October 2009

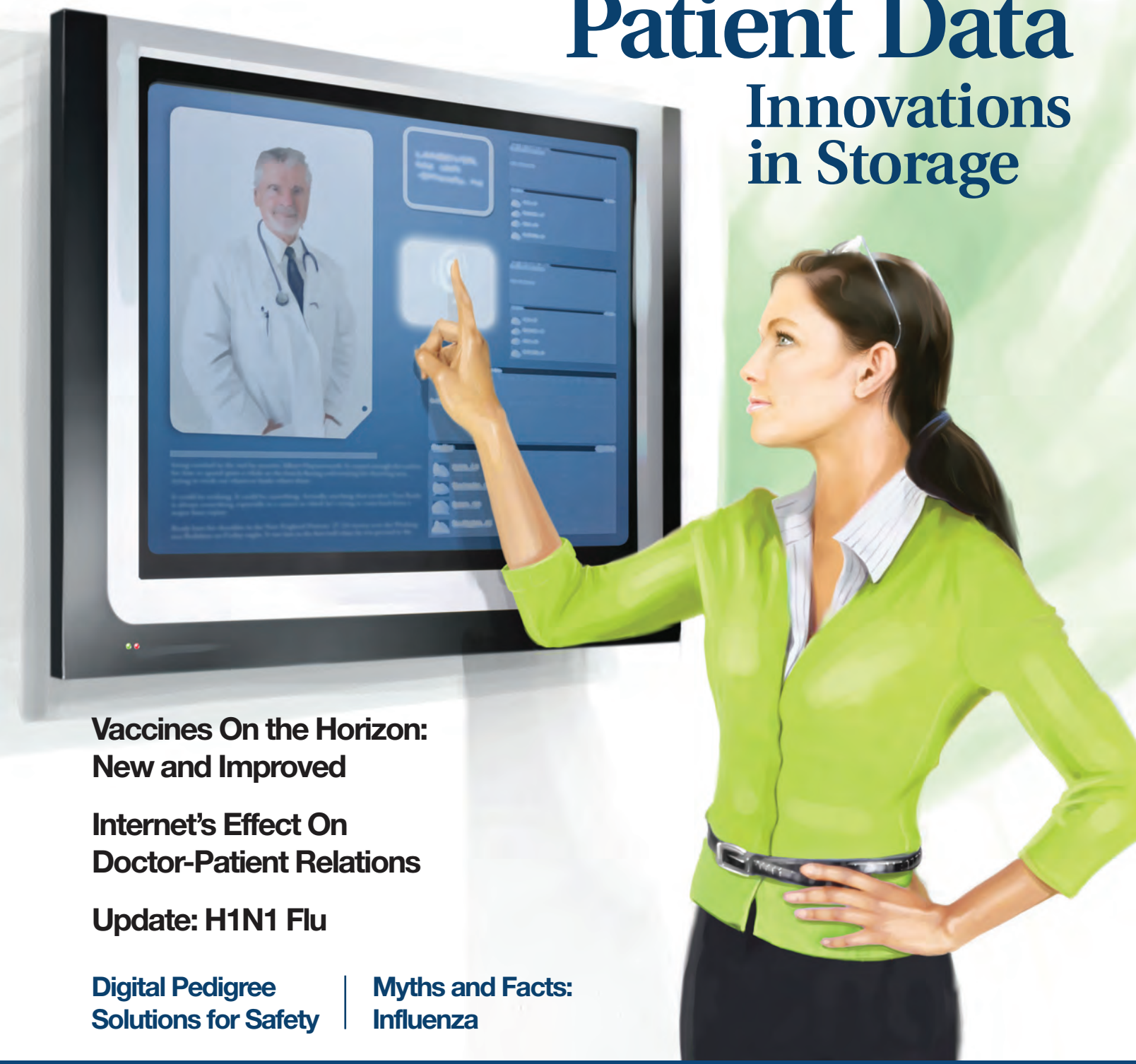
BioSupply Trends

Special Focus: INNOVATION

Quarterly

Patient Data

Innovations in Storage



Vaccines On the Horizon: New and Improved

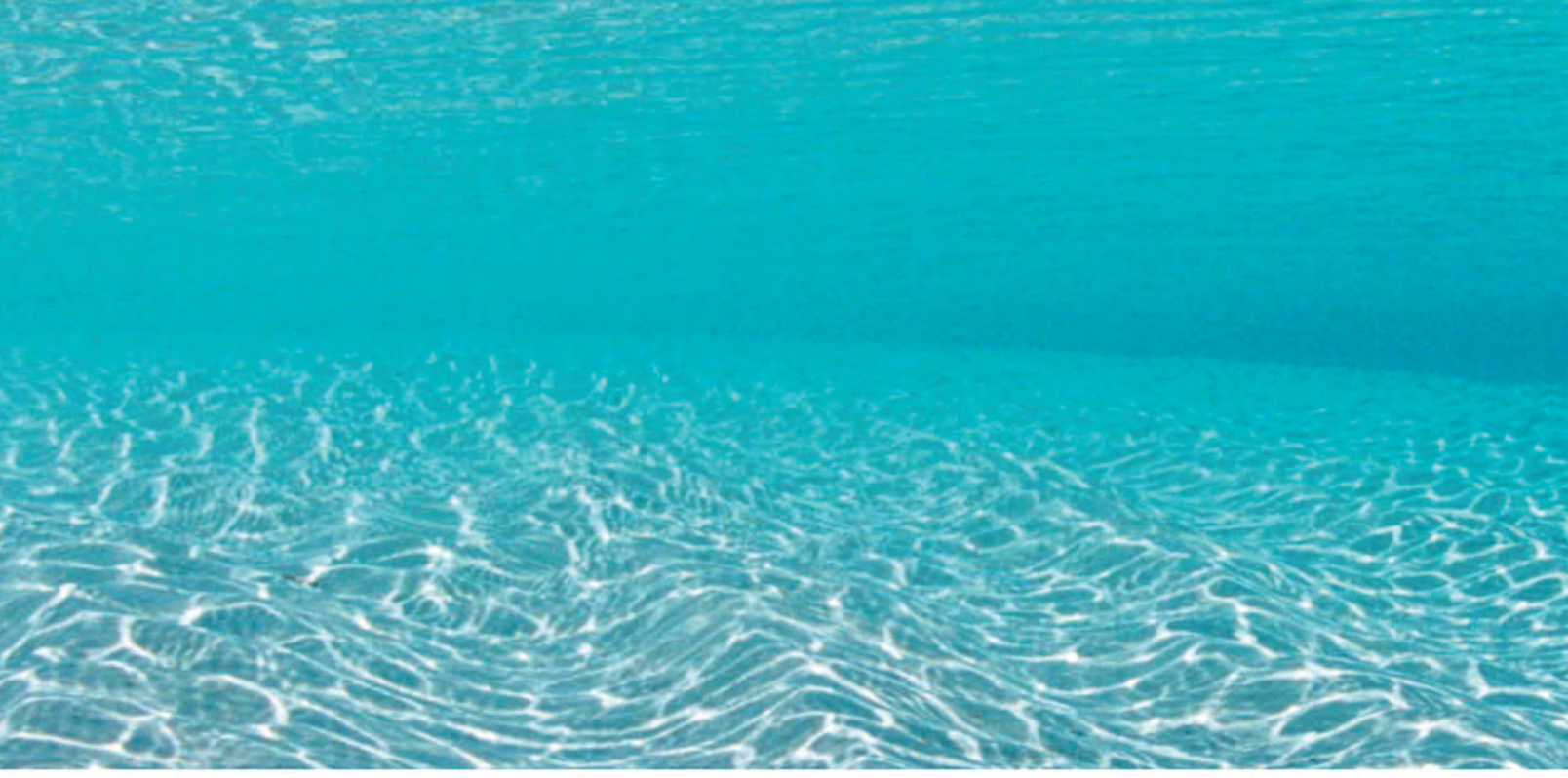
Internet's Effect On Doctor-Patient Relations

Update: H1N1 Flu

Digital Pedigree Solutions for Safety

Myths and Facts: Influenza

Immune Globulin: Understanding Access — Page 28



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use octagam®, Immune Globulin Intravenous (Human), safely and effectively.

OCTAGAM®
Immune Globulin Intravenous (Human) 5% Liquid Preparation

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions - Hyperproteinemia 8/2008

WARNING: ACUTE RENAL DYSFUNCTION and RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. octagam® 5% liquid does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

- octagam® is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI).

DOSAGE FORMS AND STRENGTHS

octagam® 5% liquid is supplied in 1.0 g, 2.5 g, 5 g , 10 g or 25 g single-use bottles

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity
- Patients with acute hypersensitivity reaction to corn

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of octagam® 5% liquid with some glucometer and test strip systems.
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome has been reported with octagam® 5% liquid and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, *e.g.* viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

Most common adverse reactions with an incidence of > 5% during a clinical trial were headache and nausea. To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- The passive transfer of antibodies may confound the results of serological testing.
- The passive transfer of antibodies may interfere with the response to live viral vaccines.

USE IN SPECIFIC POPULATIONS

- Pregnancy: no human or animal data. Use only if clearly needed.
- In patients over age 65 or in any person at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse octagam® 5% liquid at the minimum infusion rate practicable.

HOW SUPPLIED

	1g	2.5g	5g	10g	25g
Size	20ml	50ml	100ml	200ml	500ml
NDC#	67467-843-01	67467-843-02	67467-843-03	67467-843-04	67467-843-05
NDC#	68209-843-01	68209-843-02	68209-843-03	68209-843-04	

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A clear solution

IMPORTANT SAFETY INFORMATION

octagam® is contraindicated in individuals with intolerance to immunoglobulins, especially in immunoglobulin A (IgA) deficiency, when the patient has IgE mediated antibodies to IgA. Immune Globulin intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Other possible side effects with octagam® include: aseptic meningitis, hemolysis, transfusion-related acute lung disease (TRALI) and thrombotic events.

Immune Globulin Intravenous (Human) products have been reported to be associated with various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, changes in blood pressure, cutaneous reactions and/or nausea and vomiting. Cases of reversible aseptic meningitis and migraine and isolated cases of reversible hemolytic anemia and reversible increases in liver function tests have been observed with octagam®. Immediate anaphylactic and hypersensitivity reactions are a remote possibility.

As with all medicines made from human plasma, the risk of spreading infectious agents, including viruses, cannot be completely eliminated.

Some types of blood glucose testing systems falsely interpret the maltose contained in octagam® as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia.

See brief summary of PI on facing page.

[1]Ochs HD, Pinciaro PJ and the octagam® Study Group. octagam® 5%, an Intravenous IgG Product, is Efficacious and Well Tolerated in Subjects with Primary Immunodeficiency Diseases. *J. Clin Immunol* 2004,24;3:309-314

octagam®

Immune globulin intravenous (human)
5% liquid preparation

If you've been looking for an IGIV solution, take a look at octagam®.

octagam® has earned its reputation for safety and documented clinical efficacy[1].

To ensure tolerability[1], octagam® is carefully produced to retain as many of the characteristics of natural plasma as possible.

With over 40 million grams of octagam® infused world-wide, Octapharma is committed to helping PI patients live more active and healthier lives.

Ask your health care provider today about octagam® and find out if it could be the right solution for you.

For clinical or technical questions, please call our Medical Affairs team at 888-429-4535.

To order call FFF at 1-800-843-7477.

octapharma

For the safe and optimal use of human proteins

BioSupply Trends Quarterly

October 2009

Features

Special Focus: Innovation

Up Front

BioTrends Watch

BioFocus

BioSources

About BioSupply Trends Quarterly
BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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Innovation — Making a Difference

INNOVATION—THE CREATIVE PROCESS of looking at what is — and challenging ourselves to make it better, whether through new methods, techniques or practices, or new or altered products or services, has always been a source of inspiration for me. According to Wikipedia, "For innovation to occur, something more than the generation of a creative idea or insight is required: The insight must be put into action to make a genuine difference…."

As I write this, our country is grappling with the challenge of improving a healthcare system that is failing too many. Amid an array of stakeholders with diverse and competing interests, the process is complex, emotional and imperfect. At a recent executive roundtable, I wondered out loud if perhaps what we are dealing with is a "sickcare" rather than a healthcare system. And, as we think about improving our system, we might consider how to create a focus on wellness through school and workplace incentives that promote preventive vaccines, better nutrition, exercise and education. Without oversimplifying the important issues on the table, I wonder: Shouldn't preventing disease be the first line of defense to make healthcare more affordable and accessible? Can't we better serve those who are facing unavoidable health issues by lessening the burden created by disease that could have been averted?

Beyond our country's healthcare challenges, the world is preparing for the largest mass vaccination effort in history — hoping to prevent the devastating impact of a full-blown pandemic. As manufacturers switched efforts from seasonal flu vaccine to produce the novel H1N1 strain, innovative products and processes have had a real-world testing environment, with attention focused on the challenges of decreasing time to market without hindering safety or effectiveness. Yet to be seen is how the mass vaccination effort will go. New models will certainly be needed, and it is clear that with each day that passes, progress is being made to organize the many players responsible for the planning, logistics, procurement and coordination necessary to pull off this monumental effort.

This unprecedented vaccination effort has shone a new light on seasonal flu, bringing a heightened awareness to the seriousness of this disease and creating a higher demand for the vaccine — a positive, and much-needed step in prevention. The seasonal flu vaccination business has been uncertain at best, with each year presenting its own set of unique challenges. Our company, FFF, has met past challenges with new innovations in service models, such as MyFluVaccine that offers greater reliability in delivery, and VaxAmerica, a vaccine service provider model that provides turnkey vaccine solutions through a nationwide network of care sites and school and workplace settings. By understanding the risks healthcare providers face each year in trying to promote vaccination efforts, we have pioneered these new models that have reduced the risks and added benefits for our customers. This focus on innovations in service is a great source of pride for me.

Supply chain safety is another area of innovation that FFF has focused on throughout the years. We have put in place innovative systems and services to honor our pledge of Guaranteed Channel Integrity. Our feature: Verifying Pedigree: Digital Solutions in Safety, takes a look at a product's path through the supply chain and the importance of verifying custody to ensure safety. I am pleased to say that FFF created the industry's first Verified Electronic Pedigree™ (VEP). I encourage those on the front line to utilize this verification process; it is one important step in combating the issue of counterfeit product that continues to threaten patients' welfare.

As always, I hope you find our publication educational, thought-provoking and helpful to you in your practice. We welcome your feedback, suggestions and insights. ❖

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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BEFORE TROUBLE BITES.

RabAvert Rabies Vaccine—the only rabies vaccine currently available for preexposure immunization.

Due to a significant investment in our manufacturing facility, RabAvert is now available without supply restrictions for preexposure vaccination as well as postexposure prophylaxis and booster immunization.[1]

IMPORTANT SAFETY INFORMATION

Anaphylaxis, encephalitis including death, meningitis, neuroparalytic events such as encephalitis, transient paralysis, Guillain-Barré Syndrome, myelitis, and retrobulbar neuritis; and multiple sclerosis have been reported to be temporally associated with the use of RabAvert.

The most commonly occurring adverse reactions are injection site reactions, such as injection site erythema, induration and pain; flu-like symptoms; arthralgia; dizziness; lymphadenopathy; nausea; and rash.

History of anaphylaxis to the vaccine or any of the vaccine components constitutes a contraindication to preexposure vaccination with this vaccine. In the case of postexposure prophylaxis, if an alternative product is not available, vaccination should proceed with caution and close observation. A patient's risk of acquiring rabies must be carefully considered before discontinuing vaccination.

NOVARTIS VACCINES

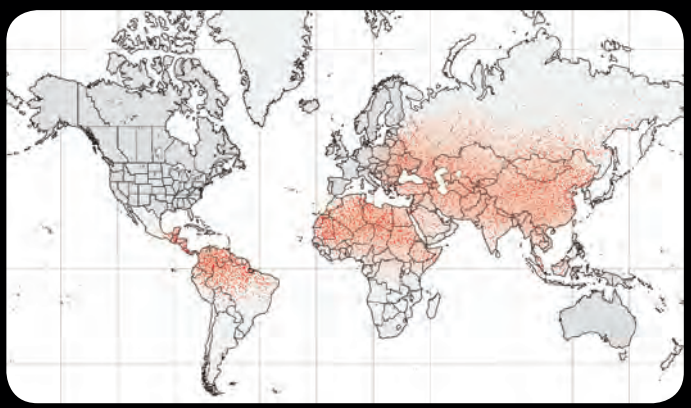
RabAvert® RABIES VACCINE

The titers you need, from a name you can trust

THE CDC RECOMMENDS PREEXPOSURE VACCINATION FOR:

- Persons whose activities bring them into frequent contact with rabies virus or potentially rabid animals, such as:
  - Veterinarians and their staff
  - Animal handlers
  - Rabies researchers
  - Certain laboratory workers
- Some international travelers if they are likely to come into contact with animals in areas where dog or other animal rabies is enzootic, and immediate access to appropriate medical care, including rabies vaccine and immune globulin, could be limited[1]

Geographic distribution of rabies hazards[2]:



North Africa	widespread
Central, East, & West Africa	widespread, epidemic level
Tropical South America	widespread, epidemic level
East Asia	widespread
Southeast Asia	widespread
South Asia	widespread, epidemic level
Middle East	widespread
Eastern Europe & Northern Asia	widespread

Epidemic: The occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time.

TO PLACE AN ORDER FOR EITHER PRE- OR POSTEXPOSURE PROPHYLAXIS, PLEASE CONTACT:

FFF Enterprises: **800-843-7477**

FFF enterprises
Helping Healthcare Care®

References

1. Centers for Disease Control and Prevention Web site. Rabies vaccine supply situation. http://www.cdc.gov/RABIES/news/RabVaxupdate.html. Accessed April 21, 2009.
2. Centers for Disease Control and Prevention Web site. Travelers' Health - Yellow Book. http://wwwn.cdc.gov/travel/yellowBookCh3-IntroGoalsLimitations.aspx#14. Accessed April 21, 2009.

Manufactured by: Novartis Vaccines and Diagnostics GmbH & Co KG, Marburg, Germany.

An affiliate of: Novartis Vaccines and Diagnostics, Inc., 350 Massachusetts Avenue
Cambridge, Massachusetts 02139 USA. NVDRAB0011-MAY09

NOVARTIS VACCINES

RabAvert RABIES VACCINE

Healthcare Reform Update

AS CONGRESS DEBATES healthcare reform, the major questions being asked are, "Will healthcare reform pass this year, and what will it look like?" The answers to both questions are most likely "yes" and "we don't know." President Obama set a deadline for the House and Senate to pass healthcare reform bills before the August recess, but that didn't happen. However, some progress was made. Five committees have jurisdiction over healthcare reform: In the House, bills need to be passed by the Education and Labor Committee, Energy and Commerce Committee and Ways and Means Committee; in the Senate, bills must be passed by the Health, Education, Labor and Pensions Committee and Finance Committee. Before recess, the three House committees did pass a version of healthcare reform. Yet, in the Senate, committees still need to pass their versions. Once that happens, all versions will have to be merged into one for the House and one for the Senate, and then each chamber will vote. Subsequently, a conference committee will work out the differences between the two versions, and the final version will go back to both chambers for a final vote.

Many constituents have expressed concerns about provisions in the different versions of healthcare legislation. Specifically, they are concerned about the increase to the deficit, the public healthcare system leading to rationing of care, increased taxes and elimination of employer health insurance benefits. Those in the rare disease community are especially concerned about access to plasma therapies and biologics. Specifically, their concerns include access to specialists who can diagnose and treat rare diseases, access to therapies in all sites of care and the requirement of step therapy (which mandates patients first fail other treatments before being granted access to plasma therapies).

It's yet to be determined if these concerns will be worked out and if a final version of healthcare reform will be decided by the end of 2009. ❖

NIH Confirms New Director

On Aug. 7, the United States Senate unanimously confirmed Dr. Francis Collins as the next Director of the National Institutes of Health.

Francis S. Collins, MD, PhD, a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the Human Genome Project, served as Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health from 1993 to 2008. With Collins at the helm, the Human Genome Project consistently met projected milestones ahead of schedule and under budget. This remarkable international project culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book. In addition to his achievements as the NHGRI director, Collins' own research laboratory has discovered a number of important genes, including those responsible for cystic fibrosis, neurofibromatosis, Huntington's disease, a familial endocrine cancer syndrome and, most recently, genes for adult onset (type 2) diabetes and Hutchinson-Gilford progeria syndrome.

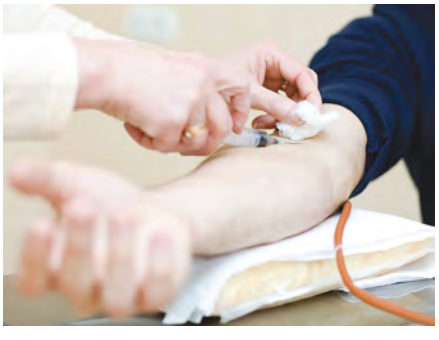
Collins has a longstanding interest in the interface between science and faith, and has written about this in *The Language of God: A Scientist Presents Evidence for Belief* (Free Press, 2006), which spent many weeks on the *New York Times* bestseller list. He has just completed a new book on personalized medicine, *The Language of Life: DNA and the Revolution in Personalized Medicine* (HarperCollins, to be published in early 2010). He has been elected to the Institute of Medicine and the National Academy of Sciences and was awarded the Presidential Medal of Freedom in November 2007. ❖

Therapy Prices Rising Under Tier IV Categories

Patients who need chronic lifesaving therapies, such as biological response modifiers, clotting factors, chemotherapy, monoclonal therapy, intravenous immune globulin therapy, etc., may now have to pay for them under Tier IV and Tier V categories in private healthcare plans, as well as Medicare Part D plans, TriCare and the Federal Employees Health Benefit Program. Previously, these therapies were covered under a health insurance company's major medical plan. But in recent years, these therapies were switched to be covered only under Tier I, II and III categories; the higher the tier number, the higher the copay. Under Tiers IV and V, patients will be required to pay a 10 percent to 30 percent copay for their therapy, which will lead to more patients being unable to afford their lifesaving therapies. ❖

Hepatitis B and C Legislation Introduced

A silent hepatitis B and C epidemic impacting America has led U.S. Rep. Michael Honda, D-Calif., to introduce bipartisan legislation in Congress that incorporates the monitoring, testing and research and education provisions contained in the hepatitis B and hepatitis C bills from the 110th Congress. In addition, in July, Rep. Honda secured a $1.8 million increase in the Labor, Health and Human Services and Education Subcommittee appropriations bill to boost the Centers for Disease Control and Prevention's ability to assess and address hepatitis.



The new legislation attempts to bring together the common concerns of the diverse viral hepatitis community to create a surveillance system to track chronic hepatitis B and C infections; support activities to promote early detection and education, particularly in vulnerable populations, and incorporate them into existing clinical programs at the state, federal and tribal levels; conduct research on improved treatments and vaccines; and meet other needs of the hepatitis community as identified by advocacy groups.

