recalls and warnings. Talk to your manufacturer, homecare company or HTC: What do they know about diverted products? Do they purchase from distributors? Use the checklist opposite to ask tough questions of your factor provider.

If you suspect that your factor is diverted or counterfeited, do not use it! Tell your doctor, manufacturer and supplier immediately, and with your doctor submit a report to the FDA. Be sure to keep a sample of your medicine as evidence even if the manufacturer asks you to send it all back.

Buy only from a reputable seller. "All homecare companies are not the same," warns Trader. Eban agrees: "Don't assume your medicine's safety is guaranteed." If your homecare company is new, small, not yet established or does not specialize in hemophilia, be sure to get proof of the way it conducts business: Where does it purchase factor? What is company policy concerning the gray market? Under what circumstances would it purchase factor from a wholesaler? Patrick Schmidt recommends asking more questions: Has the company ever been cited for code violations? When was its last pharmacy inspection? Does it keep records of shipped medicine, and for how long? Does it record every unit, each infusion? Does the company track lot numbers of individual shipments? Does it accept returned medication from its patients? Does it buy only from the manufacturer? If not, can it guarantee in writing that its providers are safe sources of factor? "If the company cannot put this in writing and can't provide it to consumers," Schmidt advises, "*run!*"

Request pedigree papers. "All patients should be allowed to see pedigrees upon request," believes Trader. "If you are sticking medicine into your veins, you have a right to know." Terry Tenbrunsel of Bayer states, "As providers of the hemophilia community, we believe that all patients should be empowered to ask their providers for pedigree documents."

Don't sell your factor. Inform your doctor, homecare company, local hemophilia organization and even the police if someone offers to buy factor from you–this is illegal, and you could be implicated as an accomplice and face a fine or even jail.

Do your homework before joining a homecare company. One homecare representative and person with hemophilia warns: "Be careful that your homecare company is really a homecare

[9] Register to receive updates of product recalls and withdrawals automatically by contacting the Patient Notification System at www.patientnotificationsystem.org or (800) UPDATE U.

company. Some companies position themselves as homecare companies. Manufacturers may sell to them, but they are actually 'shell' companies who subcontract with small pharmacies. These shell companies can lose quality control over your factor by subcontracting. One of our patients got wined and dined by one of these [companies], and signed on with them. What he didn't know was that his new company didn't have a contract with his insurance company–he was actually signing up with the subcontracted pharmacy, and paying more for his factor."

Congressman Steve Israel of New York recently introduced new legislation: The Counterfeit Drug Enforcement Act (HR 3297), nicknamed "Tim Fagan's Law" after a young New York patient who suffered terribly from injecting counterfeit drugs for his cancer treatment. This law would require comprehensive pedigrees for all drugs, give the FDA increased authority to recall drugs, and strengthen penalties for counterfeiting and diversion. In Florida, Governor Jeb Bush signed into law a "miniversion" of Tim Fagan's Law: The Prescription Drug Protection Act. The Florida law was a direct result of the investigations by the Horsemen detailed in Eban's book. Eban commented to *PEN*, "Most people cannot believe that the FDA does not regulate the supply chain. Once medicine leaves the loading docks, that's it. Safety comes down to individuals in individual states who are willing to fight lax laws. And once one state, like Florida, tightens its laws, bad wholesalers flock to states with weak drug laws, like North and South Carolina, Maryland and Georgia. Our biggest problem is that states are left to regulate wholesalers."

You can start your own campaign for safer drugs by purchasing *Dangerous Doses*, considered the contemporary definitive examination of America's drug distribution problem. Easy to read, gripping and relevant, Eban's book will educate you quickly. Once you've learned the right questions to ask, the right people to ask, and the answers to expect, you'll be ready to safeguard your factor. With so much attention focused on reimbursement in hemophilia, consumers may be factor's foremost protectors and advocates–ensuring that factor is shipped and distributed legally and, above all, safely. "The hemophilia community is a politically powerful group," notes Eban. "I would urge this community to get behind Tim Fagan's Law, and get active to make all prescription medicines safe for everyone."

Laurie Kelley is president of LA Kelley Communications, Inc. and author of ten books on hemophilia. She is a popular speaker in the worldwide hemophilia community, editor of *PEN*, and mother of an 18-year-old son with hemophilia A.

Becoming a Mover and Shaker... continued from page 3

ability to listen and follow directions, and management of fear. Many gymnastics clubs throughout the country offer educational gymnastics classes in a non-competitive, safe and developmentally appropriate environment.

Building Skills and Confidence

Becoming a confident and effective mover can enhance anyone's quality of life. Not every child will play organized sports, but children who are competent and confident movers will likely continue moving throughout life. Basic motor skills learned at a young age provide children with the physical ability and self-confidence to lead a physically active, healthy lifestyle. Adolescents and adults who haven't mastered fundamental movement skills often shy away from physical activity because the movements feel unnatural and overly strenuous; and learning them at an older age is much more challenging.

Research shows that children who lack the ability to execute basic motor skills are three times more sedentary than skilled children. Offering motor skills and gymnastics instruction to students at younger age levels will better prepare them for future sports, physical activities, and life in general. For children with hemophilia, participation in a well-designed educational gymnastics program fosters an active lifestyle, encourages prudent decisions about personal safety, reduces the risk of injury and bleeding, and produces more confident and skillful movers.

Jeff Coelho is professor of physical education and director of gymnastics instruction at the United States Military Academy at West Point, New York. His son Matthew is an active nine-year-old with severe hemophilia. His wife Suzannah teaches physical education at the West Point Elementary School.

With Access For All... continued from page 6

making medical decisions that should be made by the medical specialists treating patients in the clinical setting.

Not every insurance company in Pennsylvania is an offender, but some insurance companies in Pennsylvania have had record profits in their health insurance divisions over the last three years, as they deny access to medicine and services for patients with chronic illnesses like hemophilia. Is it the rising costs of healthcare or the rising profits of health insurers that are driving some to deny coverage for what patients really need?

We thank Representative Roy Baldwin of central Pennsylvania for understanding our serious issues, and for his strong leadership as sponsor of HB 1705. He is firmly committed to doing what is right for patients with bleeding disorders in Pennsylvania, despite strong opposition from the powerful insurance lobby. The Pennsylvania Department of Public Welfare (DPW) was considering implementing a preferred drug list for Medicaid beneficiaries with hemophilia, which would have required hemophilia patients in Pennsylvania to "fail first" on the state-preferred clotting factor before being able to receive their preferred factor replacement therapy. In an effort to make the right decision for these patients, DPW solicited a recommendation from the Pharmacy and Therapeutics (P and T) Committee. On December 14, 2005, after reviewing the hemophilia drugs, the P and T Committee recommended that Medicaid beneficiaries with hemophilia should have access to *all* factor replacement therapies. DPW has accepted that recommendation and will include all factor replacement therapies on a preferred drug list. This is one important victory for our community of patients in Pennsylvania.

Ann E. Rogers, M.S. is the executive director of the Delaware Valley Chapter, National Hemophilia Foundation.

homecare

Infusion Tracker 2™

NuFACTOR's Infusion Tracker 2 is an innovative PC-compatible software program that allows you to document, analyze, visualize and report your bleed and infusion history. You can track your bleeding history for any selected range of dates, see your history on a color-coded body map, and print and email your usage reports. You can identify target joints instantly, track the effectiveness of your prophylaxis schedule, recognize your seasonal bleed patterns, and record your lot numbers permanently. *Free.*

For more information, call NuFACTOR: 800-323-6832

manufacturer

"Time for ReFacto®" 2006 Trial Prescription Program

Enroll in this program to receive a one- to two-month complimentary supply of ReFacto, Wyeth's recombinant factor VIII concentrate. Ask your doctor if this program may be right for you. Fill out the necessary enrollment forms with your doctor, and you'll get a prescription for ReFacto. Patients currently receiving ReFacto and/or those who have participated in previous ReFacto trial prescription programs are not eligible for the 2006 program.