Asian American and Pacific Islander community populations suffer from disproportionately higher rates of hepatitis B than other ethnic groups, representing about half of chronic hepatitis B cases and half of deaths resulting from chronic hepatitis B infection. Of the approximately two million people estimated to be infected in the United States, only 200,000 patients have been diagnosed. Most infections remain undiagnosed until the late stages of the disease, often resulting in liver transplants, cirrhosis of the liver, liver cancer and, frequently, death. ❖

Good Clinical Practices Initiative Launched

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have launched a bilateral Good Clinical Practices (GCP) Initiative, designed to ensure that clinical trials submitted in drug marketing applications in the United States and Europe are conducted uniformly, appropriately and ethically. The initiative was set to begin with an 18-month pilot phase on Sept. 1, and will focus on collaborative efforts to inspect clinical trial sites and studies. Products regulated by the FDA's Center for Drug Evaluation and Research in the United States and by the EMEA for the European Union will be the focus of the initiative.

Key objectives of the FDA-EMEA GCP initiative will be to conduct periodic information exchanges on GCP-related information to streamline sharing of GCP inspection planning information, and to communicate timely and effectively on inspection outcomes; to conduct collaborative GCP inspections by sharing information, experience and inspection procedures, cooperating in the conduct of inspections, and sharing best-practice knowledge; and to share information on interpretation of GCP by keeping each regulatory agency informed of GCP-related legislation, regulatory guidance and related documents, and to identify and act together to benefit the clinical research process. ❖

MICHELLE VOGEL, *MPA, is executive director for the Alliance for Plasma Therapies, Washington, D.C. She can be reached at (888) 331-2196 or mvogel@plasmaalliance.org.*

Research

New Process Speeds Flu Vaccine Production

Antigen Express Inc., a subsidiary of Toronto, Ont.-based Generex Biotechnology Corp., is developing a new chemical process that could lead to the speedier production of safe and effective flu vaccines. The new process uses laboratory machines to string together amino acids into peptides, which are short bits of proteins designed to stimulate the body's production of immune cells against specific threats, such as influenza. This produces a dry powder that can be stored and later mixed with fluid to create vaccine doses, according to Douglas M. Powell, director of immunobiology at Antigen Express.

The peptide vaccines promise to be much more flexible, cost effective and rapid compared to the traditional way of manufacturing, explains Antigen Express President Eric von Hofe. The traditional method of developing flu vaccines involves injecting a virus into eggs where the virus replicates. It is later removed from the eggs and used in vaccines. But that process requires millions of eggs, and it can take months to produce enough material for flu vaccines. In contrast, the new peptide vaccine process takes roughly half that time.

While there are a few other peptide technologies out there, von Hofe says that Antigen Express is the only company that has tested it clinically. And in the future, if needed, the technology will be able to be used for particular strains of flu that could have a high lethality. "This is on a technology platform that is the same to be used for another peptide vaccine that we have in clinical development for breast and prostate cancer," says von Hofe. "We know that these vaccine peptides can generate the types of response that we expect them to generate."

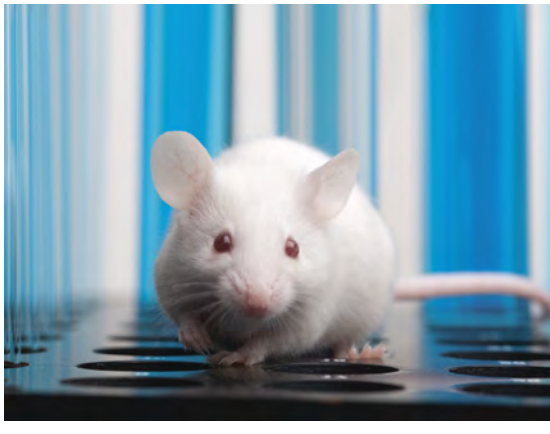
Currently, no peptide vaccines are approved for use in the U.S. However, Antigen Express reports that early phase 1 clinical trials of peptide vaccines against H5N1 avian influenza in Lebanon have shown that they are safe and well-tolerated. "The capacity exists now that you could literally make billions of doses of this vaccine," says Powell. The company is seeking funding for development of its own H1N1 vaccine. ❖

Research

Discovery to Improve Vaccine Response

The body's response to vaccination could be improved with a new finding by Sydney scientists that shows why B cells behave as they do. B cells create antibodies against different microbes to fight infection against viruses or other microbes. However, until now, it was unknown what caused the B cells to create high-quality antibodies over a period of several weeks, versus low-quality antibodies that sacrifice quality for speed.

In the study, scientists at the Garvan Institute of Medical Research demonstrated in mice that the presence or absence of the B cell surface receptor EBI2 was the determining factor. In the mice without the EBI2 receptor, most B cells headed straight to germinal centers where high-quality antibodies are created. In the mice with the EBI2 receptor, having the receptor made it impossible for B cells to go to germinal centers, thus creating more low-quality



antibodies. According to Robert Brink, project leader of the study, "We can now see that having this molecule switched on is important for short-term protection. Having it switched off is important for our long-term response." Therefore, devising strategies that inhibit EBI2 activity in B cells may enhance the long-term antibody responses that are the ultimate aim of vaccination. ❖

Insurance

IV Biologics May Shift Coverage

Surveyed pharmacy directors of both national and single state plans say coverage of immune biologics will shift from a medical benefit to a pharmacy benefit by 2014. The survey was conducted by HealthLeaders-InterStudy and Fingertip Formulary, and findings were presented in the report *Formulary Advantages in Immune Biologics: Tightening Payer Control Offers Opportunities for Differentiation*.

According to the report, payers expect that the shift of biologics from the medical benefit to the pharmacy benefit is motivated by an expectation of increased cost control. For example, 34 percent of surveyed payers currently require patients taking an IV biologic to first fail therapy with an SC biologic and will continue to enforce this requirement moving forward. An additional 38 percent of surveyed payers expect to newly implement this cost control measure over the next five years.

"Managed care organizations are looking to restrict patient access to physician-administered biologics, because these agents are harder to control in terms of cost outlays — in part due to physicians preferentially prescribing agents such as Remicade so the physician can purchase the agent at a discount relative to the reimbursement rate and thus maintain a profit margin on the procedure," said Michael Malecki, PhD, product manager for Formulary Forum. "Maintaining control of the supply chain will be critical to the future profitability of managed care organizations, and plans are aware of this fact." By 2014, for example, 84 percent of surveyed pharmacy directors say their organization will mandate IV biologics be purchased from an authorized vendor (e.g., specialty pharmacy). ❖

Research

Oral Vaccine to Replace the Needle?

Healthcare professionals could have a much easier time convincing patients to get vaccinated if it can be done orally. A new study conducted by a researcher from the Northwestern University Feinberg School of Medicine shows that an oral vaccine may not only be possible, it might actually be more effective than a shot.

Mansour Mohamadzadeh, the lead author and an associate professor of medicine in gastroenterology at the Feinberg School, developed the oral vaccine using probiotics (the healthy bacteria found in dairy products like yogurt and cheese). In the preclinical study, mice were fed the new oral anthrax vaccine and then exposed to anthrax bacteria. Eighty percent of the mice survived — comparable to the results when mice were injected with anthrax vaccine. However, "their immune response was higher and more robust than with the injected vaccine"; they had generated a much higher T and B immunity against the pathogenic bacteria.

Because the vaccine is delivered to the gut, rather than being injected into the muscle, it harnesses the full power of the body's primary immune force, which is located in the small intestine. According to the press release generated by Northwest University, the vaccine "induces a local and a systemic immune response. The vaccine targets the first line of gut immune cells called dendritic cells — the commanders-in-chief of the immune system. They engulf the vaccine, then instruct the immune system's foot soldiers — killer T-cells and B-cells — to seek out and destroy any cells in the body infected with a particular bacterium or virus."

As Mohamadzadeh explains it, "You swallow the vaccine, and the bacteria colonize your intestine and start to produce the vaccine in your gut. Then, it's quickly dispatched throughout your body. If you can activate the immune system in your gut, you get a much more powerful immune response than by injecting it. The pathogenic bacteria will be eliminated faster."

Other advantages include the presence of natural immune stimulators present in probiotics, which eliminate the need for a chemical in traditional vaccines that inflames the immune system and triggers a local immune response (which can cause side effects such as dizziness, arm swelling and vomiting). In addition, the probiotic vaccine is inexpensive to produce.

Mohamadzadeh said that probiotic vaccine technology can be applied to other diseases such as HIV, hepatitis C and flu. He is currently developing one for breast cancer.

The study was reported in a recent issue of the *Proceedings of the National Academy of Sciences*. ❖

Supplier

FDA Approves First ATryn Drug

In February, the FDA approved ATryn, an antithrombin [recombinant] for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. Developed in partnership by GTC Biotherapeutics and Ovation Pharmaceuticals, ATryn is the first transgenically produced therapeutic protein and the first recombinant antithrombin approved in the U.S.

According to a release issued by the two companies: "People with antithrombin deficiency are at increased risk for venous thromboembolic events, including pulmonary embolism and deep vein thrombosis, which can be life-threatening, particularly in high-risk situations. Antithrombin is a natural anticoagulant that plays an important role in controlling the formation of blood clots. Purified recombinant antithrombin has the same amino acid sequence as antithrombin derived from human plasma."

The drug was made available in the second quarter of 2009. ❖

Did You Know?

"Since 1988, when the Global Polio Eradication Initiative was established, the incidence of polio has decreased from an estimated 350,000 cases annually to 1,655 reported in 2008."

— Centers for Disease Control Morbidity and Mortality Weekly Report, April 3, 2009

Research

Newborns Need Time to Respond to Vaccines

In an effort to understand infants' poor immune system response to certain vaccines, a researcher at the University of Missouri School of Medicine has discovered that newborns' immune systems might require some time after birth to mature to a point where the benefits of vaccines can be fully realized. Currently, infants' poor immune system response requires additional boosters as children develop.

Habib Zaghouani, a professor of molecular microbiology and child health, "studied newborn mice and how their immune systems reacted when they were repeatedly exposed to an antigen that simulates a virus," states a press release submitted by the university. When the newborn mice were given an antigen shortly after birth, Zaghouani noticed the presence of both Th1 and Th2 cells (instrumental in the development of an effective immune response). When the antigen was given a second time, he noticed an abundance of Th2 cells working to destroy the small contingent of Th1 cells. However, when an antigen from a vaccine enters a body, it is the Th1 cells that are needed to destroy the invader and then remember how to fight the antigen for future battles (which is what happens in mature immune systems).

"We have found that after six days [after birth], the immune systems in the mice matured enough to stop the death of the Th1 cells," Zaghouani said. The study was published in the *Journal of Experimental Medicine*. ❖

Healthcare

Pharmacists Profit from Consultations

With profit margins declining on medications, consultations are becoming a new way for pharmacists to make additional revenue. According to the April 15, 2009, *Kaiser Daily Health Policy Report*, "Under existing CMS guidelines, insurers that offer Medicare Advantage (MA) plans are required to pay pharmacies for the meetings with patients, during which they discuss the importance of taking the proper medications at the appropriate times. MA beneficiaries with at least $4,000 worth of annual drug costs are eligible for the consultations at no cost." This means that some pharmacists are now earning up to $160 for a one-hour consultation with patients.

And, it's going to get more lucrative. In 2010, new Centers for Medicare & Medicaid Services (CMS) guidelines will expand the consultation benefit to more MA patients. "Under the revised guidelines, MA plans will be required to review their member rolls on a quarterly basis to identify eligible members for the program," says the report. "In addition, health plans will be prohibited from restricting access to the benefit to members with a high number of chronic health conditions and medications, and the annual drug cost limit will be reduced from $4,000 to $3,000." In 2010, pharmacists will be paid $50 to review a beneficiary's medications and make recommendations to their physician, and they will receive additional payments if they recommend a less-costly, therapeutic equivalent to the patient. ❖

Supplier

Octapharma Accepting Grant Applications

Octapharma USA is now accepting applications for the Octapharma 25th Anniversary Grants Program, which supports clinical or preclinical research focused on human protein therapies in coagulation disorders, immunotherapy, intensive care and emergency medicine. Grant applications will be accepted online only at www.octapharmagrants.com. All grant requests will be evaluated by the grants committee in October, and the first grant recipients will be announced shortly afterward. A complete description of the grants program, including the application and review process, can be viewed at the website. ❖

Did You Know?

"Some parents regard hepatitis B immunization as unnecessary, based on their misconception that this is a disease for which their children are not at risk. However, as many as 16 to 30 percent of hepatitis B cases have no known source of infection."

— National Network for Immunization Information

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Innovations in Technology: Storing Patient Information

When healthcare records soon go digital, healthcare providers will benefit from knowing what the current electronic health record options are, how patient care will be improved, and how confidential data will be secured.

By Amy Scanlin, MS

The old saying, "Out with the old and in with the new," couldn't be more apropos as innovations in healthcare policies and procedures abound. The U.S. government, with the help of leaders in the medical community, is working diligently to improve patient care while reducing costs, and one of its main areas of focus is the storage of patient information.

Out with paper files and in with electronic storage. Out with misread and mistranscribed notes and in with tablets that allow physicians to quickly and accurately make notations into patient electronic health records (EHRs). Out

with illegible paper prescriptions and in with e-scripts. The list and possibilities are endless for physicians to better store, retrieve and utilize information, as well as for patients to take a more active role in their healthcare.

Why the Need?

There are many reasons why change in the way healthcare information is stored is important today. According to 2008 Census Bureau estimates, more than 304 million people reside in the U.S. If each person went to the doctor just once each year, that's a lot of paper. Multiply that by those who have multiple visits in a year (most people) and by the age of each person, and we are talking about countless pieces of paper, storage costs, manpower and security concerns. Add lab tests, visits to various specialists, etc., and the storage requirements grow exponentially. Factor in the likelihood that many of these patients will need access to their records at a time when the records are unavailable — during emergencies or vacations, or their records are forgotten, misplaced or destroyed — and the requirements for maintaining paper files are huge.

EHRs will also prevent the possibility of another situation like Hurricane Katrina, where thousands of paper records were destroyed. "Katrina taught us all that you can lose data in a day," says Harry Rhodes, MBA, RHIA, CHPS, CPHIMS, FAHIMA, director of practice leadership with the American Health Information Management Association (AHIMA). "Those who had EHRs and the foresight to back up their data [either on the Internet or in a location away from New Orleans] could be back up and running in days."

While paper records had been the only way to track patients for hundreds of years, they are slowly becoming obsolete. The Markle Foundation found in a 2005 public opinion survey that 60 percent of adults responding would support the creation of an online personal health record (PHR) "that would allow them to check and refill prescriptions, get results over the Internet, check for mistakes in their medical record, and conduct secure and private email communication with their doctors."[1] Physicians, as well, are open to the possibilities this technology provides in improving patient care, though the medical community has indicated that security and cost concerns (starting price can be several millions) must be answered before it will fully embrace it.

The costs of not adopting an EHR system, however, will soon outweigh the current concerns, as the government has approved a bill that will begin penalizing providers that have not gone digital by the year 2014. These penalties could be as much as $3.2 million in reduced Medicare funding annually for a 500-bed hospital.[2] To avoid these penalties, providers will need to ensure that their EHR software provider is certified by the Certification Commission for Health Information Technology (CCHIT) and that the system operates in a "meaningful" way to avoid errors and improve outcomes. The term "meaningful" is at the center of debate as planners — from Congress to health information technology companies to physicians — come together to determine specifically what "meaningful use" means. It is anticipated that electronic prescribing, laboratory reporting, clinical summaries for care coordination and quality data will be covered in the definition.[3] Yet, the term "meaningful" will morph over time to meet more stringent guidelines as the technology and adoption of EHRs increase.

The costs of not adopting an EHR system, however, will soon outweigh the current concerns.

What Are the Options?

Options for upgrading to an electronic storage system include EHRs using proprietary software or open source software, as well as PHRs provided through vendors such as Google, the patient's insurance company and even software developed by a hospital's EHR.

Of course, it is possible that some healthcare providers will opt to stick with the old paper record system and just pay the penalties. However, even the smallest practice can see improvements by adopting some technology. But just scanning those old paper records into electronic storage will create a flat EHR, not one that offers the ability to create reports and easily retrieve specific data a physician might need.

At their maximum capability, EHRs provide more than just an electronic vessel in which to store papers. An EHR puts patient information into readable and accessible templates so that when providers access a patient's chart, they see the important information they need right away to make informed decisions. It lists most pressing health concerns, allergies, medications, etc., with just the click of a mouse. And, EHRs provide walls so that not every person who pulls up the file can see all of the patient's information — only those who require legal access for that specific case.

EHRs. A number of EHR vendor options for hospitals and small offices exist, including those that have developed their own proprietary software and others that utilize open source software adapted for their specific needs. Proprietary software is developed by contracting with a software developer. Open source software, on the other hand, is authored by small communities of developers that are committed to advancing healthcare information technology but are not directly compensated

Web-Based Personal Health Records (PHRs)

The following websites offer free PHRs.
A host of other sites exist for a fee.

A Smart PHR	www.thesmartphr.com
AboutMyHealth	www.aboutmyhealth.org
Dr. I-Net	www.drinet.com
EMRy STICK	www.emrystick.com
Google Health Records	www.google.com/health
HealthButler	www.healthbutler.com
Healthy Circles	www.healthycircles.com
iHealthRecord	www.ihealthrecord.org
It Runs in My Family	www.itrunsinmyfamily.com
MedicAlert	www.medicalert.org
MediCompass	www.medicompass.com
Microsoft Health Vault	www.healthvault.com
MiVIA	www.mivia.org
My Doclopedia PHR	www.doclopedia.com
My HealtheVet	www.myhealth.va.gov
myHealthFolders	www.myhealthfolders.com
MyMediList	www.mymedilist.org
NoMoreClipBoard.com	www.nomoreclipboard.com
Telemedical.com	www.telemedical.com
WorldMedcard	www.worldhealthrecord.com
ZebraHealth	www.zebrahealth.com

financially for their efforts. The software can be viewed, modified and distributed, although the software creator retains the copyright, and users obtain a license, which is typically free. A good example of open source healthcare software is OpenVista, a healthcare information system distributed with a license that allows unlimited use at any number of facilities. (See Open Source Electronic Health Record (EHR) Software on page 19 for a listing of some current software.) Each has its pros and cons.

Proprietary software can include bells and whistles that a vendor using open source software would need to add. However, in some cases, proprietary software cannot communicate with software created by another vendor, making it more difficult for doctors to treat patients outside of their system. In addition, proprietary software vendors eventually will stop supporting older versions of the software, requiring the purchase of an upgrade or an entirely new system. "Some say the proprietary software can't match the features of open source software as quickly," says Rhodes. However, when you need support for the software, it is there. You don't have to hunt for support as you do with open source software.

Open source software has already matured and developed, and some argue it is less expensive for a vendor to adapt to a customer's specific needs. The software is free, as are a lot of the innovations. However, others say open source software vendors tease you with freebies and the software becomes more costly when features are added. Open source software speaks freely with other open source software, allowing doctors treating patients on vacation to quickly access their records from their primary care provider in another location — assuming both systems speak the same language. Typically, open source software allows healthcare providers to keep current technologies within their office system, rather than purchasing an all-new system. One downside to open source software, though, is that it has not been widely proven for smaller venues and locations with more significant financial constraints.[4] Healthcare providers will likely need to hire a consultant to help piece together the system, which can be costly. There also may be integration challenges as new components are added.

An important component between the different systems is the way in which data will be transported from system to system. Clearly, the information will be encrypted so that data will not be legible between points A and B. However, no matter what the two end points are, both need to be compatible with the mode of transportation. The hypertext transfer protocol secure (HTTPS) standard allows many different systems to speak to each other without the added coordination between systems.

In addition, the CCHIT certification and technology advances will help improve the interoperability between different systems. "It's like the Good Housekeeping Seal of Approval," says Rhodes of the certification. Likewise, Health Level 7 (HL7), an accredited standards development organization (SDO), is working with other SDOs to ensure interoperability and the preservation of the meaning of patient data. HL7 has seven layers of protocol implementations, hence the name of the organization.

PHRs. Many patients are now opting to keep their own medical records through various software programs, as well as web-based PHRs. (See Web-Based Personal Health Records (PHRs) on this page for a listing of many free and fee-based sites.) Because a PHR is initiated by the patient, permission must be provided to providers, pharmacists, insurance companies, etc., for the retrieval and storage of information from PHRs, which can sometimes be problematic. However, because patients are encouraged and expected to add their own information to the record, it is more effective for patients to manage their own or a dependent's care.

Concerns in the Electronic Age

One of the main concerns for physicians and patients alike is the security of electronic records. "Actively protecting a patient's data is part of patient care," says Lisa A. Gallagher, BSEE, CISM, CPHIMS, senior director of privacy and security at Healthcare Information and Management Systems Society (HIMSS). The security of that data is the responsibility of the physician, the third party vendor who holds the patient records (if there is one) and the staff who have access to the

Open Source Electronic Health Record (EHR) Software

Website	Description	URL
ClearHealth	A suite of medical software for large and small clinics	www.op-en.org
FreeMED	An open source practice-management and EMR system	www.freemed.org
MirrorMed	Practice-management system for running a healthcare practice	www.mirrormed.org
OpenEMed	Software components designed specifically for healthcare information services	openemed.org
OpenHRE	Standard record locator, health record exchange and access control services	www.openhre.org
OpenVista	A healthcare information system used by the U.S. Veterans Administration, and open to the public domain	sourceforge.net/projectds/openvista

records. "Security is an ongoing process and physicians need to manage it. It isn't just something you do just once and are finished with it," adds Gallagher.

How does a provider know if a patient's records are truly secure? They don't unless they actively strive to know. It is the physician's responsibility to initiate controls at the office level to control who has access to the information. It is also the physician's responsibility to manage risk at the IT level and continually look for the potential for security breaches. "If physicians view the patient's data, it is because they are trying to help them," says Gallagher. Likewise, staff should not have access unless they need it. Conducting security audits of basic vulnerabilities with behavior in the workplace is key. The Department of Health and Human Services (HHS) will be providing guidance for technical safeguards for Health Insurance Portability and Accountability Act (HIPAA) by February 2010.

Security controls such as authenticity, iris scans and fingerprint scans are available. Rhodes says that 80 percent of the security risk is not out there on the Internet; it is within an office's staff. "We put up firewalls and do all these things, but we tend to be careless internally." So, as healthcare workers change job functions, they need to make sure that when their access to information needs change, it is. What they no longer need should be cancelled, and any new information they need should be added. In the event of termination or resignation, access should be taken away. In addition, even those with legitimate access should not be viewing records when there is no need. "The challenge is: Do you have the right and authority to be in this record," says Rhodes.