For more information, call Wyeth: 800-710-1379
Monday–Friday 9:00 am–5:00 pm EST

Bayer's New Needleless Transfer Device

Bayer now offers Kogenate® FS with BIO-SET® as the first integrated reconstitution system for recombinant factor VIII that eliminates the risk of accidental needlestick injuries during reconstitution. Compared to the conventional vial-to-vial reconstitution method, Kogenate FS with BIO-SET needleless reconstitution system requires fewer than half the components, eliminates the need for double-sided transfer and filter needles, and involves half the steps during the reconstitution process. BIO-SET received an enthusiastic response in Canada and several EU countries, and will be available for the US hemophilia community in early 2006. BIO-SET is a trademark of Biodome SAS.

For more information: www.kogenatefs.com/press_news.cfm

New Manufacturer Website for Hemophilia B Patients

ZLB Behring has launched a new website, *HemophiliaB*, devoted solely to information about hemophilia B, also known as factor IX deficiency, and its plasma-derived product Mononine®. Website topics include up-to-date information on hemophilia B, links to web resources, access to free educational materials, product information about Mononine, and an opportunity to sign up for free ZLB Behring quarterly e-newsletters.

For more information: www.hemophiliaB.com

ZLB's Mix2Vial™: No More Needles

Mix2Vial is a plastic, needleless transfer device now available for use with ZLB Behring factor products. Mix2Vial is efficient and convenient for nurses, pharmacists, patients and parents. It helps minimize the risk of accidental injury and the time required to prepare product, and teaches independence in learning to infuse safely. Mix2Vial includes a built-in filter, can be used on 20/20 mm products, and requires no handle to manipulate. Use with all Luer-Lok® syringes.

For more information and to view video demonstration:
www.zlbbehringmix2vial.com or call 800-504-5434

Talecris Offers Treatment for Hemophilia A Patients in United States

Talecris Biotherapeutics was launched in 2005 as a worldwide therapeutic proteins company after acquiring the contributed assets of Bayer HealthCare's plasma business. Since then, the company has focused on strengthening its business through safe and reliable supply of its current product line, which includes cost-effective, plasma-derived therapy for hemophilia A patients in the US.

For more information: www.talecrisusa.com or call 800-243-4153

nonprofit

Hemophilia Federation of America

HFA is a grassroots, consumer-based advocacy nonprofit organization for people with bleeding disorders. Join patients, industry representatives and leaders in our community, March 31–April 2 2006, for HFA's annual meeting to learn more about hemophilia, treatment and advocacy efforts to protect product and provider choice.

For more information:
www.hemophiliafed.org/symposium_2006.html

Emergency Room Awareness—*At Last!*

The Factor Foundation of America has developed an emergency treatment program called FactorFirst™, which will distribute educational material to US emergency rooms in 2006. The program was created in conjunction with the FactorFirst Steering Committee, with input from the American College of Emergency Physicians (ACEP) and the Emergency Nurses Association (ENA), and with a grant from Baxter Hyland to assist with the cost of printing the FactorFirst emergency room poster.

For more information, call Edward Burke: 727-692-5858

Johnny! Drink your factor!... continued from page 4

patient, compared with $100,000 or more per year using current factor concentrates.

Although Velander and his team believe they have chosen the "correct" animal–capable of producing biologically active factor–the production of factor in pig milk is only half the story. Milk is a hostile medium for factor because it contains enzymes that rapidly inactivate the factor. Milk also contains many proteins that make it hard to purify the factor from the milk. We can't simply drink the milk of these pigs to obtain the factor. Pig-derived factor requires sophisticated purification steps similar to those used to produce our current recombinant factor. Regrettably, the sophisticated facilities needed to separate and purify factor from pig milk would be too expensive for many developing countries. The cost of the resulting factor would also be exorbitant–far too much for the vast majority of people with hemophilia who presently don't have access to clotting factor. Even at the relatively low cost of $9,000 per person per year for clotting factor concentrate, the costs would still be unrealistic in many countries where the per capita health spending is very low. As an example, India spends approximately $10 per person per year on healthcare.[2]