If the patient's data are held by an outside vendor, as opposed to a hospital, the physician needs to look for assurances by the vendor, in HIPAA vernacular, that controls are in place for protecting data. Essentially, the physician is allowing the vendor to hold the data on his of her behalf, so the proper procedures must be in place when sending that information through a gateway to the vendor and as the vendor stores the data. An important component in the vendor/health entity relationship is whether the vendor is considered to be a business associate of the provider. The short answer is: If a vendor has access to the patient's information in the course of doing work or supporting the EHR, the vendor is likely to be considered a business associate. If, however, the vendor has responsibility for maintaining the data without access, it is not.[5] The question of whether a vendor is a business entity will be an important one, and merely providing support for the maintenance of EHRs will be considered access. This will be an important clarification.

However the data are stored, Rhodes feels a preferred way of doing so is a federated model, where each department keeps its own records on a patient, as opposed to one centralized location where the entire record is kept. When needed, these departments can also access other departments' data. However, in the federated model, there are better access controls for these "information silos."

When sending information to a third party such as an insurance company, the days of sending the entire record are going away.

One of the main concerns for physicians and patients alike is the security of electronic records.

Physicians now need to send only what is relevant and necessary to the claim, and the responsibility falls on the sender if too much information is sent. HHS is also providing guidance per the American Recovery and Reinvestment Act of 2009 (ARRA) section "Health Information Technology for Economic and Clinical Health," commonly referred to as HITECH. This will spell out specifically what healthcare providers need to know about the disclosure of relevant information.

Federal Security Laws for Health Information

The United States has an extensive body of federal and state laws and regulations that define the security and privacy requirements for collecting, creating, maintaining, using, disclosing and disposing individually identifiable health information, according to Harry Rhodes, MBA, RHIA, CHPS, CPHIMS, FAHIMA, director, practice leadership with the American Health Information Management Association (AHIMA). Among them, at the federal level, are:

- HIPAA Privacy Regulations (45 CFR § 160 and 164 Part E)
- HIPAA Security Regulations (45 CFR § 160 and 164 Part C)
- Confidentiality of Alcohol and Drug Abuse Patient Records (42 CFR Part 2)
- Family Education Rights and Privacy Act (FERPA)
- Privacy Act of 1974
- Right to Financial Privacy Act (1978)
- Privacy Protection Act of 1980
- Electronic Communications Privacy Act (1986)
- Communications Assistance for Law Enforcement Act of 1994
- Telecommunications Act of 1996
- Financial Modernization Act (Gramm-Leach-Bliley Act) (2000)
- Emergency Supplemental Appropriations Act for Defense, the Global War on Terror and Tsunami Relief (Real ID Act) (2005)

From a liability standpoint, there is concern based on interoperability and the fact that more physicians will have legal access to the EHR when providing patient care. In a perfect world, the more specialists caring for the patient, the better the patient's care. Concern arises, however, in the implicit liability of secondary physicians' duty of care should there be an injury. Also, there is a question about who is liable to an injured patient in the event of a software glitch.[6] These issues will be vetted in both the medical and legal communities.

New and Improved: What Does the Future Hold?

Technology is always advancing, and EHR systems will advance along with it. In the future, according to HIMSS, you'll find improvements such as:

- Better access to information for emergency responders
- Improved ability to transfer medical records when a patient transfers physician care
- Ability to incorporate family history information into decision making
- Access to remote patient monitoring to save office visits

Capturing Metrics of Patient Care[7]

The important part of the EHR puzzle is understanding what has happened, anticipating and planning for what is going to happen and understanding how it all applies to the business of healthcare. That's where associations such as AHIMA and HIMSS come in as they pull the information apart and translate it into plain English for their members. They also stay on top of requirement deadlines.

As the use and capability of EHRs grow, adherence to HL7 functionality models for clinical and administrative data will continue to be critical. "This includes what is needed for direct care, what needs to be captured to supplement patient care and support features, functionalities and support criteria," says Rhodes. "Creating an implementation standard, vocabulary standard, formatting standard… In the near future, you will see a lot more interoperability."

Remote access to EHRs is also turning into an important feature. Whether a physician is at home or traveling, being able to access and monitor their patients' progress is important. There is also discussion of creating a first responders database so that emergency medical services personnel will have important data for saving the lives of those who may be unable to communicate their conditions. Vehicle safety and security systems are also looking into ways to link to PHRs to provide information to first responders about their customers.

Other up-and-coming features of record storage are multimedia records capabilities, where physicians can read reports and view video or audio files related to tests, as well as continuous speech recognition for physicians to dictate a report and immediately see it on the screen.

The opportunities for improvements in healthcare and patient data security are vast as EHRs become more commonplace and capable. Soon, the days of the paper record system will be gone, and physicians will wonder how they ever treated patients with them.

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Important Safety Information

Immune Globulin Subcutaneous (Human), Vivaglobin®, is indicated for the treatment of patients with primary immunodeficiency (PI).

As with all immune globulin products, Vivaglobin® is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A deficiency who have known antibody against IgA. If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately and treat as medically appropriate.

Vivaglobin® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical trials, the most frequent adverse event was injection-site reaction, consisting of mild or moderate swelling, redness, and itching. No serious local site reactions were observed, and reactions tended to decrease substantially after repeated use. Other adverse events irrespective of causality included headache, gastrointestinal disorder, fever, nausea, sore throat, and rash.

As with all immune globulin (Ig) products, patients receiving Ig therapy for the first time, receiving a new product, or not having received Ig therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored in a clinical setting during the initial administration.

Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella.

In clinical studies, administration of Vivaglobin® has been shown to be safe and well tolerated in both adult and pediatric subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy were not studied in pediatric subjects under two years of age.

Please see brief summary of Prescribing Information on adjacent page.

Manufacturing and Distribution:
Vivaglobin® is manufactured by CSL Behring GmbH and distributed by CSL Behring LLC.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

CSL Behring

℞ **only**

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE
Vivaglobin® Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS
As with all immune globulin products, Vivaglobin® Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS
Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin® Immune Globulin Subcutaneous (Human).

If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS
General-Administer Vivaglobin® Immune Globulin Subcutaneous (Human), subcutaneously. **Do not administer this product intravenously.** The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests - After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions - Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin® Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C - Animal reproduction studies have not been conducted with Vivaglobin® Immune Globulin Subcutaneous (Human). It is also not known whether Vivaglobin® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Vivaglobin® should be given to a pregnant woman only if clearly needed.

Pediatric Use - Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use - The clinical study of Vivaglobin® Immune Globulin Subcutaneous (Human), did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
In clinical studies, administration of Vivaglobin® Immune Globulin Subcutaneous (Human), has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see **CONTRAINDICATIONS**).

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*Excluding infections
† Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events** (Rate**)
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)†

*Excluding infections
**Rate = number of reactions/infusion
†Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

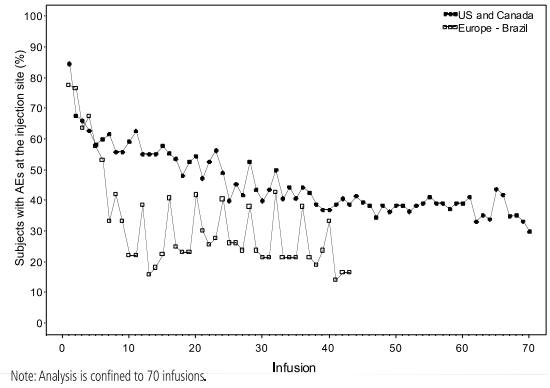
Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

*Excluding infections
**Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Immune Globulin Subcutaneous (Human), Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

HOW SUPPLIED
Vivaglobin® Immune Globulin Subcutaneous (Human), is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL vial
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL vial
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE
Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin® Immune Globulin Subcutaneous (Human), is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

Based on April 2007 revision

The Cyber-Doctor Will See You Now

Today's consumers rely on Internet research to self-diagnose everything from headaches to heart disease, and it's a trend that has irrevocably altered the dynamic of traditional doctor-patient relations.

By Trudie Mitschang

A decade or so ago, troubling medical symptoms were almost always diagnosed by a trip to the doctor's office or clinic. While a patient might gather anecdotal information from family members or co-workers prior to seeing a healthcare professional, for the most part, the doctor was considered the primary source when it came to diagnoses and treatment recommendations. From a relationship standpoint, physicians have historically been viewed as an authority figure, which makes sense, since they've always had almost exclusive access to necessary health information. But with the rapid proliferation of the Internet, the balance of power has shifted. As more and more people access the Internet to address their healthcare concerns, technology may actually be serving to alter the traditional relationship between doctors and their patients.

"I always Google my symptoms before I go to the doctor," says Tammie Allegro, a marketing operations coordinator in Temecula, Calif. "Sometimes you only get a couple of minutes with the doctor, so I want to make sure I am asking all the important questions. If there's something I think the doctor does not know or has not addressed, I feel confident I can find it online."

From a patient perspective, having virtually unlimited access to healthcare information is both enlightening and empowering. The 24/7 availability of medical statistics, advice and online support groups allows patients to assume much greater responsibility for their healthcare. Essentially, the Internet alters the doctor-patient relationship by redefining who is in control.

"Many patients and their families are getting better informed through the use of the Internet. In most cases, this is helpful because it allows the patients to go through things at their own speed and go back through it again if they need to," says Melvin Berger, MD, medical director at CSL Biotherapies, King of Prussia, Pa. "The better informed a patient becomes, the more they can participate in their own care."

Does the Doctor Still Know Best?

Consumers who regularly use the Internet are generally savvier and more opinionated regarding their healthcare decisions than their computer-illiterate counterparts. In addition to being more vocal during checkups and consultations, these patients may exhibit different motivations for seeking medical care. And, instead of going to their physicians for clarification on what certain symptoms might mean, they may instead seek to confirm their own suspicions based on personal research.

"I definitely use the Internet to research conditions and symptoms and to gain a better understanding of an identified condition, either for myself or a family member," says Janice Breuer, a trade show specialist in Murietta, Calif. "I have also consulted several blogs for anecdotal entries on prescription drug side effects, especially since I believe many doctors are quick to prescribe and tend to gloss over potential drug complications."

From a patient perspective, having virtually unlimited access to healthcare information is both enlightening and empowering.

Whether this changing dynamic of the doctor-patient relationship constitutes a positive evolution depends on who you ask. For progressive physicians who have a comfort level with the Internet themselves and do not feel threatened by highly proactive patient behavior, this new level of interaction can be mutually beneficial. But for physicians with patients who continually present them with reams of information from questionable sources, and for those physicians who prefer to practice in a more traditional mode or who are not Internet savvy, ongoing doctor-patient relations could be strained, if not severed.

Welcome to the "Misinformation" Age

The American Medical Association recommends that Internet users treat information on the web with a high degree of skepticism, and encourages patients to pay attention to the source of the information, citation of references, disclosure of competing interests, and timeliness of the information. Few consumers follow this advice.

Health information gleaned from the Internet can offer many benefits, including helping consumers manage their own care, but it can also lead to unwise decisions when the information accessed is confusing, inaccurate or

Reputable Healthcare Websites Worth a Second Look

The Cleveland Clinic Health Information Center
With information on nearly 1,000 health topics, this site offers podcasts and webcasts of health information, along with transcripts of web chats with physicians answering health questions. Also provided is a live chat service 10 a.m. to 1:30 p.m. EST Monday through Friday (except holidays).
http://www.clevelandclinic.org/health/

healthfinder
Developed by the U.S. Department of Health and Human Services, healthfinder links to carefully selected information and websites from more than 1,500 health-related organizations. Much of the content is bilingual in Spanish, and additional features include a drug interaction checker, online checkups and health newsletters.
http://www.healthfinder.gov/

Mayo Clinic
MayoClinic.com is popular because of its breadth of information and consumer-friendly content. The site is regularly reviewed by Mayo Clinic staff for accuracy, and offers helpful resources such as healthy living guides, health tools, treatment decision guides, blogs and podcasts.
http://www.mayoclinic.com/

MedicineNet.com
The content on this site is produced and edited by a nationally recognized network of more than 70 U.S. board-certified physicians. MedicineNet.com is owned and operated by WebMD and is part of the WebMD Network. The website provides easy-to-read, indepth, authoritative medical information for consumers. Web videos, daily health news, a signup for an email newsletter and a symptom checker are additional features.
http://www.medicinenet.com/

MedlinePlus
MedlinePlus offers more than 18,000 links to accurate and current medical information on the Internet that has been evaluated by the National Library of Medicine. It includes drug information, an illustrated medical dictionary, the latest health news, directories of doctors, dentists and hospitals, surgery videos and interactive health tutorials. A toggle feature translates the site into Spanish with links to Spanish-language information. The GoLocal initiative adds links to local resources in more than 18 states with hospital information available in the other states.
http://www.medlineplus.gov

NetWellness
NetWellness is a nonprofit consumer health website that provides more than 55,000 pages of high-quality information created and evaluated by medical and health professional faculty at the University of Cincinnati, Case Western Reserve University and the Ohio State University.
http://www.netwellness.org/

both. One challenge consumers and physicians face is that information on the Internet is not regulated, which can create a challenge for doctors treating misinformed patients who believe everything they read. And while reputable sites like WebMD, Medscape and MayoClinic.com do exist, the hundreds of thousands of consumer health websites and the fallibility of search engines make the chance of accessing misinformation on the Internet extremely high.

"Every new technology has its downside. A lot of patients are getting, and posting, incomplete and/or incorrect information on the web," says Berger. "This can particularly occur in chat rooms and unsupervised websites or blogs." Berger adds that in order to correct a lot of misconceptions and incorrect impressions that were being posted in patient chat rooms regarding his own area of expertise, he and a colleague prepared an illustrated article targeted at patients, with corresponding FAQs. The posting was well-received and has since been repurposed on various industry websites.

To see how a consumer might access inaccurate healthcare information, consider your own search engine habits. For many people, a web search starts by entering a simple term or phrase, such as "abdominal pain," into a popular search engine such as Google or Yahoo! Unfortunately, broad terms like this do not often lead to high-quality health websites. Only 35 percent of sites identified by these search engines were based on proven, scientific claims and did not endorse a product, according to research published in August 2003 by Michael Slater and Donald Zimmerman of Colorado State University's Department of Journalism and Technical Communication, Boulder, Colo. The study went on to say that a significant number of promotional sites (20 percent) touted unproven treatments, and some of these included "pseudoscientific claims" that could be misleading. An additional investigation found that less than one-quarter of the first pages of links displayed by search engines led to relevant sites.

In another study conducted by the Department of Psychology, Rice University, Houston, Texas, a group of 34 students from the science magnet high school in Houston searched for the terms "vaccine safety" and "vaccine danger" using Google and then answered questions regarding the accuracy of the health information on the returned sites. The students were also asked to describe the lessons they learned in the exercise and to answer questions regarding the strength of evidence for seven statements regarding vaccinations. The results were telling: Of the 34 participants, 59 percent thought that the Internet sites were accurate on the whole, even though more than half of the links that the students viewed were, in fact, inaccurate on the whole. A high percentage of the students left the first exercise with significant misconceptions about vaccines; 53 percent reported inaccurate statements about vaccines in the lessons they learned. Of the 41 verifiable facts about vaccines that were reported by participants in their lessons-learned statement, 59 percent were incorrect.

Regulating Content: An Uphill Battle

The sheer mass of information on the Internet makes regulation very difficult if not impossible. Currently, agencies regulate only overtly dangerous health information that violates laws protecting consumers. There are also a few organizations such as URAC (formerly known as the Utilization Review Accreditation Commission) and HONcode (Health on the Net Foundation) that rate health information websites, and while both organizations aim to keep consumers informed about the quality of website content, results are mixed. Unfortunately, the efficacy of these rating systems is questionable since it can prove difficult to verify the reliability of information on approved sites. Part of the reason for this is that websites are constantly changing; what is deemed accurate today could be completely inaccurate tomorrow, and there's simply not enough manpower available to keep round-the-clock tabs on individual sites.

Health information gleaned from the Internet can offer many benefits, including helping consumers manage their own care, but it can also lead to unwise decisions when the information accessed is confusing, inaccurate or both.

Given the lack of an industry-wide rating or monitoring system, some healthcare providers and larger healthcare organizations are taking matters into their own hands through proactive communications aimed at consumers. A few years ago, Kaiser Permanente launched an online health education site with more than 40,000 pages of physician-approved health-related information. The idea of using a health plan's website to house healthcare information is a good one, and, with physician support, can encourage consumers to use the web as a supplement, not a substitute, for face-to-face-physician visits.

The Internet and the Future of Healthcare

Many economists believe that the healthcare system of the future will be completely patient-centric, a revolution triggered in part by access to medical information via the Internet. Even the selection of a physician typically begins in a web browser these days. Reports, practice profiles and performance reviews of healthcare professionals and organizations are increasingly available online, and more and more patients are basing their decisions — at least in part — on information acquired on the web. Consumer advocates argue that the disclosure of performance data is helpful because it encourages consumers to choose qualified providers.

Opponents, however, argue that performance ratings may not tell the whole story, and unfairly penalize practitioners that treat high-risk patients. Other arguments suggest that such ratings may discourage physicians from treating high-risk patients for fear of losing credibility.

Another way the Internet is affecting healthcare is that it has diminished the consumer's reliance on the choices of managed care providers. Today, a consumer can research various procedures online, select the one they prefer and demand the selected treatment from their physician. If the physician is unwilling to offer the requested treatment or services, in many cases, the consumer may simply find another physician who will meet their demands.

"Once patients and families learn of a doctor's special expertise or interest, they may specifically seek out the doctor who can best help with their particular problem," says Berger. "We have gotten many patients specifically seeking help with adverse reactions to certain treatments or wanting assistance with various protocols because they learned of our expertise via the Internet."

Embracing a 21st Century Practice Model

There are many reasons why consumers are increasingly drawn to the Internet for health-related information. For one thing, the rapidly changing landscape of treatments, technology and medical breakthroughs makes it impossible for any single clinician to keep completely up to date, and consumers know it. Add to that the cost-containment efforts of current healthcare models that reduces clinicians' time with patients; patients who feel rushed often leave frustrated and have the impression that their concerns were not adequately addressed. Turning to the Internet to get the answers they seek has become a common next step. Other factors include increased consumer interest in alternative approaches to healthcare, which are freely promoted online; the anonymity offered by Internet research (answers to questions can be sought without the embarrassment of face-to-face communication with a physician); and the convenience of being able to access health information from the comfort and privacy of the home. These behaviors are all part of the changing attitudes of healthcare consumers, and with a new generation of future patients for whom "Google" is a commonly used verb, it's less of a trend and more of a 21st century paradigm shift — one healthcare providers may do well to embrace.

When you look at the Internet's influence on the future of healthcare and the changing roles between physicians and the patients they care for, it's clear that physicians who want to remain relevant and progressive may want to familiarize themselves with some of the most accessed healthcare websites, and have a working knowledge of sites that deal with their areas of expertise. For those willing to take an even bolder step forward, the opportunity exists to get involved in a more hands-on way by creating consumer-centric content for websites, authoring relevant blogs or contributing articles and commentary to existing reputable sites. By doing so, physicians can begin to bridge the communication gap created by the world-wide web, and partner with consumers to create the healthcare model of the future. ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

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Immune Globulin: The Long and Short of It

Unpredictable fluctuation in supply and demand, combined with the current reimbursement model, is the root of the problem of affordable IG treatment.

By Chris Ground

Immune globulin (IG) is a critical drug for tens of thousands of individuals in the U.S. who depend on it to treat a host of primary immune and autoimmune diseases. Without IG treatment — especially with the IG product that's right for them — patients risk chronic debilitation, permanent physical damage and even death. That is why the availability of IG is so critical when it comes to patient care.

But availability is problematic because the IG supply and demand for it are continually fluctuating. Since its introduction in 1981, IG has gone through prolonged cycles of short supply followed by briefer periods of ample supply. When product supply fluctuates, price adjustments follow. And at times, this poses problems due to the current reimbursement model. When prices are at their highest, typically during short supply, the current reimbursement model fails to adequately compensate healthcare providers, leaving physicians little choice but to limit or stop treatment. Here's why.

The Short Versus Long Market

The IG market is a classic supply and demand situation. When supply is low, it is called a short market, which means demand is higher than supply, resulting in increased prices. When there is ample supply, it is known as a long market, one where demand isn't keeping pace with supply, typically resulting in decreased prices.

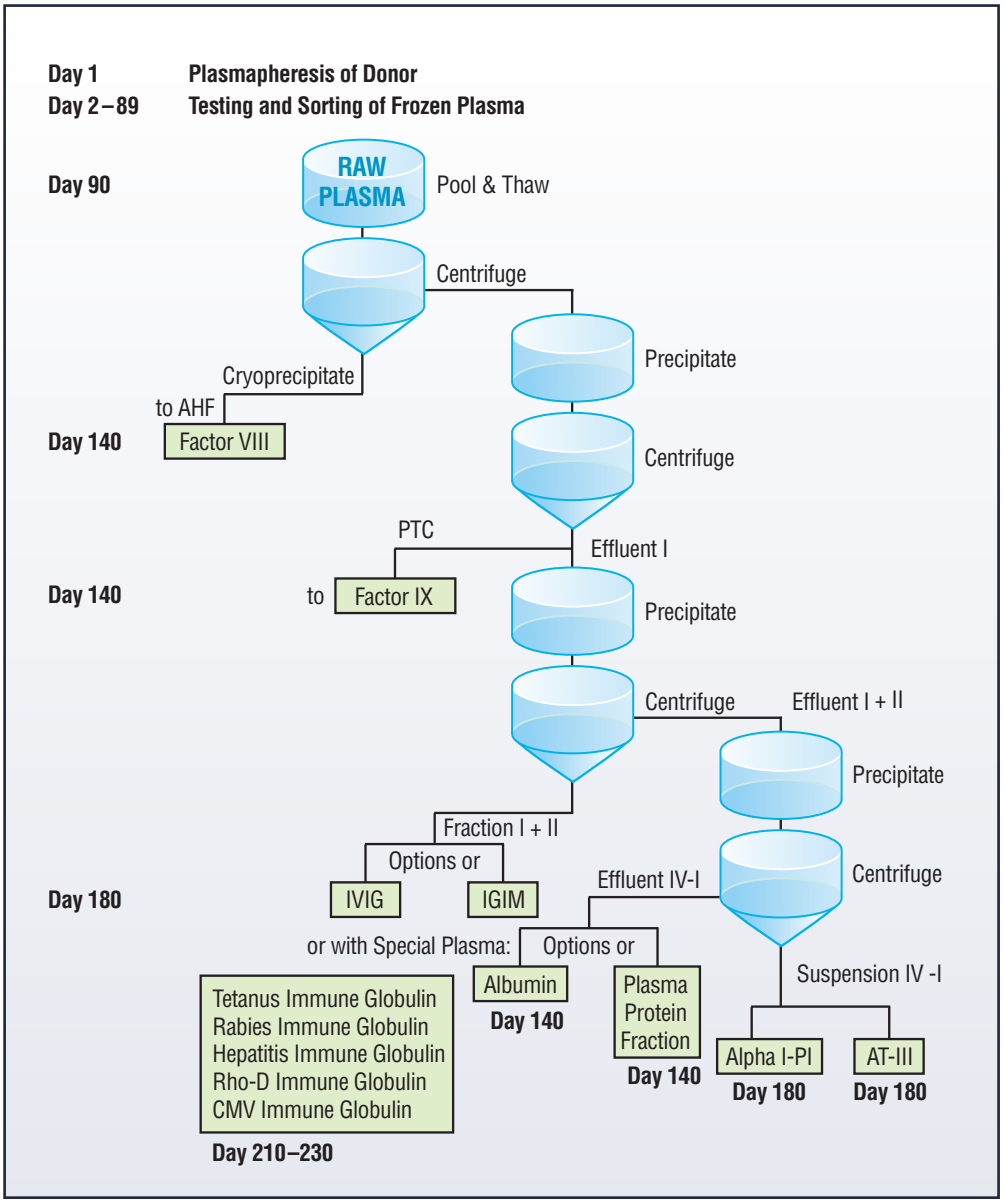
Why a market switches from short to long and back again is primarily a result of current and predicted demand (although historically there have been a few other reasons). Over the years, the number of patients needing IG treatment has steadily increased. And the numbers multiply as doctors prescribe IG for off-indicated uses and research expands to determine the effectiveness of IG to treat other conditions.

As demand increases, manufacturers ramp up production, unfortunately too much at times, which causes a long market. When this happens, manufacturers are forced to cool production until demand can catch up. For IG, though, it's hard to predict just how much to cut back because plasma availability remains an uncertain limiting factor to increase supply levels (although this is changing as more plasma collection centers open in the U.S.). In addition, the IG manufacturing process, called fractionation, is lengthy, taking approximately seven to nine months from when an individual donates plasma to when the medication is ready for use. When demand does catch back up with supply, a short market returns.

The High Cost of IG

This may sound simple, but it is more complicated with IG. When compared to most other drug therapies, IG is high-cost, primarily because of the expense of plasma procurement, testing and fractionation. Fractionation — the months-long, arduous process of converting plasma into its three main commercial proteins: IG, factor and albumin (see Table 1) — is only cost-effective if there is relatively equivalent demand for each of these products. When IG was first used to treat primary immune deficiency (PIDD) and autoimmune disorders (namely, idiopathic thrombocytopenic purpura or

Facts of Fractionation



ITP), there was enough demand for each of the products. That changed when full-litre or total protein portfolio pull-through was reduced, caused first by the introduction of recombinant factor, which competed against fractionated plasma-derived factor, and followed by a decrease in albumin demand due to the release of a damaging and unfounded report. Without enough demand for factor and albumin, there was pressure to increase the cost of IG.

The High Cost of Low Reimbursement

As IG costs increase, the reimbursement model for IG has become a problem for healthcare providers. In recent years, the reimbursement model, once based on average wholesale price (AWP), was changed to an average sales price (ASP) model. Although it was meant to apply mostly to Medicare reimbursement, private insurance companies are now beginning to follow Medicare's lead to reduce their reimbursement costs.

Current Medicare reimbursement formulas are based on quarterly drug pricing data submitted to the Centers for Medicare and Medicaid Services (CMS) by drug manufacturers, from which ASPs are calculated. Healthcare providers, then, are reimbursed the ASP plus a set percentage of ASP (currently, it is 4 percent for care given in hospital outpatient settings and 6 percent for treatment in physician offices).

When prices are at their highest, typically during short supply, the current reimbursement model fails to adequately compensate healthcare providers, leaving physicians little choice but to limit or stop treatment.

While the ASP rate changes each quarter, it is based on data from sales reports from the previous two quarters. That means the rate at which physicians are being reimbursed lags behind the economic realities of current prices. In a rising price

Worksheet: Medicare IVIG Reimbursement

	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Cell 7	Cell 8	Cell 9
Product	Average Sales Price (ASP)* Per Gram	4% of ASP (.04 x ASP) or 6% of ASP (.06 x ASP)	Reimbursement Per Gram	Your Cost Per Gram	Over/Under IVIG Cost Per Gram	Number of Grams	Total Over/Under IVIG Cost	Cost of Infusion Administration	Net
Carimune NF	$57.367								
Flebogamma 5% DIF	$70.209								
Gammagard Liquid	$72.794								
Gammagard S/D	$57.367								
Gamunex	$70.592								
Octagam	$71.218								
Privigen	$66.135								

Directions:

- In Cell 2, enter 4% of ASP or 6% of ASP, based on your facility type: 4% for Hospital Outpatient; 6% for Physician Office.
- Add Cell 1 and Cell 2 and record result in Cell 3.
- Enter data in Cell 4.
- Subtract Cell 4 from Cell 3 and record in Cell 5.
- Enter data in Cell 6.
- Multiply Cell 5 by Cell 6 and record in Cell 7.
- Enter data in Cell 8.
- Subtract Cell 8 from Cell 7 and record in Cell 9.

*Published by CMS for reimbursement rates effective October 1, 2009 through December 31, 2009.

Calculate Your Reimbursement Online:
www.bstquarterly.com/IVIGCalculator.aspx

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- **Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.[1] Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (*see Warnings and Precautions [5.2]*). Privigen does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (*see Dosage and Administration [2.3], Warnings and Precautions [5.2]*).**

1 INDICATIONS AND USAGE

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of the following conditions.

1.1 Primary Humoral Immunodeficiency

Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

1.2 Chronic Immune Thrombocytopenic Purpura

Privigen is indicated for the treatment of patients with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

3 DOSAGE FORMS AND STRENGTHS

Privigen is a liquid solution containing 10% IgG (0.1 g/mL) for intravenous infusion.

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Because it contains the stabilizer L-proline, Privigen is contraindicated in patients with hyperprolinemia.
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (*see Contraindications [4]*). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤25 mcg/mL) (*see Description [11]*). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Privigen is contraindicated in patients with antibodies against IgA *and* a history of hypersensitivity reaction (*see Contraindications [4]*).

5.2 Renal Failure

Ensure that patients are not volume depleted before administering Privigen. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction, administer Privigen at the minimum infusion rate practicable (*see Boxed Warning, Dosage and Administration [2.3]*).

5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Privigen and other IGIV product treatments. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.[2]

5.4 Thrombotic Events

Thrombotic events may occur following treatment with Privigen and other IGIV products.[3-5] Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (*see Dosage and Administration [2.3]*). Weigh the potential risks and benefits of IGIV against those of alternative therapies in all patients for whom Privigen therapy is being considered.

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with Privigen (*see Adverse Reactions [6, 6.1]*) and other IGIV product treatments. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[6] AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (*see Patient Counseling Information [17]*). Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.[7-9] Hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration and/or intravascular RBC destruction.[10]

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (*see Adverse Reactions [6, 6.1]*). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

Monitor patients for clinical signs and symptoms of hemolysis (*see Patient Counseling Information [17]*). If these are present after Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment.[11] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions (s*ee Patient Counseling Information [17]*). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (*see Dosage and Administration [2.2]*).

5.9 Transmissible Infectious Agents

Privigen is made from human plasma. Based on effective donor screening and product manufacturing processes (*see Description [11]*), Privigen carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Privigen. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare professional to CSL Behring Pharmacovigilance at 1-866-915-6958. Before prescribing Privigen, the physician should discuss the risks and benefits of its use with the patient (*see Patient Counseling Information [17]*).

5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.
- Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.
- If signs and/or symptoms of hemolysis are present after an infusion of Privigen, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.11 Interference With Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >10% of clinical study subjects with PI were headache, pain, nausea, fatigue, and chills.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data (*see Warnings and Precautions [5.5, 5.6]*). The most common adverse reactions observed in >10% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.

6.1 Clinical Trials Experience

Because different clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen intravenously every 3 or 4 weeks for up to 12 months (*see Clinical Studies [14.1]*). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 57.5% were male and 42.5% were female.

The safety analysis included all 80 subjects, 16 on the 3-week schedule and 64 on the 4-week schedule. The median doses of Privigen administered intravenously ranged from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg). A

total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule. Of the 1038 infusions, 435 were administered to females and 603 to males.

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint. The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2 lists the temporally associated AEs that occurred in more than 5% of subjects during a Privigen infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

Table 2: Adverse Events Occurring in >5% of Subjects With PI During a Privigen Infusion or Within 72 Hours After the End of an infusion, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=80]	Infusions (%) [n=1038]
Headache	35 (43.8)	82 (7.9)
Pain	20 (25.0)	44 (4.2)
Fatigue	13 (16.3)	27 (2.6)
Nausea	10 (12.5)	19 (1.8)
Chills	9 (11.3)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)
Pyrexia	6 (7.5)	10 (1.0)
Cough	5 (6.3)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).

Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that occurred in one subject and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (DAT) at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg intravenous infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 59.6% were female and 40.4% were male.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 3 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP during a Privigen infusion or within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen, *irrespective of causality*.

Table 3: Adverse Events Occurring in >5% Subjects With Chronic ITP During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle*, *Irrespective of Causality*

Adverse Event	Subjects (%) [n=57]	Infusions (%) [n=114]
Headache	37 (64.9)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	22 (19.3)
Nausea	6 (10.5)	6 (5.3)
Epistaxis	6 (10.5)	6 (5.3)
Vomiting	6 (10.5)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding, which was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse events is voluntary and from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

Privigen Postmarketing Experience

Adverse reactions reported during worldwide postmarketing use of Privigen do not differ from what has been observed in clinical studies with Privigen and from what is known for IGIV products.

General

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, and rubella.[13] The immunizing physician should be informed of recent therapy with Privigen so that appropriate measures may be taken (*see Patient Counseling Information [17]*).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Privigen. It is not known whether Privigen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Privigen should be given to pregnant women only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.[14,15]

8.3 Nursing Mothers

Use of Privigen in nursing mothers has not been evaluated.

8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency

Privigen was evaluated in 31 pediatric subjects (19 children and 12 adolescents) with PI. There were no apparent differences in the safety and efficacy profiles as compared to those in adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and effectiveness of Privigen have not been established in pediatric patients with PI who are under the age of 3.

Treatment of Chronic Immune Thrombocytopenic Purpura

Safety and effectiveness of Privigen have not been established in pediatric patients with chronic ITP who are under the age of 15.

8.5 Geriatric Use

Clinical studies of Privigen did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Use caution when administering Privigen to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency (*see Boxed Warning, Warnings and Precautions [5.2]*). Do not exceed recommended doses, and administer Privigen at the minimum infusion rate practicable.

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environment brought on by a short market, healthcare providers often are paying more, sometimes substantially more, than the Medicare reimbursement rate, and therefore, are not fully reimbursed. This has forced many physicians to stop treating patients who rely on IG, simply because they can't afford to continue operating at a deficit. The result is that patients either go without treatment or resort to going to a hospital where treatment is mandated.

In addition, "Medicare rates primarily cover the cost of the drug itself," says Kris McFalls, patient advocate for *IG Living* magazine, written for patients who depend upon IG products and for their healthcare providers. "For IVIG, reimbursement rates allow minimal to no reimbursement for the cost of acquisition, distribution, supplies or nursing. Subcutaneous IG (SCIG), which is covered under the durable medical equipment benefit, does cover part of the cost of the pump, but SCIG reimbursement is available only to PIDD patients."

What's more, reimbursement formulas for IG products often squeeze out physician and patient choice. Not all products are priced the same. So, to keep costs down and maximize profit margins, infusion providers may treat patients with only one or two of the less expensive IG products. In short, their decision is based upon profitability versus need. "IG products do not come in a generic form, and although some patients have no ill effects from changing products, many patients do,"

explains McFalls. "Switching patients from one product to another can cause serious, long-lasting side effects, as each product uses different methods and ingredients to purify and stabilize IG products." Jordan Orange, MD, PhD, FAAAAI, chair of the American Academy of Allergy, Asthma and Immunology's Primary Immunodeficiency Diseases Committee, clarifies this by saying, "A specific IVIG product needs to be matched to patient characteristics. A change in IVIG product should occur only with the active participation of the prescribing physician."

It is crucial for physicians to support an overhaul of the reimbursement model.

The Role of the Healthcare Provider

What does this mean for healthcare providers in the current long market — a condition that started prior to the end of 2008? As of this writing, prices have temporarily stabilized and reimbursement rates have caught up with the cost of IG, which means most reimbursement rates will cover or exceed the cost of IG products. In this phase of the cycle, physicians can now return to treating IG patients as needed. Nonetheless, a short market is sure to return, encumbered by the same reimbursement issues that continue the fluctuating cycle.

To bring about stability, it is crucial for physicians to support an overhaul of the reimbursement model. Reform efforts are underway. At the federal level, the IVIG Access Act of 2009 was introduced in April. Among other things, the legislation grants the Secretary of Health and Human Services authority to update the payments for IVIG based on new or existing data, allows coverage for related items and services, and requires MedPAC to review IVIG payment and provide recommendations within a two-year period for any additional payment changes.

For the thousands of patients who rely on it, IG is a miraculous product. What IG does for patients is incredible, and there are still patients yet to be diagnosed, treated and brought back to health. Surely problems surrounding supply and reimbursement need to be resolved for their sake. The answer lies in stabilizing the market: having enough product so that the probability of success is high, but not so much product that physicians can't afford to nurture patient demand. The key is affordable demand, which is highly dependent on revising the current ASP reimbursement model. ❖

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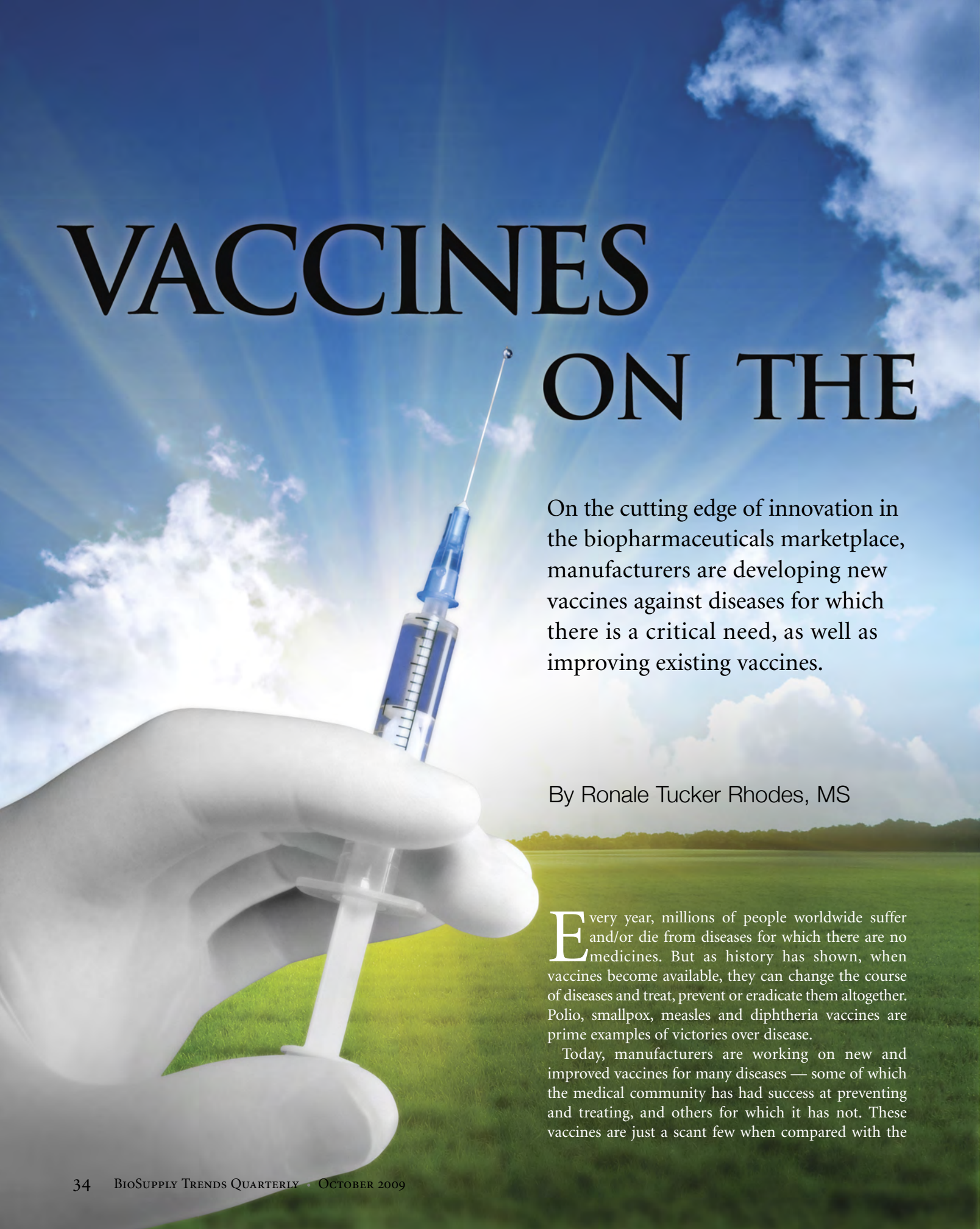
VACCINES ON THE



On the cutting edge of innovation in the biopharmaceuticals marketplace, manufacturers are developing new vaccines against diseases for which there is a critical need, as well as improving existing vaccines.

By Ronale Tucker Rhodes, MS

Every year, millions of people worldwide suffer and/or die from diseases for which there are no medicines. But as history has shown, when vaccines become available, they can change the course of diseases and treat, prevent or eradicate them altogether. Polio, smallpox, measles and diphtheria vaccines are prime examples of victories over disease.

Today, manufacturers are working on new and improved vaccines for many diseases — some of which the medical community has had success at preventing and treating, and others for which it has not. These vaccines are just a scant few when compared with the

myriad medical conditions unanswered by vaccines, but their importance cannot be overstated. While there are hundreds of vaccines in clinical trials, the following vaccines on the horizon focus on illnesses that have been plaguing society for a considerable time.

HORIZON

New Vaccines on the Horizon

Malaria. Malaria is a mosquito-borne disease that causes more than 2.7 million deaths each year, according to the World Health Organization.[1] The potentially fatal blood disease is caused by a parasite that is transmitted to human and animal hosts by the Anopheles mosquito. The human parasite, Plasmodium falciparum, digests the red blood cell's hemoglobin, and changes the adhesive properties of the cell it inhabits, which in turn causes the cell to stick to the walls of blood vessels. When the infected blood cells stick to the capillaries in the brain, blood flow is obstructed, causing a condition called cerebral malaria.

GlaxoSmithKline Biologicals and the Malaria Vaccine Initiative have partnered with scientists in African research centers to develop a vaccine against malaria. The vaccine is intended for children under the age of 5 who are most vulnerable to the disease. The Phase 3 trial of the most advanced vaccine candidate, RTS,S, begun in May, will evaluate the vaccine's efficacy in two groups of children. The first group, ages 6 weeks to 12 weeks, will be vaccinated as part of their regular schedule of infant immunizations. The second group is children ages 5 months to 17 months.[2]

The Phase 3 trial builds on more than 10 years of clinical research in Africa. Recent Phase 2 studies showed that over an eight-month follow-up period, RTS,S cut the incidences of malaria in children by 53 percent and didn't interfere with other childhood vaccinations given simultaneously. However, unlike vaccines against smallpox or measles, the malaria vaccine provides only partial protection against disease. It is unknown how long the vaccine's protection lasts.

If the required regulatory clearances are granted and international and African national public health authorities recommend its use, RTS,S could be introduced in 2012 for children age 5 months to 17 months. Once the vaccine is recommended for use in infants, full availability is anticipated by 2014.

HIV/AIDS. Acquired immunodeficiency syndrome (AIDS) is the fourth leading cause of death globally. Every day, 7,500 people become newly infected with the human immunodeficiency virus (HIV), the cause of AIDS. To date, more than 20 million people have died from AIDS, and more than 33 million people are living with HIV. HIV is a virus that gradually attacks immune system cells, making the body more vulnerable to infections, and making it more difficult to fight off those infections. A person is said to have AIDS when they have developed a very advanced HIV infection, although that can often take years.

Testing of the first AIDS vaccine, which was developed by Merck & Co., occurred in 2007 with disappointing results. Known as the STEP Study, the trial was brought to an early end after preliminary analyses suggested that those who received the vaccine picked up HIV infections at rates higher than controls.[3] Scientists hypothesized that the administration resulted in an immune response to the adenovirus that included activated helper T-cells. And, since T-cells are targeted by HIV, the vaccine effectively gave HIV more cells to infect. That hypothesis has since been disproved.

The newest HIV/AIDS vaccine was developed at the University of Cape Town in South Africa with technical help from the National Institutes of Health (NIH). The trial will seek to determine the immune response of HIV-negative people to two experimental vaccines — SAAVI DNA-C2 and SAAVI MVA-C.[4] A trial of 12 volunteers in the United States began earlier this year. Testing on an additional 36 healthy volunteers began in July in South Africa. The trial is projected to last several years.

Cancer. Cancer represents a group of diseases that presently kills some 560,000 Americans each year. Only two cancer vaccines — for hepatitis B and genital human papillomavirus (HPV) — currently have FDA approval, and both are strictly preventive, targeting viruses that can lead to cancer. The new "therapeutic cancer vaccines" being tested are not preventive; instead, the vaccines are injected into people already inflicted with cancer in an effort to make their immune systems fight growing tumors. Four cancer vaccines have achieved positive results in Phase 3 clinical trials. These vaccines are for lymphoma, melanoma, kidney cancer, prostate cancer and colorectal cancer.

Lymphoma is a blood cancer that is often fatal. Biovest International Inc. tested its BiovaxID vaccine in a multicenter

Phase 3 clinical trial, and found that the vaccine prolongs first remission duration in patients with follicular lymphoma. Biovest intends to seek approval for the vaccine in the U.S. and internationally.

Melanoma, the least common type of skin cancer, is by far the most serious form of the disease.[5] Accounting for about 4 percent of skin cancer cases, it causes approximately 79 percent of skin cancer deaths. In the United States, the number of new cases of melanoma has more than doubled in the past 20 years. About 8,650 people in the United States are expected to die of melanoma during 2009.

Renal cell carcinoma, also known as renal cell cancer or renal cell adenocarcinoma, is the most common type of kidney cancer. The American Cancer Society (ACS) estimates that there will be about 57,760 new cases of kidney cancer (35,430 in men and 22,330 in women) in the United States in 2009, and about 12,980 people (8,160 men and 4,820 women) will die from this disease.[6]

Today, manufacturers are working on new and improved vaccines for many diseases — some of which the medical community has had success at preventing and treating, and others for which it has not.

Both melanoma and kidney cancer are the targets of the vaccine Oncophage, manufactured by Antigenics, which has received fasttrack and orphan drug designations from the U.S. Food and Drug Administration (FDA).[7] Oncophage is a therapeutic vaccine made from individual patients' tumors. More than 800 cancer patients around the world have been treated with Oncophage in clinical trials. A Phase 3 study compared conventional treatment for melanoma versus treatment with the Oncophage vaccine, and found that the vaccine caused tumors to shrink in twice as many patients as those receiving a standard FDA-approved therapy.[8] In 2007, results from a Phase 3 trial of Oncophage in kidney cancer showed a 45 percent improvement in recurrence-free survival associated with Oncophage in patients with intermediate-risk kidney cancer, although a significant improvement was not observed in the overall patient population. And, in 2009, interim survival data showed that Oncophage appeared to lower the risk of death by almost 46 percent in the intermediate-risk population. Final results are expected in 2010.