On the other hand, in developed countries that can more easily afford factor concentrates, Velander believes that abundant lower-cost factor would open the door for the development of alternative delivery methods. Presently, the only effective way to administer factor is through intravenous infusion. Other delivery methods, such as oral, inhaled or subcutaneous (beneath the skin), are highly inefficient and ineffective. These methods waste precious and expensive factor because the large and fragile factor molecules are not easily absorbed; and in the digestive system, factor is rapidly broken down and destroyed. But with abundant and relatively inexpensive factor, Velander's team believes that we can afford to "waste" most of the factor–in other words, it won't matter that some factor is destroyed by the digestive system or lost due to lack of absorption. We can afford to waste factor in order to achieve a more convenient delivery method and improve patient quality of life.

Experiments with mice have shown that factor IX ingested on an empty stomach is completely destroyed in the gastrointestinal system: none reaches the blood. When factor is ingested after a meal, however, 4% to 11% of the factor IX shows up in the bloodstream. Although a loss of 90% or more of the ingested factor is unacceptable at today's costs, this could be an acceptable tradeoff if costs were much lower. One of the goals of the research funded by the NIH grant is to develop an oral factor formulation that will "protect" the factor IX long enough for at least 5% of it to be absorbed into the bloodstream. In essence, this means converting a person with severe hemophilia into a person with moderate or mild hemophilia, thus avoiding most spontaneous bleeds and associated joint damage. As an added bonus, factor administered orally at a young age may help prevent inhibitors. In experiments with mice, factor IX administered orally did not elicit antibody (inhibitor) formation, but when factor IX was injected intravenously, 100% of those mice developed inhibitors. It's speculated that feeding factor to babies as soon as hemophilia is diagnosed may reduce the risk of inhibitor formation through tolerization. Should this prove to be true, then oral factor could achieve two objectives at once: it could decrease the frequency of bleeds and tolerize the individual to factor, reducing the formation of inhibitors. Velander is particularly interested in developing an oral dose of factor IX for children, from infants up to possibly age five. "The oral therapy would be a godsend, a true miracle," says Velander. "If you have an abundance of the protein, you can potentially overcome the inefficiencies of orally delivered therapies."[3]

More abundant and less expensive factor IX would surely be great news for people with hemophilia B, and would certainly expand the availability of factor concentrates in developing countries. Yet some researchers are highly skeptical of Velander's projections, and consider them over-optimistic. Indeed, during the past two decades, the entire transgenic industry has suffered from over-optimistic predictions about the potential of proteins made by transgenic animals. These rosy predictions, and the lack of viable products after years of research, resulted in a loss of investor confidence and shortage of venture capital, causing a shakedown of world leaders in the industry. Just a little over a decade ago, news releases from transgenic companies forecast that people with hemophilia would soon receive their factor just by drinking the milk of transgenic animals. It was further predicted that developing countries would raise their own flocks of transgenic sheep or goats to fully supply their citizens with low-cost clotting factor. As it turns out, these early predictions grossly underestimated the technical challenges, the high cost of conducting research, and the amount of time needed to develop transgenic animals capable of producing biologically active clotting factor. Similar over-optimistic expectations accompanied the introduction of recombinant clotting factor in the early 1990s. At the time, the community expected that recombinant technology using cell culture bioreactors (which currently produce all of our recombinant clotting factors) would create an inexpensive and endless supply of factor concentrate. As we now know, the supply is neither endless nor inexpensive.[4]

Velander's team has much work ahead. Over the next five years of the NIH grant, the team plans to scale-up the recovery and purification of transgenic recombinant human factor IX from small laboratory techniques to commercial-scale processes. It also plans to test the efficacy a purified factor IX product in hemophilia B dogs, and develop an oral dosage form of factor IX. By the end of the NIH grant, Velander expects to have a factor IX product ready to go directly into clinical trials. Within three years, Velander also hopes to apply what he learns from working with factor IX to the development of a pig-derived factor VIII product.