Prostate cancer is the most common cancer, other than skin cancers, and is the second leading cause of cancer death in American men, behind only lung cancer. The ACS estimates that during 2009, approximately 192,280 new cases of prostate cancer will be diagnosed in the United States. The ACS also estimates that 27,360 men in the United States will die of prostate cancer in 2009. Prostate cancer accounts for about 10 percent of cancer-related deaths in men.[9]

Now, after decades of failures and false starts for developing a vaccine to treat prostate cancer, a new study shows promising results.[10] Provenge, manufactured by Dendreon, is a biologic drug given by infusion to spur the immune system to fight advanced prostate cancer that doesn't respond to anti-androgen treatment. In the Phase 3 study of 512 men with advanced metastatic, androgen-independent prostate cancer, overall survival was significantly better for those for taking Provenge than those taking a placebo. Specifically, Provenge extended median survival by 4.1 months and improved four-year survival by 38 percent. Dendreon plans to submit the study's results to the FDA in the fourth quarter of 2009; after that, the FDA will have six months to review the material.

Excluding skin cancers, *colorectal cancer* is the third most common cancer diagnosed in both men and women in the United States and the third leading cause of cancer-related deaths in the United States. The ACS estimates the number of colorectal cancer cases in the United States in 2009 to be 106,100 new cases of colon cancer (52,010 in men and 54,090 in women) and 40,870 new cases of rectal cancer (23,580 in men and 17,290 in women). Overall, the lifetime risk for developing colorectal cancer is about 1 in 19 (5.3 percent). It is expected to cause about 49,920 deaths (25,240 in men and 24,680 in women) during 2009.[11]

A cancer vaccine with a twist is making headway in clinical trials at the University of Pittsburgh School of Medicine.[12] The new vaccine triggers the immune system to attack a faulty protein, MUC1, that's often abundant in colorectal cancer tissue and precancerous tissue. It has already proven safe in patients with advanced pancreatic cancer, and is now in clinical trials to gauge the immune response it elicits in patients with a history of advanced adenomas. However, not all colorectal tumors produce abnormal MUC1, so it's possible to develop colorectal cancer even if the vaccine is effective. Investigators have been

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Before administering Adacel vaccine, please see brief summary of full Prescribing Information on next page.

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Learn more about pertussis disease and prevention at **www.ADACELVACCINE.com**.

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References: 1. Centers for Disease Control and Prevention (CDC). Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR*. 2006;55(RR-17):1-37. **2.** CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2006;55(RR-3):1-43. **3.** Adacel vaccine [Prescribing Information]. Swiftwater, PA. Sanofi Pasteur Inc.; 2008. **4.** Sanofi Pasteur Inc. Data on file (Adacel direct and indirect doses, 2005-2009 US, Sanofi Pasteur and VaxServe), February 2009. MKT17191.

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Brief Summary: Please see package insert for full prescribing information.

INDICATIONS AND USAGE Adacel vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of Adacel vaccine as a primary series, or to complete the primary series, has not been studied. Vaccination with Adacel vaccine may not protect all of vaccinated individuals.

CONTRAINDICATIONS A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Adacel vaccine or any other tetanus toxoid, diphtheria toxoid or pertussis containing vaccine or any other component of this vaccine is a contraindication to vaccination with Adacel vaccine. Because of uncertainty as to which component of the vaccine may be responsible, none of the components should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. (1,2) Encephalopathy within 7 days of a previous dose of a pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination with Adacel vaccine. (1-3)

WARNINGS Persons who experienced Arthus-type hypersensitivity reactions (e.g., severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid containing vaccines more frequently than every 10 years, even if the wound is neither clean nor minor. (1,2,5,6) If Guillain-Barré syndrome occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give Adacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.(1-3) In the following situations, Adacel vaccine should generally be deferred:

- Moderate or severe acute illness with or without fever, until the acute illness resolves. (1,2)
- In adolescents, progressive neurologic disorder, including progressive encephalopathy, or uncontrolled epilepsy, until the condition has stabilized. (2)
- In adults, unstable neurologic condition (e.g., cerebrovascular events and acute encephalopathic conditions), until the condition has resolved or is stabilized. (1)

PRECAUTIONS General Before administration of Adacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See **CONTRAINDICATIONS** and **WARNINGS.**) Epinephrine Hydrochloride Solution (1:1,000) and other appropriate agents and equipment should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. If Adacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and/or Parent or Guardian Before administration of Adacel vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with Adacel vaccine or other vaccines containing similar components. The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of child-bearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy surveillance system to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. If they are pregnant or become aware they were pregnant at the time of Adacel vaccine immunization, they are encouraged to contact directly or have their health-care professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE). Reporting adverse events after vaccination to VAERS (Vaccine Adverse Event Reporting System) by recipients and/or parents or guardian should be encouraged. The toll-free number for VAERS forms and information is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. (See **PRECAUTIONS, General.**) For information regarding simultaneous administration with other vaccines refer to the **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with Adacel vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study. (7)

Nursing Mothers It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.

Pediatric Use Adacel vaccine is not indicated for individuals less than 11 years of age. (See **INDICATIONS AND USAGE.**) For immunization of persons 6 weeks through 6 years of age against diphtheria, tetanus and pertussis refer to manufacturers' package inserts for DTaP vaccines.

Geriatric Use Adacel vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of Adacel vaccine in individuals 65 years of age and older as clinical studies of Adacel vaccine did not include participants in the geriatric population.

ADVERSE REACTIONS The safety of Adacel vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive (3,393 adolescents 11-17 years of age and 2,448 adults 18-64 years) received a single dose of Adacel vaccine. The principal safety study was a randomized, observer-blind, active controlled trial that enrolled participants 11-17 years of age (Adacel vaccine N = 1,184; Td vaccine N = 792) and 18-64 years of age (Adacel vaccine N = 1,752; Td vaccine N = 573). Study participants had not received tetanus or diphtheria containing vaccines within the previous 5 years. Solicited local and systemic reactions and unsolicited adverse events were monitored daily for 14 days post-vaccination using a diary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physician's office or to an emergency room, onset of serious illness and hospitalizations. Information regarding adverse events that occurred in the 6 month post-vaccination time period was obtained from the participant via telephone. Approximately 96% of participants completed the 6-month follow-up evaluation. In the concomitant vaccination study with Adacel and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination using a diary card. Local adverse events were only monitored at site/arm of Adacel vaccine administration. Unsolicited reactions (including immediate reactions, serious adverse events and events that elicited seeking medical attention) were collected at a clinic visit or via telephone interview for the duration of the trial, i.e., up to six months post-vaccination. In the concomitant vaccination study with Adacel vaccine and trivalent inactivated influenza vaccine, local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. All unsolicited reactions occurring through day 14 were collected. From day 14 to the end of the trial, i.e., up to 84 days, only events that elicited seeking medical attention were collected. In all the studies, participants were monitored for serious adverse events throughout the duration of the study. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

Serious Adverse Events in All Safety Studies Throughout the 6-month follow-up period in the principal safety study, serious adverse events were reported in 1.5% of Adacel vaccine recipients and 1.4% in Td vaccine recipients. Two serious adverse events in adults were neuropathic events that occurred within 28 days of Adacel vaccine administration; one severe migraine with unilateral facial paralysis and one diagnosis of nerve compression in neck and left arm. Similar or lower rates of serious adverse events were reported in the other trials and there were no additional neuropathic events reported.

Solicited Adverse Events in the Principal Safety Study Most selected solicited adverse events (erythema, swelling, pain and fever) that occurred during Days 0-14 following one dose of Adacel vaccine or Td vaccine were reported at a similar frequency. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 63 to 78% of all vaccinees. In addition, overall rates of pain were higher in adolescent recipients of Adacel vaccine compared to Td vaccine recipients. Rates of moderate and severe pain in adolescents did not significantly differ between the Adacel vaccine and Td vaccine groups. Among adults the rates of pain, after receipt of Adacel vaccine or Td vaccine, did not significantly differ. Fever of 38°C and higher was uncommon, although in the adolescent age group, it occurred significantly more frequently in Adacel vaccine recipients than Td vaccine recipients. (7) Among other solicited adverse events headache was the most frequent systemic reaction and was usually of mild to moderate intensity. In general, the rates of the events following Adacel vaccine were comparable with those observed with Td vaccine. Local and systemic solicited reactions occurred at similar rates in Adacel vaccine and Td vaccine recipients in the 3 day post-vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). The rates of unsolicited adverse events reported from days 14-28 post-vaccination were comparable between the two groups, as were the rates of unsolicited adverse events from day 28 through 6 months. There were no spontaneous reports of whole-arm swelling of the injected limb in this study, nor in the other three studies which contributed to the safety database for Adacel vaccine.

Adverse Events in the Concomitant Vaccine Studies

Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the Adacel vaccine administration site) were similar when Adacel and Hep B vaccines were given concurrently or separately. However, the rates of injection site erythema (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the Adacel vaccine administration site were increased when co-administered. Swollen and/or sore joints were reported by 22.5% for concomitant vaccination and 17.9% for separate administration. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vaccination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (7)

Local and Systemic Reactions when Given with Trivalent Inactivated Influenza Vaccine The rates of fever and injection site erythema and swelling were similar for recipients of concurrent and separate administration of Adacel vaccine and TIV. However, pain at the Adacel vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% for separate administration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unsolicited adverse events were similar between the 2 study groups. (7)

Additional Studies An additional 1,806 adolescents received Adacel vaccine as part of the lot consistency study used to support Adacel vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Adacel vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolicited adverse events and serious adverse events were collected for 28 days post-vaccination. Pain was the most frequently reported local adverse event occurring in approximately 80% of all participants. Headache was the most frequently reported systemic event occurring in approximately 44% of all participants. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days. (7) An additional 962 adolescents and adults received Adacel vaccine in three supportive Canadian studies used as the basis for licensure in other countries. Within these clinical trials, the rates of local and systemic reactions following Adacel vaccine were similar to those reported in the four principal trials in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was comparable to the rates reported in four principal trials conducted in the US. (7) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous reports among the 962 Adacel vaccine recipients in the supportive Canadian studies.

Postmarketing Reports The following adverse events have been spontaneously reported during the post-marketing use of Adacel vaccine in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting or the strength of causal association to Adacel vaccine. *General disorders and administration site conditions:* Large injection site reactions (>50 mm), extensive limb swelling from the injection site beyond one or both joints, Injection site bruising, sterile abscess. *Nervous system disorders:* Paraesthesia, hypoesthesia, Guillain-Barré syndrome, facial palsy, convulsion, syncope, myelitis. *Immune system disorders:* Anaphylactic reaction, hypersensitivity reaction (angioedema, edema, rash, hypotension) *Skin and subcutaneous tissue disorders:* Pruritus, urticaria. *Musculoskeletal and connective tissue disorders:* Myositis, muscle spasm. *Cardiac disorders:* Myocarditis

Additional Adverse Events Additional adverse events, included in this section, have been reported in conjunction with receipt of vaccines containing diphtheria, tetanus toxoids and/or pertussis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. Such reactions may be associated with high levels of circulating antitoxin in persons who have had overly frequent injections of tetanus toxoid. (8) (See **WARNINGS.**) Persistent nodules at the site of injection have been reported following the use of adsorbed products. (4) Certain neurological conditions have been reported in temporal association with some tetanus toxoid containing vaccines or tetanus and diphtheria toxoid containing vaccines. A review by the Institute of Medicine (IOM) concluded that the evidence favors acceptance of a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. Other neurological conditions that have been reported include: demyelinating diseases of the central nervous system, peripheral mononeuropathies, and cranial mononeuropathies. The IOM has concluded that the evidence is inadequate to accept or reject a causal relation between these conditions and vaccines containing tetanus and/or diphtheria toxoids.

Reporting of Adverse Events The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records of the manufacturer and lot number of the vaccine administered in the vaccine recipient's permanent medical record along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine. The Act further requires the health-care professional to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table. These include anaphylaxis or anaphylactic shock within 7 days; brachial neuritis within 28 days; an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this Adacel vaccine package insert. (9-11) The US Department of Health and Human Services has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. Reporting of all adverse events occurring after vaccine administration is encouraged from vaccine recipients, parents/guardians and the health-care provider. Adverse events following immunization should be reported to VAERS. Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967 or visit the VAERS website at www.vaers.hhs.gov. (9-11) Health-care providers should also report these events to Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463 (1-800-VACCINE).

DOSAGE AND ADMINISTRATION Adacel vaccine should be administered as a single injection of one dose (0.5 mL) by the intramuscular route. Adacel vaccine should not be combined through reconstitution or mixed with any other vaccine. Just before use, shake the vial well until a uniform, white, cloudy suspension results. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered. When administering a dose from a rubber-stoppered vial, do not remove either the stopper or the metal seal holding it in place. The preferred site is into the deltoid muscle. The vaccine should not be injected into the gluteal area or areas where there is a major nerve trunk. Do NOT administer this product intravenously or subcutaneously. Five years should have elapsed since the recipient's last dose of tetanus toxoid, diphtheria toxoid and/or pertussis containing vaccine. There are no data to support repeat administration of Adacel vaccine. The use of Adacel vaccine as a primary series or to complete the primary series for tetanus, diphtheria, or pertussis has not been studied.

STORAGE Store at 2° to 8°C (35° to 46°F). **DO NOT FREEZE.** Product which has been exposed to freezing should not be used. Do not use after expiration date.

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recruiting subjects for the trial since 2008 and expect to finish gathering data in the fall of 2011.

Ear infection. Otitis media, more commonly known as an ear infection, is the most frequently diagnosed illness in children less than 15 years of age in the U.S. More than 80 percent of children will experience at least one ear infection before their third birthday. A new study conducted at Nationwide Children's Hospital in Columbus, Ohio, shows that a pain-free vaccine could ward against ear infections.[13] The vaccine was tested by placing a droplet of formula on the outer ears of chinchillas and then rubbing it into the skin. The vaccine works by prompting an immune response that reduces or eliminates NTHI, one of the bacteria commonly responsible for ear infections.

What goes on behind the scenes to actually produce a vaccine ready to introduce to the market is quite complex.

E. coli. Escherichia coli are a large and diverse group of bacteria, and while most strains are harmless, others can make individuals sick. Some kinds of E. coli can cause diarrhea, others cause urinary tract infections, respiratory illness and pneumonia, and still others are used as markers for water contamination.[14] Enterotoxigenic E. coli (ETEC) is responsible for 60 percent to 70 percent of all E. coli diarrheal disease, kills two to three million children each year in the developing world, causes health problems for U.S. troops serving overseas, and is responsible for what is commonly called traveler's diarrhea.

Now, separate studies are showing promise for a vaccine to prevent ETEC. Investigators from the Memphis Veterans Medical Center and the University of Tennessee Health Science Center described promising early results for two experimental vaccines.[15] Both were largely effective at preventing E. coli from gaining a foothold in the digestive tracts of mice. The vaccines were designed to block the infection by preventing a protein at the end of the E. coli's whip-like flagella from attaching to a second protein, known as EtpA. EtpA is secreted by the E. coli bacteria and apparently plays a role in helping the bug stick to the intestinal tract of the unsuspecting patient. The interaction between the two proteins is a key step in the infection process.

A Michigan State University researcher has developed a working vaccine for ETEC.[16] The researcher's breakthrough was discovering a way to overcome the minuscule molecular size of one of the illness-inducing toxins produced by the E. coli bug. Since the toxin was so small, it did not prompt the body's defense system to develop immunity, allowing the same individual to repeatedly get sick, often with more severe health implications. So, he created a biological carrier to attach to the toxin that, once introduced into the body, induces a strong immune response. The vaccine was tested on mice and findings show that the biological activity of the toxin was enhanced by more than 40 percent, leading to its recognition by the body's immune system. After immunizing a group of 10 rabbits, the vaccine led to the production of the highest neutralizing antibody ever reported for this type of the toxin. Human clinical trials could begin late in 2009.

Shigellosis. Shigellosis is endemic throughout the world, with approximately 164.7 million cases — 163.2 million in developing countries and 1.5 million in industrialized countries. Each year, 1.1 million people are estimated to die from shigella infection, and 580,000 cases of shigellosis are reported among travelers from industrialized countries. A total of 69 percent of all episodes and 61 percent of all deaths attributable to shigellosis involve children less than 5 years of age.[17]

Recently, the University of Maryland, Baltimore (UMB), has licensed a pediatric vaccine against shigella bacteria to PATH, an international nonprofit group, to support clinical trials, with the goal of developing a vaccine suitable for children in resource-poor countries.[18] The UMB vaccine candidate is a multivalent vaccine designed to ultimately target five disease-causing strains of the bacteria. It is hoped that when the shigella project moves to late clinical trials, a large pharmaceutical company will finalize a version of the vaccine.

Addiction. A vaccine to treat addiction is closer now than ever before, according to experts at the National Institute on Drug Abuse (NIDA).[19] Research has led scientists to better understand how the addiction process works, which has led to the initial designing and testing of vaccines that may cure addiction in drug abusers and help them avoid relapses. Currently, vaccines are being looked at for nicotine, cocaine and methamphetamine addiction. The vaccines work by blocking the drug's reward influence in the brain and producing a new conditioned behavior in addicts: If they use the drug and don't get the high, they will learn to stop using it. None of the vaccines has been submitted to the FDA for approval. The nicotine vaccine is the closest and should be submitted in three years. A large test of the cocaine vaccine will start in the fall, with an FDA submission expected in four to five years. There's no timetable for the methamphetamine vaccine, which is not ready for human tests.

Improved Vaccines on the Horizon

Vaccines currently exist for a host of diseases. However, due to various reasons, continued research and development for improved vaccine response is often needed. Four diseases are currently at center stage for improvement.

Neisseria meningitides (meningococcus). The recently released vaccine to prevent meningitis, Menactra (manufactured by sanofi pasteur), may soon have company. Novartis AG has developed Menveo, a vaccine to prevent meningitis that can be administered to individuals ages 11 to 55.[20] In clinical

trials, Menveo has been shown to elicit a protective immune response against four of the most common serogroups — A, C, W-135 and Y — of neisseria meningitides. The FDA has requested additional information on the clinical and CMC (chemistry manufacturing and control) sections of the biologics license application before it will make a decision to grant approval. No new clinical trials are required, and it is expected that Novartis will be able to respond to all questions in 2009.

Influenza. Each year, manufacturers go back to the drawing board to determine which strains of the flu virus to include in the influenza vaccine. This is determined based on information gathered over the previous year about the strains of flu viruses that are infecting humans and how they are changing. Three of several examples of improved seasonal flu vaccines include Novavax's virus-like-particle (VLP) vaccine Phase 2 clinical trials, and Protein Sciences Corp.'s and Antigen Express' flu vaccines which can be produced faster than had been possible previously.

Novavax's VLP vaccine may be differentiated from other influenza vaccines in several ways.[22] First, it includes three viral proteins (incorporated in the vaccine as three separate VLPs), which is important for inducing a broad immune response. In addition, the vaccine is made in cell culture rather than eggs, which permits an exact genetic match to the flu strains causing illness since there is no requirement for adapting the vaccine to grow in eggs.

Protein Sciences is among several small companies also trying to make influenza vaccines by methods that are faster than growing them in chicken eggs, the technique now generally used.[23] Instead of growing whole viruses, it produces just a protein from the virus and it does so in genetically modified insect cells. The company recently has been awarded a $35 million federal grant for the development of this technology.

And, Antigen Express, a Toronto-based company, has developed a peptide vaccine which promises to be much more flexible, cost effective and rapid (taking approximately half the time) compared to the traditional way of manufacturing. The company is currently seeking funding for the development of its own H1N1 vaccine. (See the news story on Antigen Express on page 10.)

When a new strain of the flu develops that cannot be protected against by the seasonal flu vaccine, it is sometimes necessary to produce a new, secondary influenza vaccine. This is especially the case when the strain causes a pandemic, such as in the case of the new H1N1 (swine) flu. Five manufacturers are currently developing a swine flu vaccine, and as many as 160 million doses of swine flu vaccine will be available sometime in October.

One of the stirring prospects in the vaccine world involves the possibility of eradicating the flu pandemic. Sanofi pasteur has recently developed a vaccine (proven to be safe and effective in humans and ferrets) that does not need to be re-created each year to protect against different strains because the vaccine attacks an unchanging element of the virus.[24]

Tuberculosis. Improvements in the efficacy of the current tuberculosis vaccine are in progress. A team of Italian researchers discovered a new role for type I interferon for improving the ability of dendritic cells to stimulate an immune response against the bacterium known to cause tuberculosis.[25] The researchers speculate that type I interferon may give the current vaccine the boost necessary to elicit a protection immunity against the mycrobacterium tuberculosis. According to the U.S. Centers for Disease Control and Prevention, one-third of the world's population is infected with tuberculosis, with nearly nine million people getting sick with the disease each year. Of those nine million, almost two million will die.

The Way Ahead for Future Vaccines

What goes on behind the scenes to actually produce a vaccine ready to introduce to the market is quite complex. On average, it takes 10 to 15 years and nearly $600 million.[26] The time involved includes preclinical research (synthesis and purification processes, as well as animal testing), clinical studies (Phase 1 through 3), new drug applications, reviews and approvals.[27] Then, the vaccine has to be manufactured. Manufacturing biopharmaceuticals is both expensive and time-intensive, often taking two to three years.

But the lengthy process that it takes to develop vaccines may change. In July, the NIH bestowed a $13 million grant to Dr. Annie De Groot and her colleagues at the University of Rhode Island to find a way to speed the development of vaccines.[28] The five-year grant will be used to explore De Groot's vision of using computer software to design lean, mean, more potent vaccines, and then use a faster process for testing their effectiveness in humans. "The objective, actually, is to get some of this basic research into the clinic, to go from 20 years for making a vaccine to, perhaps, five," said De Groot.