Within five years, we'll know whether Velander's optimism is warranted. If all goes well, within a decade we may have a low-cost, abundant supply of factor on the market. We may indeed be saying to our children, *Johnny! Drink your factor!*

[2, 4] *Plasma-derived and Biotech Products: What Is the Future of Haemophilia Therapy?* Brian O'Mahony, www.wfh.org/2/docs/Publications/Treatment_Products/Monographs/OP1_Plasma-derived_Biotech_products.pdf.

Letters... continued from page 2

travel letter] in English, and I couldn't explain why we had all these medical supplies with us. I said to my wife, "Kristin, I should have had our letter translated into Spanish to speed things along in the explanation." I wanted to share this story with your *PEN* readers. It may help someone someday.

David Prior
VERMONT

Your personal stories of your travels had an impact on me. They really bring home the unbelievable circumstances faced by some of these families, and make me appreciate all the more what my family has. I am going to have my children read these stories in the hope that they will appreciate what other kids, less fortunate than they, deal with every day.

My family and I will continue to sponsor several families personally through Save One Life. If you need materials, money, gifts or medical supplies, let me know. I'll do whatever I can personally and corporately. Your stories touched me and moved me to say I'd like to do more.

Eric Hill
President, BioRx
NORTH CAROLINA

I'm always eager to share the details of my trip to the Dominican Republic in order to illustrate how lucky the US hemophilia community is when compared to the rest of the world. Most of the time, though, it seems that my words don't impart the same sense of need and urgency that I have experienced.

I'm really glad that you devoted an issue to your travels around the world. Your words and pictures definitely get the message across. It's heart-wrenching to know that the unnecessary suffering not only happens, but continues. I hope that this issue will be a catalyst for people to take more action.

Mothers of children with hemophilia are overwhelmed just taking care of their own children, and you've managed to help and give hope to countless families across the world. Whether it was inspiration or a higher power that called you to this emotionally taxing work, the world's hemophilia community is so blessed to have you as its advocate. Bravo!

Andy Blackledge
ARIZONA

My 15-year-old son Corey has hemophilia. We both just finished reading *PEN* and were very moved by the stories about children in other countries suffering so much because of lack of medical care and factor VIII, and poverty.

We want to know how we can help. From what I understand, the cost [of sponsorship through Save One Life] is $20.00 per month to sponsor a child. Corey wants to donate part of his earnings from work.

I cannot believe how lucky we are. We worry about insurance premiums and choice of homecare companies, and these families worry about keeping their children alive and fed!

Tracy and Corey Orsic
OHIO

Editor's Note: Please see www.saveonelifeinc.org for more information about Save One Life.

I would like to share this story with all those who benefit from factor donation so they may not take it for granted. My wife Gina and I now live at Johnson Bible College, where I am studying for the next four years before returning back to my native Haiti. My wife received a phone call in November from Haiti informing her that Paul-Marc, her hemophilic 21-year-old brother, had died. When she asked what happened, the caller said that Paul-Marc was having some teeth extracted and bled to death as a result. This is the second child my wife's mother lost in the very same way.

I have two boys with hemophilia, and even though they are now in America that does not mean they are out of danger. The reason is that we don't qualify for free care. Only Laurie Kelley and her company help us when we have an emergency. Therefore, I am asking you all reading this to be thankful for the donation of factor you have been receiving though Project SHARE℠.

Raymond Pierre-Louis
Director, Christianville
GRESSIER, HAITI

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name and date of birth of child(ren) with hemophilia

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PEN maintains a special network of patients and parents to provide us with information for upcoming articles and projects. We want to get your ideas, opinions and experiences periodically through telephone surveys, interviews, or written questionnaires. If you'd like to be on our elite team, check "Yes" in the box at left, and send or email this form to us.

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