As technology improves, not only will we continue to see more vaccines that will prevent or treat diseases, but we may see more of them in record time. ❖

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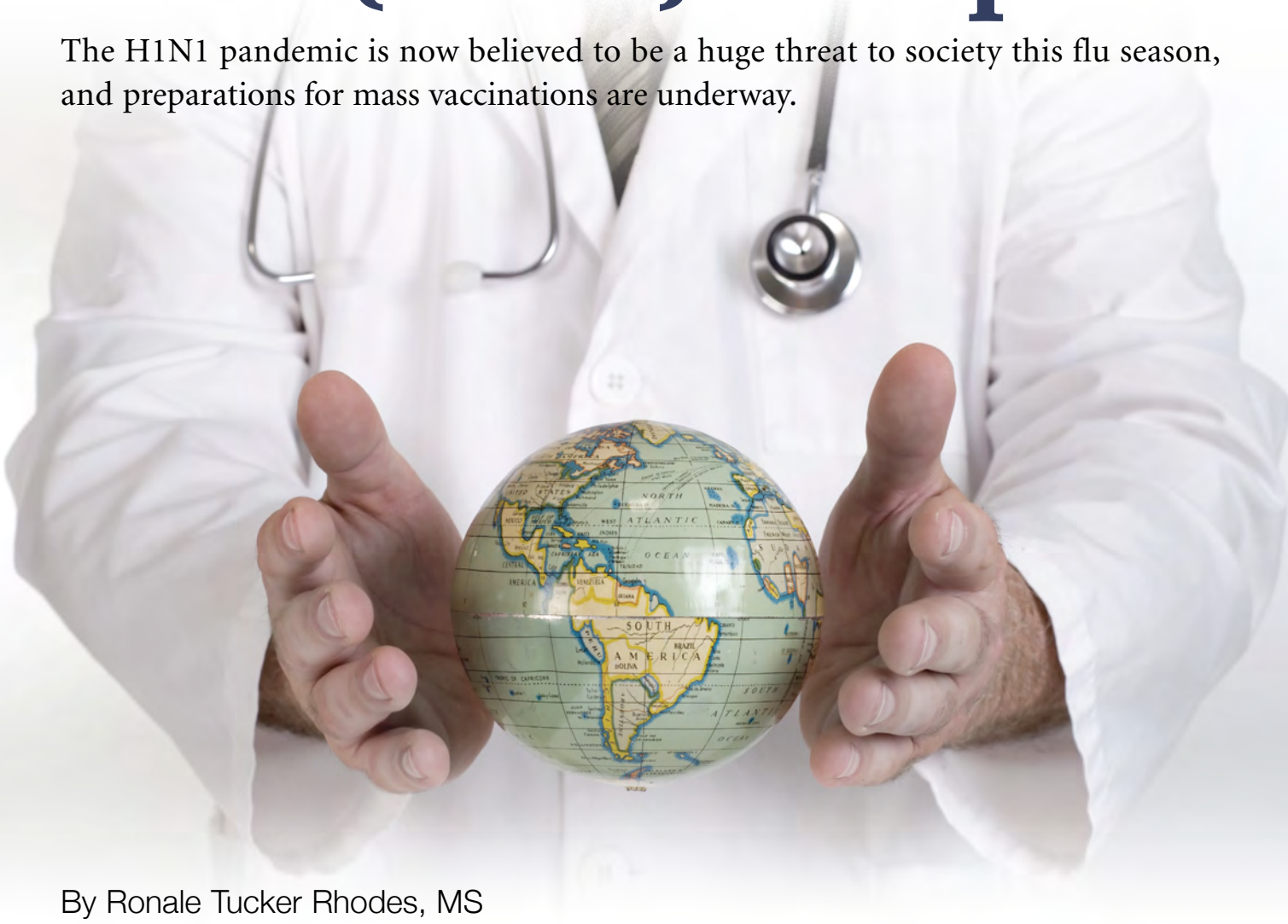
NOVARTIS VACCINES

H1N1 (Swine) Flu Update

The H1N1 pandemic is now believed to be a huge threat to society this flu season, and preparations for mass vaccinations are underway.



By Ronale Tucker Rhodes, MS

New estimates about the spread of H1N1 flu in the U.S. show that infection could possibly be much higher than originally thought. An Aug. 24 report[1] released by the President's Council of Advisors on Science and Technology estimates that "swine flu could infect half the U.S. population this fall and winter, hospitalizing up to 1.8 million people and causing as many as 90,000 deaths — more than double the number that occur in an average flu season." The 86-page report also states that the virus could cause symptoms in 60 million to 120 million people, more than half of whom might seek medical attention.

And, while the U.S. federal government wasn't initially armed with these numbers, steps to prepare the country for the worst have already been taken. For starters, the federal government has provided grants to cash-strapped states that are ill-prepared financially to handle this crisis due to the deep recession. In addition, federal agencies, drug manufacturers and local governments have been fiercely working to get healthcare providers the needed vaccines and to effectively roll out an immunization campaign to manage the pandemic.

Current Spread of H1N1

Worldwide, the H1N1 pandemic "has caused significant disruptions and economic damage in parts of the Southern Hemisphere," contributing to the deaths of more than 1,799 people in at least 168 countries.[1] The Centers for Disease Control and Prevention (CDC) reported that the most recent individual statistics for the numbers of H1N1 flu cases in the

U.S. between April 15, 2009, and July 24, 2009, were 43,771 confirmed and probable cases.[2] Of those, 5,011 people were hospitalized and 302 people died. However, the CDC recognizes that those numbers are likely far from the actual numbers. The more likely number was about one million people during that time frame.

Individual case counts, which are what the CDC was collecting since the first reported case of H1N1, are an inaccurate representation of the true burden of the disease, says the CDC, because many people likely became mildly ill with H1N1 flu but never sought treatment. In addition, many people who sought treatment were never officially tested or diagnosed. This is because testing was limited to hospitalized patients. Recognizing this, the CDC decided to stop tracking individual statistics and, instead, switch to the traditional surveillance system of aggregate national reports. The aggregate report, which can be viewed at www.cdc.gov/h1n1flu/update.htm#totalcases, shows the total number of hospitalizations and deaths weekly, as reported by individual states and territories.

As of the end of August, a total of 9,079 hospitalizations and 593 deaths associated with H1N1 flu were reported to the CDC. And, during the last two weeks of August, H1N1 influenza activity increased in Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina and Tennessee where outpatient visits to healthcare providers for influenza-like illness increased to a level usually seen only during peak winter periods. Also since the end of August, 33 of the 101 influenza-associated pediatric deaths in the U.S. were due to the H1N1 virus.

The Disease Burden in Populations

Aside from the novel strain of this flu, what makes H1N1 even more unusual is the age distribution it affects. Older adults who are typically most at risk of serious complications from seasonal flu appear to be least affected by H1N1. The hypothesis is that these individuals may have built up some immunity to H1N1 because they were previously exposed to a different strain of swine flu that appeared in 1976, either through inoculation or infection.

Looking at the individual statistical data collected April 15 through July 24, 2009, the CDC has categorized those groups that are at greatest risk of infection from the H1N1 flu.[2] Individuals at highest risk appear to be age 25 and younger. The data specifically show 26.7 cases of H1N1 per 100,000 people ages 5 through 24 years, 22.9 per 100,000 cases in people ages 0 through 4 years, and only 6.97 people per 100,000 in those ages 25 to 49 years. The rates were lowest for individuals ages 50 to 64 (3.9 per 100,000) and those ages 65 and older (1.3 per 100,000). The data also show that the hospitalization rate was highest among children ages 0 through 4 (4.5 per 100,000), followed by individuals 5 through 24 years (2.1 per 100,000) and individuals ages 65 and older (1.7 per 100,000).

Underlying medical conditions play a major role in the rate of hospitalization for those infected with the H1N1 virus, much as they do with the seasonal flu virus. However, unlike with the seasonal flu, the CDC has indicated obesity as an additional underlying health condition that places people at greater risk of serious H1N1 flu-related complications.

H1N1 Vaccine

Five manufacturers have been in production of the H1N1 vaccine for the U.S. — sanofi pasteur, Novartis Vaccines, GlaxoSmithKline, MedImmune and CSL Biotherapies — all of which already produce U.S.-licensed seasonal vaccine.[3] Having a license for the seasonal flu vaccine is key to getting the new H1N1 vaccine in circulation as soon as possible. Manufacturers with a seasonal flu license will not be required to apply for a new H1N1 license. Instead, they will follow recent recommendations by the FDA to evaluate the 2009 H1N1 vaccines using the same regulatory process to approve new viral strains contained in the annual seasonal influenza vaccines. These strain change supplements are not required to be supported by new clinical data, which is expected to expedite the licensure process for the pandemic vaccine.

Manufacturers with a seasonal flu license will not be required to apply for a new H1N1 license.

Sanofi Pasteur was the first manufacturer to submit a supplemental application for licensure of its influenza A(H1N1) 2009 monovalent vaccine in mid-August.[4] This supplemental process will likely be the process that all manufacturers will use for this year's H1N1 vaccine for licensure, according to Luke Noll, a vaccine specialist for FFF Enterprises, Inc., Temecula, Calif. However, it should be noted that while clinical data are not required, manufacturers will make available immunogenicity and safety data through clinical studies. These clinical trials began in July by the National Institute of Allergy and Infectious Diseases (NIAID), and in mid-August by individual manufacturers under contract with Health and Human Services.

Register Online to Receive H1N1 in Your State

Healthcare providers that intend to receive and administer novel H1N1 vaccine must register with their state health department. Currently, preregistration to determine vaccine needs is being accepted in all states and territories. When vaccine becomes available for distribution, preregistration information will be used to send a provider agreement and order form.

To find your state health department's preregistration web page, log on to www.fffenterprises.com/News/H1N1StateRegistration.aspx. This site provides convenient, one-click links to all state health departments.

Register now!
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Why are additional trials needed by NIAID? These trials are "intended to generate data that are outside a [manufacturer's] clinical development plan but that may be needed to support licensure or use of the vaccine under emergency use authorization (EUA)."[5] EUAs are issued by the FDA to "permit either the use of an unapproved medical product or an unapproved use of an approved medical product during certain types of emergencies with specified agents." As of this writing, all clinical trials by both the NIAID and manufacturers had produced positive results to protect against the H1N1 strain with no adverse effects. However, they are still ongoing.

The H1N1 influenza vaccine will be made using the same processes and facilities that are used to make the seasonal influenza vaccine. While the World Health Organization (WHO) recommended that countries use vaccines with adjuvants (an ingredient used to boost the body's immune response), that is unlikely in the U.S. since there are no licensed flu vaccines with adjuvants in the U.S. "The adjuvanted vaccine was being considered," explains Noll. "However, it would probably be the last resort because of the additional legal requirements of using an unlicensed product." Instead of testing an adjuvanted vaccine, says Noll, manufacturers and the NIAID are testing two doses of vaccine at various potency levels in both adults (7.5 mcg, 15 mcg and 30 mcg) and children (7.5 mcg and 15 mcg), respectively. In addition, those who are worried about thimerosal (a preservative used in vaccines that is a form of mercury), needn't be. There will be a thimerosal-free vaccine available for pregnant women and children.

As of this printing, the FDA has approved vaccines in production, and it is expected that they will be ready for distribution in mid-October. However, the WHO reported in July that the swine flu viruses being used to make the vaccine were not growing enough of a key ingredient, producing half as much "yield" as regular flu viruses.[6] And, U.S. officials in mid-August slashed their estimate of how many swine flu vaccine doses will be available.[7] The Department of Health and Human Services (HHS) had originally said that 120 million doses would be on hand in mid-October, but it changed that estimate to about 50 million doses, followed by another 20 million doses delivered each week after that.

Originally, it was thought that individuals would need two doses of the H1N1 vaccine spaced three weeks apart to protect them against the virus. However, recent findings by manufacturers and the NIAID have shown that a single dose of the vaccine triggers a protective immune response in more than 90 percent of the adults treated.[8] In one study, reported on in the Sept. 10 issue of the *New England Journal of Medicine*, 240 healthy volunteers ages 19 to 64 who were broken into two groups (those younger than age 50 and those 50 and older) received an initial dose of the vaccine followed by a second dose 21 days later. The younger group received a 15 mcg dose (the standard dose used for a single strain in the seasonal influenza vaccine), and the older group received a 30 mcg dose. Data showed that three weeks after the first of the two scheduled vaccines, 96.7 percent of participants who received the lower dose and 93.3 percent of those treated with the higher dose achieved the desired immune response.

According to the NIAID, preliminary analyses of their trial data align with these findings, and studies are ongoing.[9] It is anticipated, then, that only one dose of the H1N1 vaccine will be needed when it becomes available in October. In addition, because only one vaccine will be needed, more vaccine will be available than originally antiticipated.

Anticipating a need for some protection against the H1N1 flu prior to the availability of the injectable vaccine, the CDC announced in late September that 3.4 million doses of inhalable H1N1 vaccines will be available the first week of October, with the initial influx of 195 million doses purchased by the U.S. government. The nasal spray vaccine, known as FluMist, is approved for healthy people between the ages of 2 and 49, but it is not approved for pregnant women because it contains a live virus.

This advertisement is distributed as part of the American Lung Association's *Faces of Influenza* educational initiative. For more information, please visit www.facesofinfluenza.org.

Are *you* a Face of Influenza?

(More than 4 out of 5 people reading this are — get immunized.)

Influenza is not the common cold. It's serious. There are many "faces" of influenza.

In fact, annual influenza vaccination is recommended for more than 4 out of every 5 people.

Influenza vaccine is safe and effective and annual vaccination is the best way for people to protect themselves and their loved ones against influenza and its complications. Vaccination typically begins in October and can continue through March. In most seasons, influenza virus activity peaks in February or March, so vaccination throughout the entire influenza season is beneficial and recommended.

To learn more about the American Lung Association *Faces of Influenza* program, visit our Web site www.facesofinfluenza.org.

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American Lung Association's Influenza Prevention Program

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Are You a "Face" of Influenza?

There are many "faces" of influenza — people who should be immunized against influenza every year. More likely than not, each one of us knows someone whose well-being, good health, or life depends on getting an influenza immunization each and every year. Take the quiz below to see if you are a "face" of influenza.

- ☐ Are you a close contact, such as a parent, sibling, grandparent, or babysitter, of a child younger than 6 months of age?
- ☐ Do you have a child 6 months – 18 years of age?[1]
- ☐ Will you be an expectant mother during the influenza season (September – May)?
- ☐ Are you 50 years of age or older?
- ☐ Do you have a chronic health condition, such as asthma, chronic obstructive pulmonary disease (COPD), heart disease, or diabetes?
- ☐ Do you live with someone with a chronic medical condition, such as asthma, COPD, heart disease, or diabetes?
- ☐ Do you work in a health-care profession or facility?[1,2]

If you checked one or more of these questions you could be one of the many "faces" of influenza, people who should get vaccinated against influenza each and every year. Talk to your doctor or health-care provider about influenza vaccination today.

Influenza is not the common cold. It's serious.

Annual immunization is the best way to protect against influenza. We at the American Lung Association urge you and your loved ones to get vaccinated as soon as you can. Vaccination typically begins in October and can continue through March. In most seasons, influenza virus activity doesn't peak until February or March. Influenza vaccination is a safe and effective way to help prevent influenza.[2]

FACES OF INFLUENZA™
American Lung Association's Influenza Prevention Program
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The Government Plan

There is little doubt that the H1N1 flu will get a jump on the vaccine. Therefore, the CDC reported in August that approximately 159 million persons in the U.S. would be given priority. These include 5 million pregnant women, 4 million parents and caregivers of children younger than 6 months old, 14 million healthcare workers, 102 million people between ages 6 months and 24 years, and 34 million adults between ages 19 and 64 with chronic diseases. In addition, the CDC recommended that individuals ages 25 through 64 years only be vaccinated after these groups. Should there not be enough vaccine available for the priority populations, they have further prioritized the order of vaccine dispensing.

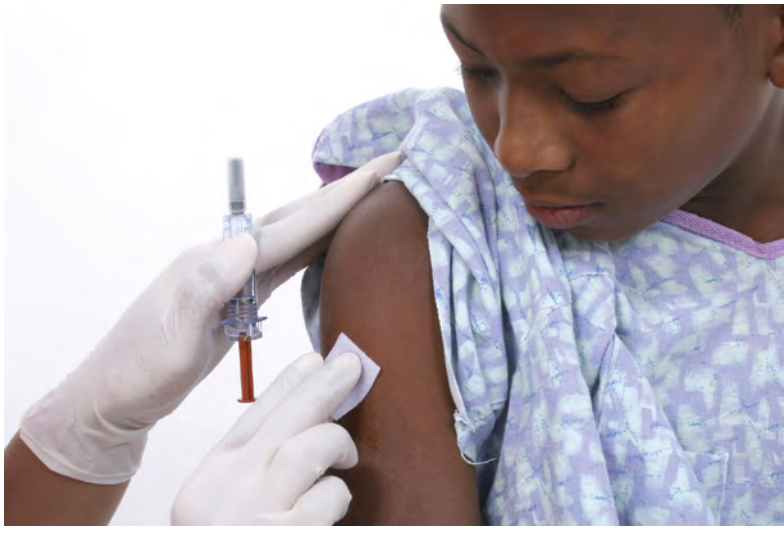
The plan is to ship the vaccine to "clinics, offices, health departments and other project area-designated sites which may include a mix of public health and private sector sites via centralized distribution" — the same process that is used to ship vaccines for the childhood immunization program to immunization providers.[3] According to the CDC, the "key benefits of using a centralized, third-party distributor to support H1N1 vaccine distribution is that it allows distribution of doses to a much larger number of provider sites than would be feasible with direct manufacturer distribution."

The amount of vaccine distributed to each project area will be in proportion to its population. And, in addition to the vaccine, the HHS will provide needles, syringes, Sharps containers and alcohol swabs.[3]

The CDC reported in August that approximately 159 million persons in the U.S. would be given priority.

The Healthcare Provider Role

The main role of healthcare providers is to not only encourage H1N1 vaccination, but to ensure that those who are getting vaccinated do so safely. All individuals need to be screened for contraindications (such as egg allergy), and all need to be provided with information sheets describing the vaccine's risks and benefits, signs and symptoms of adverse events to look for following vaccination, as well as how to report adverse events.[10]



Healthcare providers need to prepare for the worst and expect the best. Could the predictions for the spread of the H1N1 pandemic be worse? Yes. It could be as severe as the 1918 pandemic that killed 675,000 people in the U.S. and up to 50 million worldwide, said Homeland Security Secretary Janet Napolitano.[11] However, it's more likely that this pandemic will mirror 1957 when flu killed about 70,000 people in the U.S. and one to two million worldwide. ❖

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Verifying Pedigree:
Digital Solutions for Safety

Electronic drug pedigree systems can thwart counterfeiting efforts, promote patient safety and protect brand identity. And, they may hold the key to the future of supply chain security.

By Trudie Mitschang

Counterfeit products within the pharmaceutical supply chain pose a health threat to patients worldwide. According to an article published by the Center for Medicine in the Public Interest, worldwide counterfeit pharmaceutical sales are increasing at about 13 percent annually — nearly twice the pace of legitimate pharmaceuticals — and could become a $75 billion industry by 2010. That's an alarming 92 percent jump from 2005. Obviously, there is money to be made, and opportunistic criminals are cashing in.

"When I started in the biopharmaceutical business in 1988, it was readily apparent that there were some hazardous practices rampant in the industry," says Patrick M. Schmidt, chief executive officer, FFF Enterprises, Inc. Schmidt notes that on April 12 of that same year, the Prescription Drug and Marketing Act (PDMA) was signed into law to mandate that prescription drug products purchased by consumers would be safe and effective, and to prohibit the unacceptable risk of counterfeit, adulterated, misbranded, subpotent or expired drugs being sold to the American public. Unfortunately, more than 20 years later, the pharmaceutical industry still has not fully implemented the PDMA's pedigree requirement of recording a pharmaceutical product's path through the distribution supply chain.

While Congress and the FDA have taken actions to protect the marketplace and consumers from the inherent dangers of counterfeit medications, significant security gaps remain. One area of risk involves the product pedigrees themselves, which are intended to authenticate a drug's history. Unfortunately, as with the drugs themselves, paper pedigrees are often vulnerable to tampering; a recent case in New Jersey involved the fraudulent pedigrees and sale of $7.3 million worth of stolen AIDS treatment products. In this instance, having a pedigree was not enough. The fact is that if the pedigree can't be verified, it may be worth less than the paper on which it's printed. That is why the implementation of electronic pedigrees may be an idea that is truly overdue.

Embracing Digital Age Solutions

In recent years, the need for improved drug-tracking technology has taken on increased urgency, especially since authorities have begun ramping up drug pedigree enforcement activity. According to some reports, many states, including Florida and Nevada, have issued drug pedigree fines ranging from $18,000 to $1 million. In response, some distributors and manufacturers have invested hundreds of thousands of dollars in electronic pedigree systems and radio frequency identification technology (RFID). RFID uses attached tags containing silicon chips and antennas that send and receive data on a radio frequency from an RFID transceiver. In widespread use within the retail industry, RFID has yet to be fully embraced by the pharmaceutical industry. Critics note the technology is not without its problems. For one thing, the RFID tags make use of radio waves, which are susceptible to any outside force that interferes with the transmission of radio signals. Another common issue arises from inventory storage methods. When large numbers of products with RFID tags are stored together in the same scanning field, the reader can energize multiple tags at once, which sometimes causes them to transmit their signals simultaneously. This information overload interferes with the RFID reader's function and can prevent it from being scanned. In addition, there's the considerable infrastructure costs associated with deploying most RFID systems.

For many in the pharmaceutical industry, the absence of federally mandated pedigree regulations has created its own unique challenges. Some states have adopted their own pedigree requirements, making it difficult for manufacturers to comply. Several years ago, Florida made drug pedigrees mandatory, and currently, 31 states require manufacturers and distributors to document pedigree. With the exception of California, most exempt the original manufacturer of record, but they do require subsequent wholesale distributors to complete and pass pedigree in paper or electronic form. Other common exemptions include transactions that take place within the normal chain of distribution, meaning the transaction did not deviate from the customary drug shipment route.

In 2004, the California Board of Pharmacy (CBP) sponsored legislation that made comprehensive changes to the wholesale distribution system to protect against counterfeit drugs. The initiative requires an electronic pedigree on drugs, and states that retail pharmacies might not be able to receive drug shipments if the drugs did not carry electronic pedigrees from the manufacturers. The law was intended to go into effect Jan. 1, 2009, but the CBP moved the compliance deadline to 2015 after numerous pharmaceutical companies and industry associations requested more time to prepare. While that buys more time, clearly the clock is ticking.

"Historically, distributors have been resistant to implementation of electronic pedigrees, and many companies in the supply chain have been slow to respond to new proposed guidelines," says Chris Ground, senior vice president of national accounts, FFF Enterprises, Inc. "I think the need for this technology is becoming increasingly clear, and more companies and organizations are partnering together to see it implemented."

While Congress and the FDA have taken actions to protect the marketplace and consumers from the inherent dangers of counterfeit medications, significant security gaps remain.

Leading the Way in Supply Chain Safety

While some within the industry have been slow to get behind electronic pedigree technology, others have made it their mission to blaze new trails in supply chain safety. Ground notes that FFF launched its Verified Electronic Pedigree (VEP) system in 2004 — a first in the nation. Since its implementation, the company has worked diligently to assure that VEP continues to meet or exceed all pedigree legislation enacted throughout the United States. VEP allows customers to easily verify online

the pedigree of pharmaceuticals purchased from FFF within seconds of logging in.

"FFF has long been committed to ensuring a safe, secure drug supply for our customers," says Schmidt. "We believe our VEP system validates FFF's unique business model of purchasing only from the manufacturer and distributing only to the healthcare provider."

In recent years, the need for improved drug-tracking technology has taken on increased urgency, especially since authorities have begun ramping up drug pedigree enforcement activity.

Schmidt maintains this business model is the single most effective way to secure the pharmaceutical supply channel, without the need for expensive technology and hardware. "Limiting the number of transactions protects products — and patients — from the risks of secondary and gray market distributors, which is typically where counterfeiters enter the supply channel," he adds.

FFF's VEP system employs a sophisticated pharmaceutical pedigree security system, developed by FFF's partner SupplyScape Corp., that is as easy to use as the most popular search engines — and it does not increase cost to FFF customers. The system is hosted by Boston-based SupplyScape, which designed the VEP architecture to meet or exceed state and federal pedigree requirements.

"VEP allows our customers to document FFF's channel security and comply with the state and federal regulations," Schmidt explains. "I think this system also demonstrates that RFID, while a helpful technology for e-pedigree deployment, is not a necessary part of an in-compliance system. VEP demonstrates that we can provide regulatory-compliant pedigrees without RFID. The combination of our unique business model and the ability to verify its security with VEP provides a high-impact, affordable solution that protects healthcare providers from new burdens and additional costs."

Electronic Pedigree Benefits

While compliance is the primary motivation for implementing an electronic pedigree solution, many potential additional benefits can be derived from the use of electronic pedigrees. These include improved patient safety and protection of product-revenue streams from diversion and counterfeiting; better shelf-life management; greater inventory availability; streamlined business processes; and enhanced recall management.

Within the industry, there are undoubtedly many arguments for and against the implementation of drug pedigrees, but the need for an industry-wide response has been brewing for more than two decades. Consider the following:

- Congress passed the Prescription Drug Marketing Act (PDMA) with a drug pedigree requirement in 1987.
- While the FDA has been hesitant to implement the requirement due to the burden of manual record keeping, it has been encouraging adoption of electronic technology to enable pedigrees.
- Many states have already enacted laws requiring drug pedigrees, and more are likely to follow. California is set to require electronic pedigrees by 2015.
- Public confidence in the pharmaceutical industry has been undermined by the existence of dangerous counterfeit or adulterated drugs within the supply chain.

If the pharmaceutical industry can come together to see electronic pedigrees implemented, the means by which counterfeiters can introduce illegitimate products will eventually be eliminated. Additionally, by closing safety gaps in the drug distribution network, manufacturers can stem the loss of revenues, profits and brand reputations caused by counterfeits within the supply chain. ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

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When thrombotic risk is high in hereditary antithrombin deficiency

Proceed Safely

When it comes to treating patients with hereditary antithrombin deficiency, Thrombate III is the proven therapy to prevent thromboembolic events in high-risk situations, such as[1]:

- Surgery
- Obstetrical procedures (including childbirth)
- Acute thromboembolism

And the long-term safety experience with Thrombate III is unmatched[1,2]:

- More than 16 years of post-marketing experience[3]
- Pasteurized to inactivate viruses, with no confirmed case of virus transmission
- Purified to remove proinflammatory antibodies and cytokines

To order, call Talecris USA Customer Service at **1-800-243-4153** or visit **www.thrombate.com**.

For technical questions, call Talecris Clinical Communications at **1-800-520-2807** or visit **www.thrombate.com**.

Thrombate III—treating hereditary antithrombin deficiency for more than 16 years.

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Important Safety Information

Thrombate III is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism. In clinical studies with Thrombate III, the most common side effects were dizziness, chest tightness, nausea, and a foul taste in the mouth. The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III is made from human plasma. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease, cannot be totally eliminated. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C.

Please see brief summary of Thrombate III full Prescribing Information on adjacent page.

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)

Printed in USA May 2009 TH48-0509

THROMBATE III®
Antithrombin III (Human)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAVENOUS USE ONLY

DESCRIPTION
Antithrombin III (Human), THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III.

THROMBATE III is prepared from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn. When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pH of 6.0–7.5, a sodium content of 110–210 mEq/L, a chloride content of 110–210 mEq/L, an alanine content of 0.075–0.125 M, and a heparin content of not more than 0.004 unit/IU AT-III. THROMBATE III contains no preservative and must be administered by the intravenous route. In addition, THROMBATE III has been heat-treated in solution at 60°C ± 0.5°C for not less than 10 hours.

Each vial of THROMBATE III contains the labeled amount of antithrombin III in international units (IU) per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.

The manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

An individual production step in the THROMBATE III manufacturing process has been shown to decrease TSE infectivity of that experimental model agent. The TSE reduction step is the Effluent I to Effluent II + III fractionation step (6.0 logs). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL PHARMACOLOGY
Antithrombin III (AT-III), an alpha$_2$-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by AT-III occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on AT-III. AT-III is also capable of inactivating other components of the coagulation cascade including factors IXa, Xa, XIa, and XIIa, as well as plasmin.

The neutralization rate of serine proteases by AT-III proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect in vivo of heparin is mediated by AT-III, heparin is ineffective in the absence or near absence of AT-III.

The prevalence of the hereditary deficiency of AT-III is estimated to be one per 2000 to 5000 in the general population. The pattern of inheritance is autosomal dominant. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with AT-III levels of 40%–60% of normal. These episodes usually appear after the age of 20, the risk increasing with age and in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary antithrombin III (AT-III) deficiency during pregnancy has been reported to be 70%, and several studies of the beneficial use of Antithrombin III (Human) concentrates during pregnancy in women with hereditary deficiency have been reported. In many cases, however, no precipitating factor can be identified for venous thrombosis or pulmonary embolism. Greater than 85% of individuals with hereditary AT-III deficiency have had at least one thrombotic episode by the age of 50 years. In about 60% of patients thrombosis is recurrent. Clinical signs of pulmonary embolism occur in 40% of affected individuals. In some individuals, treatment with oral anticoagulants leads to an increase of the endogenous levels of AT-III, and treatment with oral anticoagulants may be effective in the prevention of thrombosis in such individuals.

In clinical studies of THROMBATE III conducted in 10 asymptomatic subjects with hereditary deficiency of AT-III, the mean in vivo recovery of AT-III was 1.6% per unit per kg administered based on immunologic AT-III assays, and 1.4% per unit per kg administered based on functional AT-III assays. The mean 50% disappearance time (the time to fall to 50% of the peak plasma level following an initial administration) was approximately 22 hours and the biologic half-life was 2.5 days based on immunologic assays and 3.8 days based on functional assays of AT-III. These values are similar to the half-life for radiolabeled Antithrombin III (Human) reported in the literature of 2.8–4.8 days.

In clinical studies of THROMBATE III, none of the 13 patients with hereditary AT-III deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with THROMBATE III for high thrombotic risk situations (11 surgical procedures, 5 deliveries) developed a thrombotic complication. Heparin was also administered in 3 of the 11 surgical procedures and all 5 deliveries. Eight patients with hereditary AT-III deficiency were treated therapeutically with THROMBATE III as well as heparin for major thrombotic or thromboembolic complications, with seven patients recovering. Treatment with THROMBATE III reversed heparin resistance in two patients with hereditary AT-III deficiency being treated for thrombosis or thromboembolism.

During clinical investigation of THROMBATE III, none of 12 subjects monitored for a median of 8 months (range 2–19 months) after receiving THROMBATE III, became antibody positive to human immunodeficiency virus (HIV-1). None of 14 subjects monitored for $\geq$ 3 months demonstrated any evidence of hepatitis, either non-A, non-B hepatitis or hepatitis B.

INDICATIONS AND USAGE
THROMBATE III is indicated for the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

Subjects with AT-III deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

AT-III in plasma may be measured by amidolytic assays using synthetic chromogenic substrates, by clotting assays, or by immunoassays. The latter does not detect all hereditary AT-III deficiencies.

The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

CONTRAINDICATIONS
None known.

WARNINGS
THROMBATE III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

PRECAUTIONS
General
1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. THROMBATE III, once reconstituted, should be given alone, without mixing with other agents or diluting solutions.
4. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted THROMBATE III product in accordance with biohazard procedures.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

Laboratory Tests
It is recommended that AT-III plasma levels be monitored during the treatment period. Functional levels of AT-III in plasma may be measured by amidolytic assays using chromogenic substrates or by clotting assays.

Drug Interactions
The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to THROMBATE III. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established. The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

ADVERSE REACTIONS
In clinical studies involving THROMBATE III, adverse reactions were reported in association with 17 of the 340 infusions during the clinical studies. Included were dizziness (7), chest tightness (3), nausea (3), foul taste in mouth (3), chills (2), cramps (2), shortness of breath (1), chest pain (1), film over eye (1), light-headedness (1), bowel fullness (1), hives (1), fever (1), and oozing and hematoma formation (1). If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

CAUTION
℞ only

U.S. federal law prohibits dispensing without prescription.

Talecris BIOTHERAPEUTICS

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Research Triangle Park, NC 27709 USA
U.S. License No. 1716

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Myths vs. Facts

A Look at Seasonal and H1N1 Flu Facts

This year's flu season is shaping up to be one of the most challenging in history, with the new H1N1 (swine) strain adding to the questions and myths that already surround seasonal flu. Here are the facts.

By Ronale Tucker Rhodes, MS

In April, the 2009-10 flu season changed dramatically with the first reports of a novel strain that was proving virulent in Mexico. That we are now in the midst of a pandemic has created more questions than answers and has added a new layer of myths that healthcare providers have already been faced with addressing for their patients regarding seasonal flu vaccine. The media attention has had the positive effect of educating the public about the seriousness of the seasonal flu, however despite the ramp up in communication, the general public is still uncertain about the seriousness of this double threat.

The same misconceptions surrounding the seasonal flu also appear to be taking hold with the new H1N1 flu, for which vacccine should soon be available. Not only do many people think the seasonal flu is not that serious, but they also believe that reports about how serious and widespread the H1N1 flu will become are overblown. What's worse, many are afraid of the new H1N1 vaccine, and according to early estimates, have no intention of becoming vaccinated. If these early indications prove true, more people will become infected with the flu — seasonal, H1N1 or both — this year because they are unprotected. And, each preventable case will result in numerous others due to the highly contagious nature of the disease. That's why it's more important than ever to communicate the true facts about seasonal and pandemic H1N1 influenza and the vaccines that can help to prevent them.

Seasonal Flu

Myth: The seasonal flu isn't that serious.

Fact: The seasonal flu is highly contagious. Each year, more than 200,000 individuals are hospitalized and approximately 36,000 die from flu-related complications.[1] The flu can disrupt your work, school and social life for up to two weeks, with symptoms that include fever, headaches, cough, sore throat, nasal congestion, extreme tiredness and body aches.[2] And, because it can easily be passed from a low-risk individual to a high-risk individual, it can lead to serious complications, including pneumonia and worsening of chronic conditions.[3]

Myth: The seasonal flu vaccine doesn't protect against getting the flu.

Fact: The seasonal influenza vaccine prevents the disease in approximately 70 to 90 percent of healthy people under age 65. The reason the vaccine doesn't prevent some individuals

from being infected with the flu is due to several variables. First, the vaccine's effectiveness will vary due to a person's age and health status. In addition, the effectiveness will depend upon the match between virus strains in the vaccine and virus strains in circulation.[4] The virus strains in the vaccine are determined through extensive monitoring conducted throughout the year to determine which are the most prevalent to circulate among the population. While the vaccine protects against these most common strains, it is possible for individuals to contract a different strain of the flu that is not included in the vaccine.

Myth: In some years, the seasonal vaccine isn't effective even against the major strains.

Fact: A decreased effectiveness level of the flu vaccine in a given year (notably, the 2007-2008 year) is a phenomenon that happens only every 15 to 20 years, when the best guess of serotypes ends up being incorrect because of a genetic shift of the viruses. Even if a vaccine is not as effective in a particular year, in most cases, it still can provide cross-protection benefits. For instance, in 2007, the vaccine's overall effectiveness was a good match; it was 58 percent effective against circulating influenza A viruses.[5]

Myth: The seasonal flu vaccine will give me the flu.

Fact: A flu vaccine will not cause the flu. Because the viruses in the flu shot are killed (inactivated), it is biologically unable to cause illness.[1] However, it is possible for some side effects to occur soon after the shot, usually lasting one to two days. These include soreness, redness or swelling where the shot was given, a low-grade fever and aches.

Myth: People don't need a seasonal flu shot every year.

Fact: Influenza strains change each year. If you had an influenza vaccine last year, your body built up antibodies to those strains to protect you against infection. And while those antibodies provide a natural immunity to the strains they were developed to protect against, they will not protect you from each year's new circulating strains.[6]

Myth: Failing to get a flu shot is a personal choice that doesn't affect anyone else.

Fact: Getting the flu means also becoming a carrier. Flu symptoms don't start until one to four days after the virus enters the body, so even the most conscientious individuals may unknowingly spread the virus.[7] Everyone, then, has a responsibility for doing what they can to halt the spread of the influenza virus, especially those who come into contact with young children and individuals with compromised immune systems.

Myth: The seasonal flu vaccine is necessary only for the old and very young.

Fact: The flu vaccine is for everyone who is over 6 months old, especially those who don't want to be sick with the flu or inadvertently spread the virus to others if they become infected. The Centers for Disease Control and Prevention recommend certain groups of people be vaccinated each year:[1]

- Children ages 6 months up to their 19th birthday
- Pregnant women
- People 50 years of age and older
- People of any age with certain chronic medical conditions
- People who live in nursing homes and other long-term care facilities
- People who live with or care for those at high risk for complications from flu, including healthcare workers; household contacts of persons at high risk for complications from the flu; and household contacts and out-of-home caregivers of children younger than 6 months of age (these children are too young to be vaccinated).

Myth: It's too late in the season.

Fact: October and November are the recommended months for vaccination. However, getting a flu shot later in the season, from December through March, can still protect individuals. Flu season begins in the fall, but it usually peaks after January 1st.[1]

Pandemic H1N1 (Swine) Flu

Myth: The H1N1 flu isn't much different from the seasonal flu.

Fact: The H1N1 flu is both a completely different strain of flu from the seasonal flu and it is pandemic. The H1N1 strain is a new, mutated strain of an influenza A virus subtype H1N1 (a virus type that causes the yearly seasonal flu), and is referred to as the "novel H1N1." Commonly called the "swine flu," it is thought to be a reassortment of four known strains of influenza A virus: one endemic in (normally infecting) humans, one endemic in birds, and two endemic in pigs (swine).[8] The World Health Organization declared the H1N1 flu a pandemic in May because it is a new, mutated strain for which there is no built-up immunity. In addition, the H1N1 flu spread globally, and until this month, there was no vaccine to prevent it.

Like seasonal flu, symptoms include fever, cough, sore throat, nasal congestion, headache, chills and fatigue. However, additional symptoms in H1N1 flu include vomiting and diarrhea. Conjunctivitis is rare, but has been reported.

Myth: The H1N1 flu isn't that serious.

Fact: Just like the seasonal flu, the H1N1 flu is very serious. Since the first reported case of H1N1, almost 2,000 deaths have occurred worldwide. Based on the effects of H1N1 in the Southern Hemisphere, the estimates of how widespread this flu will become have increased substantially. It is now thought that the H1N1 flu could infect half the U.S. population this fall and winter, hospitalize up to 1.8 million people and cause as many as 90,000 deaths.[9] (See the H1N1 Swine Flu Update on page 44.)

Considering past pandemics, there is definitely a need for concern. There have been three previous pandemics: the 1918 pandemic, known as the Spanish flu, which killed approximately 50,000 people; the 1957 pandemic, known as the Asian flu, which

killed two million individuals worldwide; and the 1968 Hong Kong flu pandemic, which killed one million people globally. In August, Homeland Security Secretary Janet Napolitano said that, while the H1N1 pandemic would not likely be the world's worst, it would likely mirror the 1957 pandemic, which killed 70,000 people in the U.S.[10]

Myth: There is no way to prevent the H1N1 flu.

Fact: Like seasonal influenze, H1N1 is a vaccine-preventable disease. Vaccine manufacturers have spent months developing a vaccine that, through clinical testing, has shown to be effective in preventing the H1N1 flu. The vaccine, scheduled to be available to the public beginning in mid-October, has recently shown to be effective with a single dose, just like the seasonal flu vaccine.

Myth: An H1N1 flu vaccine isn't needed if an antiviral drug is taken.

Fact: Antiviral drugs are not intended to be used to prevent the flu; they are a treatment once someone has been exposed to the virus. The first line of defense against any flu is vaccination. A flu vaccine exposes the body to inactivated (killed) strains of the flu virus, which helps the body to build up immunity to the flu.

Antiviral drugs, on the other hand, are a class of medication used specifically to treat viral infections.[11] Antiviral drugs do not destroy their target pathogen (in this case, the H1N1 virus) as the vaccine does, but rather inhibits its development. Individuals who have been infected with the H1N1 flu should use antiviral drugs to help minimize the effects of the flu; they can make symptoms milder and may prevent serious flu complications. In addition, individuals who have been exposed to the H1N1 virus should consider taking an antiviral as a pre-symptom measure of treatment.

Myth: The seasonal flu vaccine will protect me against the H1N1 flu.

Fact: The H1N1 flu is a new strain of influenza, and it will require a separate vaccine in addition to the seasonal flu vaccine. Each year, the seasonal flu strains mutate to create new strains. This means individuals have to be revaccinated each year with the new seasonal flu vaccine to help protect them from infection against the mutated strains. However, the H1N1 flu virus strains causing the current outbreak are novel and are not the mutated strains found in seasonal flu. In fact, the H1N1 flu strains are very different from human H1N1 viruses found in seasonal flu; therefore, vaccines for this past human seasonal flu provide no protection from these H1N1 flu viruses.[12]

Myth: The H1N1 flu vaccine will make me sick.

Fact: The injectable vaccines that have been created to help prevent the H1N1 flu are inactivated, meaning they are killed. Inactivated vaccines are different from live vaccines that are made from live viruses or bacteria that have been weakened. Live vaccines have a slight possibility of causing the disease itself. Inactivated vaccines, on the other hand, are made from viruses or bacteria that have been killed, and therefore, cannot cause the disease that it is given to prevent.[13] As such, the injectable H1N1 flu vaccine cannot make individuals sick.

Myth: The H1N1 flu vaccine isn't safe because it hasn't gone through long-term clinical trials.

Fact: Clinical trials by manufacturers of the H1N1 vaccine began in mid-August and are still ongoing. These trials are being conducted at multiple sites throughout the U.S. and worldwide, and are using the same study methodologies as all other clinical drug trials. To date, thousands of individuals, both adults and children, have been inoculated with the H1N1 vaccine, and all trials have produced positive results to protect against he H1N1 strain with no adverse effects.

Myth: Only older adults and children are most in need of the H1N1 flu shot.

Fact: Nearly everyone needs to be vaccinated with the H1N1 vaccine. While children and older adults have been most at risk from serious complications from seasonal flu, this is not the case for H1N1 flu. The Centers for Disease Control and Prevention has tracked individual cases and has found that individuals ages 5 through 24 are those at highest risk from H1N1 flu, followed by children ages 0 to 4. Also at high risk are pregnant women and those with chronic diseases.[14] However, even if individuals don't fall within a high-risk category, they are still potential carriers of H1N1 flu, and should they become infected, they risk infecting those with whom they come in contact. ❖

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RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

Home of the

In planning for the flu season ahead, experience matters:

CSL BIOTHERAPIES: AN UNWAVERING COMMITMENT TO INFLUENZA PREVENTION

CSL Biotherapies of Melbourne, Australia, with U.S. headquarters in King of Prussia, Pennsylvania, marked over 40 years of experience in the influenza vaccine market. During those years, the prominence of CSL Biotherapies in the marketplace has grown dramatically. **Our company now operates one of the world's largest influenza vaccine production centers for global markets, licensing and marketing flu vaccines in 27 countries.**

This heritage underpins our strong commitment to the safety, quality and reliability that are so critical to customers of influenza vaccines worldwide. **In 2002, this commitment was reflected in the total removal of the mercury-derived preservative thimerosal from the flu vaccine manufacturing process. In addition, latex is no longer used in vaccine containers.**

CSL Biotherapies' recognized scientific expertise in the early prediction of influenza strain changes allows rapid improvement of vaccine production to ensure prompt delivery to market. Since flu season comes to the Southern Hemisphere months before hitting the Northern Hemisphere, we annually bring prior experience to bear in providing many of the antigens found in the Northern Hemisphere presentation of our influenza virus vaccine. In Summer 2009, CSL Biotherapies will further accelerate access to U.S. vaccine customers by opening a syringe fast-filling line in its state-of-the-art facility in Kankakee, Illinois.

We are extremely proud of our standing as a reliable supplier of influenza vaccine to the United States and other countries throughout the Northern Hemisphere. **However, at CSL Biotherapies, we understand that our commitment to flu prevention does not stop at delivering quality vaccines.** We also offer patient advocacy and educational support to help spread the word about and underscore the importance of influenza vaccination. Our team is very passionate about its role in providing this service.

Much remains to be done to improve vaccine access, increase vaccination awareness, counter misinformation about flu vaccines, and further prevent the spread of influenza with the weapons we have at hand.

Flu Fighters

Our support to the National Foundation for Infectious Diseases (NFID) produced a **Best Practices Report, "Immunizing Healthcare Personnel Against Influenza,"** which has become an invaluable reference for healthcare organizations.

Likewise, we developed **"Season Pass," a program designed to help colleges/universities find ways to improve flu immunization rates on campus.** Such efforts are beginning to bear fruit. In the 2008-2009 flu season, for example, a 70% increase in immunizations over the previous year was seen at Arizona State University*. This level of increase indicates that providing information related to the benefits of influenza vaccination, and providing convenient access to vaccines services is a strong recipe for reinforcing a wellness attitude among students and improving vaccination rates on campus.

More recently , **"Flu-Free and a Mom-to-Be,"** a consumer campaign developed by the National Women's Health Resource Center (NWHRC) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) through an educational grant provided by CSL Biotherapies, has been selected by the National Influenza Vaccine Summit to receive the 2009 Immunization Excellence Award for Best Corporate Campaign. This prestigious award recognizes individuals and organizations that have made extraordinary contributions toward improving influenza vaccination rates in their communities. **This campaign is the first of its kind to help emphasize the importance of immunizing pregnant women.**

The CSL Biotherapies team will continue to focus on the timely delivery of high-quality flu vaccines and relevant educational programs to create a positive vaccination experience for consumers and healthcare providers. Through such efforts, we are convinced that we can help stem the spread of influenza throughout the world, preserving health and saving lives.

To learn more about CSL Biotherapies and our seasonal influenza vaccine activities in the United States, please visit us online at www.cslbiotherapies-us.com.

*Markus A. L., Director of Health Services, Arizona State University, Tempe, Arizona. Influenza Vaccination: Challenges for Adolescent and College Healthcare. *Medscape Infectious Diseases* – Posted 01/15/2008.

CSL BIOTHERAPIES 1968-2008 40 years In Influenza Vaccines Production

CSL Biotherapies

Committed to Saving Lives

by TRUDIE MITSCHANG

WHEN YOU THINK about characteristics that define outstanding leadership, the ability to inspire others is certainly near the top of the list. As the president of CSL Behring, Peter Turner is both an inspired and inspirational leader, equally comfortable in his roles as corporate visionary and roll-up-your-sleeves team builder. For Turner, leadership boils down to setting clear objectives and putting resources in place to see those objectives achieved.

"It's important to help people see the significance of your plan and to encourage them to achieve more than they thought was possible," Turner says. "An old philosophy involved getting people to work on their weaknesses to improve performance. I believe it's better to build on the strengths of each individual and then bring everyone together as a well-oiled team. That's good leadership."

A well-respected name in the biopharmaceuticals industry, Turner played an instrumental role in CSL's successful 2004 acquisition of Aventis Behring, and has served as president of the company ever since. Under his leadership, the firm has introduced two major new global products and brought a number of existing products into new markets. An industry veteran, Turner's career spans an impressive 40-plus years, including more than 20 years of plasma fractionation research and development, production, engineering and business expertise. As one might expect, Turner has garnered his fair share of professional awards over the years. Last year, he was honored with the Robert W. Reilly Leadership Award at the 2008 Plasma Protein Forum in Washington, D.C., a recognition he says carried particular significance.

"This award meant a lot to me because it came from industry peers," explains Turner. "It's always nice to be acknowledged for your efforts, but I also feel the most rewarding feedback comes from the patients we serve. When someone says, 'I was really ill and your products improved my quality of life,' — that's what matters."

Today, Turner oversees a worldwide operation with more than 9,000 employees where his reputation as a smart, intuitive and compassionate individual has earned him the admiration of employees throughout the organization.

"Working with Peter Turner, I am struck by his genuine nature and his forthright leadership style," remarks Adam Tyler, senior director, national accounts and coagulation sales. "Peter operates beyond pretense and politics by formulating objectives, setting the course and holding the organization — and himself — accountable for outcomes and results. Peter's commitment to excellence stems from a genuine passion for patients. Where other organizations often shy away from producing products for small patient populations, Peter embraces the challenge because he knows CSL Behring can make a tangible difference in the lives of individuals with rare and serious diseases."

Passion for Exceptional Patient Care

When it comes to success in any industry, innovation plays an instrumental role both behind the scenes and in the marketplace. A company's ability to respond to consumer trends, supply shortages and market fluctuations, while also positioning itself on the forefront of product development, is directly linked to its longevity. For CSL Behring, an organization that has evolved from a fairly small operation in Australia to become a recognized global leader in plasma therapies, the road to success has been paved with a corporate philosophy that is characterized by a passion for exceptional patient care. The company's accomplishments include developing the world's first pasteurized plasma protein solution; marketing the world's

first pasteurized factor VIII; and being the first company to offer nanofiltered intravenous immune globulin (IVIG). Today, innovation remains an active force at CSL Behring, and is, in fact, one of its core values.

"Innovation plays into all aspects of what we do," says Turner. "I think it's always important to look at how a job is being done and envision ways of doing it better. In an industry like ours, opportunities for improvement require an investment in new processes, new products and infrastructure, and the thinking leader recognizes when it's appropriate to make investments to drive performance."

Turner points out that innovation of plasma protein therapies is ultimately about improving the medical benefits of the products themselves for the benefit of CSL's customers. CSL, he notes, is often referred to internally as an acronym for "Committed to Saving Lives."

"At CSL, we are in the business of researching, developing, manufacturing and marketing products that save lives and improve the quality of life for people with rare and serious medical conditions," notes Turner. "It's very rewarding to be part of an industry that helps people lead better lives."

With Turner at the helm, it's easy to see why CSL Behring is a company known for improving the quality of life for patients with rare and serious diseases worldwide. This commitment is reflected in the company's support of patient-based programs and activities and its ongoing partnerships with patient advocacy organizations. Turner's passion for patient care is tangible; it's also a key reason CSL Behring is firmly positioned on the leading edge of the plasma protein biotherapeutics industry.

Peter Turner is both an inspired and inspirational leader, equally comfortable in his roles as corporate visionary and roll-up-your-sleeves team builder.

A Lifelong Pursuit of Excellence

One attribute many leaders have in common is a lifelong pursuit of learning and a desire to explore new avenues of personal growth. Turner is no exception; he cites his diverse background in manufacturing, research and engineering with giving him a solid platform for career success.

"If I had stayed in my functional role based on my educational background, I would not have had the ability to learn about the business as a whole, the industry sector, and how healthcare works in different countries," says Turner. "This has been a tremendous opportunity for me — I'm still inspired by what CSL does and the benefits we bring to people." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

Influenza: Nothing to Sneeze At

For many, seasonal flu signifies aches, pains and fever, plus a few missed days at work or school. But for approximately 36,000 Americans each year, influenza is a serious, fatal, yet preventable disease that claims victims of all ages.

by TRUDIE MITSCHANG

"I'm healthy; I don't need a flu shot." "The flu shot gives you the flu." "I'll take my chances — the flu isn't that big of a deal." Many excuses keep people from being immunized against seasonal flu. None is valid. And despite evidence to the contrary, many people still consider the flu more of a nuisance than a life-threatening virus. The reality is, complications related to seasonal flu kill nearly 40,000 people annually and hospitalize even more. In this issue, we feature three patients with influenza to emphasize the need for annual flu vaccines for children, teens and adults.

From Slight Fever to Sudden Fatality

In early December 2003, 15-month-old Breanne Palmer's parents tried to get her vaccinated against the flu, but because she had been diagnosed with an ear infection, her pediatrician would not vaccinate her.

During the evening of Dec. 20, Breanne developed a slight fever and began to show flu symptoms. The next morning, Breanne's fever rose to 101.5 degrees Fahrenheit. Her parents took her to the pediatrician, where the influenza diagnosis was made. Breanne was given antibiotics and sent home. When Breanne went to bed that night, her temperature was almost normal. However, as the night wore on, her temperature climbed again very rapidly, reaching 105.5 degrees. When she began to have difficulty breathing, Breanne's parents called 911.

At the hospital, Breanne's temperature rose to 107 degrees. Her temperature was lowered by doctors in the emergency room, but Breanne had to be transferred to another hospital for more intensive care. A special life-support machine was needed as the virus began to attack Breanne's heart and brain stem. However, after being transferred to yet another hospital, doctors told Breanne's parents that the damage to her young body was so extensive there was nothing the life-support machine could do. Breanne died in her mother's arms on Dec. 23, 2003, from influenza A.

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Complications Take the Life of a Healthy, Active Teen

Diane and Michael McGowan's healthy 15-year-old son, Martin, died from complications as a result of the flu in 2005. "One flu shot could have saved his life," says Diane. "As his mother, I wish that he had been vaccinated."

The day before Martin died, Diane noticed he looked a little under the weather. Martin insisted that he felt fine and that he could not miss baseball tryouts that day. After tryouts, Martin was exhausted and complained that his legs hurt from running.

Around 2:30 a.m., Martin was vomiting, had a fever of 102 degrees Fahrenheit, and was experiencing increasing pain in his legs. A short time later, a decision was made to take Martin to the emergency room. Initial testing showed Martin was infected with the flu. He also was diagnosed with compartment syndrome — a serious condition that limits blood circulation to muscles and causes severe pain. Participation in the baseball tryouts while infected with the flu likely caused the compartment syndrome in his legs. To treat the compartment syndrome, Martin was taken to surgery that afternoon. During surgery, his heart stopped and he could not be revived. Martin died just 24 hours after his first symptom of the flu appeared.

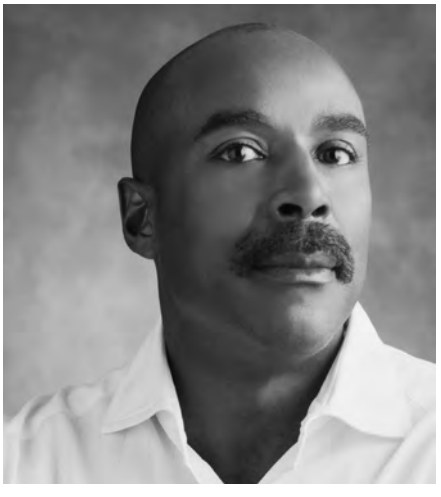
Professional Football Player Tackled by Flu

At age 32, five-time pro bowler and former Philadelphia Eagles wide receiver Mike Quick was tackled by the flu. The virus hit him so hard that he was hospitalized for three days.

"It can knock you down harder than any tackle," Mike says. "Even though I was devoted to maintaining my fitness and health, influenza hit me one New Year's Eve and by New Year's Day, I was hospitalized and on IVs. I vowed I would do all I can to prevent that from threatening my health again by getting immunized."

Mike also has his family to be concerned about. His son, Ronson, and his mother both suffer from heart disease — a condition that puts them at high risk for developing complications from the flu and are therefore recommended for annual immunization. To protect themselves, both his son and mother are vaccinated annually, as well as Mike's sister, who is a caregiver.

Quick has demonstrated time and again that he is willing to take risks to win. But he knows where to draw the line. "Don't take a chance with your health this influenza season," he says. "I didn't realize the seriousness of the flu until I was hospitalized from it, but now I encourage everyone to get immunized."



Making Vaccination a Priority

The Centers for Disease Control and Prevention (CDC) recommends annual influenza vaccination for people with a high risk of developing complications from the influenza virus, such as seniors and people with chronic medical conditions, including heart disease and diabetes. Additionally, the vaccine is recommended for those who are likely to spread the virus to people at risk. Today, CDC guidelines have expanded to also include children of all ages.

"My wife and I lost our healthy, beautiful daughter, Amanda, to the flu when she was just 4½ years old. At that time, she did not fall within the CDC's influenza vaccination recommendations," says Richard Kanowitz, president of Families Fighting Flu. "Now all kids six months through 18 years are recommended to get vaccinated against the flu every year. What happened to my daughter can happen to any child. It's our responsibility as parents to protect our children."

Kanowitz goes on to emphasize that the responsibility does not just rest with the general public; healthcare providers need to set an example by being vaccinated annually, and take advantage of all opportunities to spread the message about influenza vaccination.

"Providers that don't conduct clinics need to make flu vaccination a top priority by discussing it with all parents as they bring their children in for visits throughout the season and urging them to get themselves and their kids vaccinated each and every year," Kanowitz says. ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

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More Plasma Products: Better Prices

BY KEITH BERMAN, MPH, MBA

THIRTY-FIVE YEARS ago, a first-class postage stamp cost 10 cents. A movie ticket was less than $2. The average new car cost about $4,500. And the price of a bottle of 5% or 25% human serum albumin offered by a leading U.S. supplier was around $40.[1]

Decades of price inflation have pushed up that first-class stamp to 44 cents. A movie ticket today easily tops $7. An average new car will now set you back nearly $28,000. And the price of a unit of albumin today? It's still well under $50 on most hospital group purchasing contracts — for the very same 5% (250 ml) and 25% (50 ml) albumin products that cost about $40 in 1974.

Had the price of albumin tracked with the Producer Price Index since the mid-1970s, we would expect to pay well over $120 per bottle today.[2] But — notwithstanding a few painful spikes during past supply shortages — average prices for albumin have soldiered on in the same low range, seemingly oblivious to decades of price inflation.

The Shrinking Albumin Price Mystery

How can we explain what amounts to a healthy drop in real albumin prices over all these years? Have manufacturers somehow found some way to produce it more cheaply? On the contrary, costs of donor plasma procurement, testing and downstream purification have increased over the years.

The answer to this mystery lies in what makes production of human plasma products so unique and different from conventional drug manufacturing. And, it all starts with plasma. Through many purification steps that branch into different paths, this costly and precious raw material is "fractionated" into the various therapeutic proteins we know. Depending on the product and the length of its purification path, the manufacturing process can take as long as six to eight months. But back in 1974, few individual products were extracted from each liter of donor plasma. In fact, there was just a small handful of them: albumin and its close relative PPF[3], intramuscular immune globulin (IMIG) and several clotting factors used mainly to treat hemophilia patients.

The cost of that plasma and those months of processing consume about 70 percent of all industry expenses. By contrast, conventional drug companies spend less than 20 percent of their annual budgets on chemicals and manufacturing; the rest is marketing and sales, research and development and other non-manufacturing costs.[4]

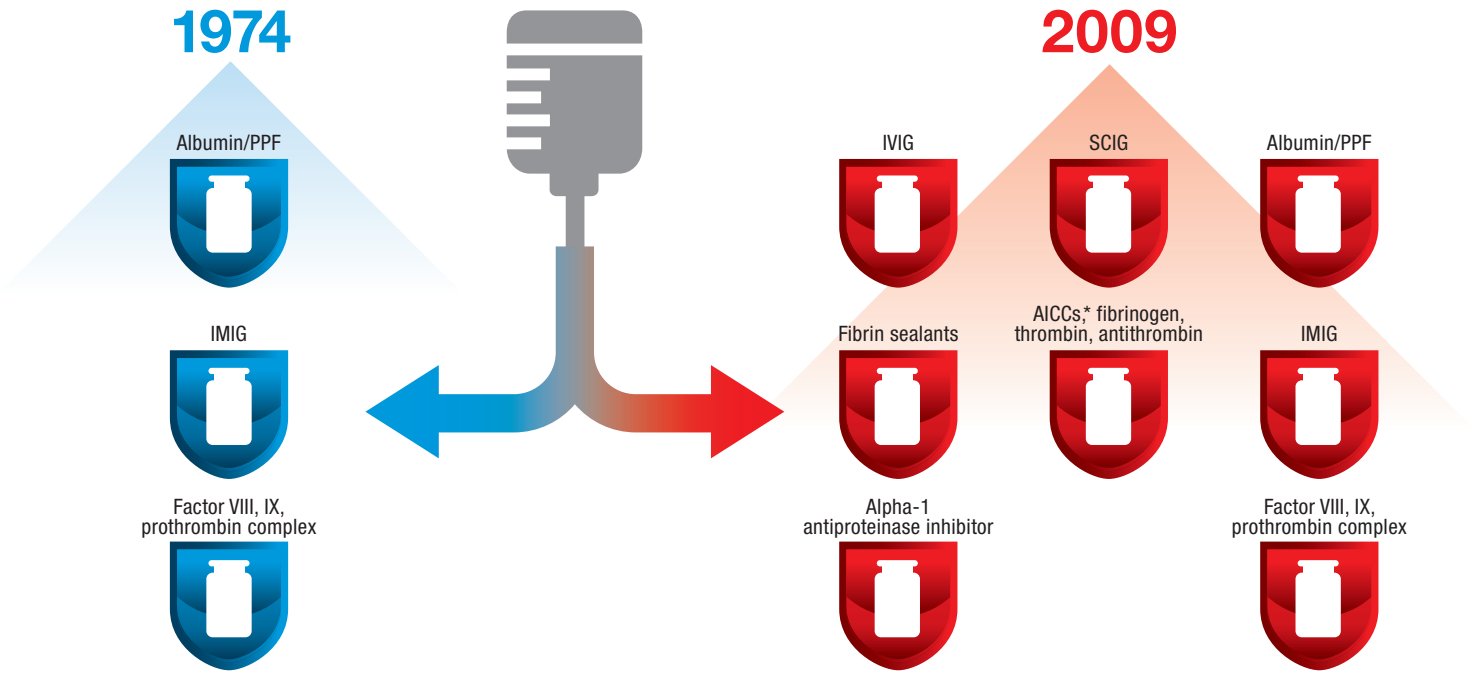
With just a few other products purified from each liter of plasma, each bottle of albumin in 1974 had to "carry" a big portion of that hefty plasma and shared manufacturing cost.

Had the price of albumin tracked with the Producer Price Index since the mid-1970s, we would expect to pay well over $120 per bottle today.

New Products Soak Up Costs

Since the mid-1970s, a wave of new products has arrived, all purified from that same liter of plasma (See Figure 1).

Figure 1. Products Extracted from Donor Plasma



* Anti-inhibitor coagulation complex concentrates

The active proteins in intravenous immunoglobulin (IVIG), alpha-1 antiproteinase inhibitor, fibrin sealant, thrombin, antithrombin and subcutaneous immune globulin products now purchased and administered thousands of times each day once were discarded as "waste." The latest product — human fibrinogen concentrate — was just launched this year.

More widely used products, like albumin and IVIG, clearly absorb a larger chunk of the plasma cost burden, while others that meet the needs of smaller patient populations account for less. But each does its part to soak up that big fixed cost.

A Special Innovation Bonus

Other potentially therapeutic proteins in human plasma await discovery. And, important new clinical uses for existing products will be found. When the next breakthrough comes along, you'll now know that it also comes with a bonus: sales that will help keep down prices of other plasma products you purchase for years to come. ❖

References

1. The Marketing Research Bureau, Inc., Orange, Conn.
2. Producer Price Index: Finished Goods. U.S. Department of Labor. Bureau of Labor Statistics.
3. Plasma protein fraction, human, 5%
4. The Source (Summer 2007), 18-19. Plasma Protein Therapeutics Association. Accessible at http://www.pptaglobal.org/UserFiles/File/TheSource_Summer2007_Full.pdf.

KEITH BERMAN *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Berman previously worked in product development, reimbursement development and market research roles at Baxter Healthcare, Siemens Medical and MiniMed Technologies (now a Medtronic division). Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

BioProducts

Next Generation FlexPen

The new FlexPen features 30 percent lower dose force than the conventional FlexPen, making the injection process more convenient for diabetics who inject insulin on a regular basis. Color-coded labels, packaging and cartridge holders aid identification of correct insulin. And, the new NovoTwist needle makes it easier to attach the needle to the pen.
Novo Nordisk, (+45) 4444-8888, www.novonordisk.com

Crono S-PID 50 Pump

The new Crono S-PID 50 is the newest high-volume ambulatory infusion pump intended for the controlled subcutaneous administration of prescribed medications to the patient. It is used with a dedicated 50 mL syringe, is small in dimension and light-weight in design, which makes it ideal for home therapy.
IntraPump, (866) 211-7867, www.intrapump.com/crono_s_pid_50.html

Zyrtec Perfect Measure

The new Children's Zyrtec Perfect Measure is for children ages 6 and older and adults, and is dispensed directly into the mouth using a prefilled spoon. One prefilled spoon contains 5 mL of Zyrtec.
Zyrtec, (866) 948-6883, www.zyrtecprofessional.com/products-dosing.html

KL30 Cassette Dispenser

The new KL30 all-in-one counting and verification dispensing system utilizes drug-specific cassettes to automate the hands-free dispensing of a pharmacy's top oral solid medications. The 30 cassettes manage 25 to 35 percent of orders in a typical pharmacy. The system incorporates one- or two-way interfacing with pharmacy management systems and includes all-new software, a large touch-screen and user-friendly directions.
KirbyLester, (800) 641-3961, www.kirbylester.com/products_KL30.htm

Vacuette Safety Needle System

The Vacuette Premium Safety Needle System is a blood collection device formatted in both tube-touch and skin-touch models. The phlebotomist cannot draw a patient's blood without having engaged the safety system, and the needle is encapsulated once pulled out of the patient after blood collection. Features include an integrated, multiple-sample needle and safety shield, and product gauges in 20G, 21G and 22G.
MedPro, (859) 225-5375, www.medprosafety.com/products.html

Sharps By Mail System

The new 18-gallon Medical Professional Sharps Disposal By Mail System can be used to collect all medical waste in a facility, including red bag (biohazard) waste and existing Sharps containers. The product is permitted by the United States Postal Service for transport to Sharps' medical waste disposal facility. The product was developed based on feedback from the medical community as a comprehensive solution to reduce the cost of medical waste disposal outside of the hospital setting.
Sharps, (800) 772-5657, www.sharpsinc.com/18gallon_sdbm.htm

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BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Reimbursement Rates: Hospital Outpatient ASP+4% (per gram)	Reimbursement Rates: Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$59.662	$60.809
FLEBOGAMMA 5% DIF	Grifols	J1572	$73.017	$74.422
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.706	$77.162
GAMMAGARD S/D	Baxter	J1566	$59.662	$60.809
GAMUNEX	Talecris Biotherapeutics	J1561	$73.416	$74.828
OCTAGAM	Octapharma	J1568	$74.067	$75.491
PRIVIGEN	CSL Behring	J1459	$68.780	$70.103

See the related article on IVIG reimbursement in this issue on page 28.

Rates are effective October 1, 2009 through December 31, 2009.

REFERENCE TABLES

IG Reference Table

Product	Size	Manufacturer	Indications
CARIMUNE NF (Lyophilized)	3 g, 6 g, 12 g	CSL Behring	PIDD, ITP
FLEBOGAMMA 5% DIF (Liquid)	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	PIDD
GAMMAGARD LIQUID (10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Baxter BioScience	PIDD
GAMMAGARD S/D (Lyophilized, 5% or 10%)	2.5 g, 5 g, 10 g	Baxter BioScience	PIDD, ITP, CLL, KD
GAMUNEX (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris Biotherapeutics	PIDD, ITP, CIDP
OCTAGAM (Liquid, 5%)	1 g, 2.5 g, 5 g, 10 g, 25 g	Octopharma	PIDD
PRIVIGEN (Liquid, 10%)	5 g, 10 g, 20 g	CSL Behring	PIDD, ITP
VIVAGLOBIN (Liquid, 16%)	3 mL, 10 mL, 20 mL	CSL Behring	PIDD

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Idiopathic thrombocytopenic purpura
KD Kawasaki disease
PIDD Primary immune deficiency disease

Influenza Vaccine Reference Table

Administration Code: G0008 Diagnosis Code: V04.81

Product	Size	Indicated Age Group	CPT Code
FLUZONE Pediatric	0.25 mL prefilled syringe	6–35 months	90655
AFLURIA	0.5 mL prefilled syringe	18 years and older	90656
FLUZONE	0.5 mL 10 single-dose vial 0.5 mL prefilled syringe	36 months and older	
FLUZONE+	5 mL multi-dose vial	6–35 months	90657
AFLURIA	5 mL multi-dose vial	18 years and older	90658
FLUVIRIN	5 mL multi-dose vial 0.5 mL prefilled syringe	4 years and older	
FLUZONE+	5 mL multi-dose vial	6 months and older	

+Fluzone vaccine CPT code 90657 is for vaccination of children 6-35 months of age. Fluzone vaccine CPT code 90658 is for vaccination of individuals 3 years of age and older.

BioResources

The following websites provide useful information about innovative healthcare resources.

Allied Vaccine Group

The Allied Vaccine Group is comprised of websites dedicated to presenting valid scientific information about the sometimes confusing subject of vaccines. It is intended to be the portal of vaccines, including scientific research and the pros and cons of research results.
www.vaccines.org

Agency for Healthcare Research and Quality

AHRQ is part of the U.S. Department of Health and Human Services and is the lead agency charged with supporting research designed to improve the quality of healthcare, reduce its cost and broaden access to essential services. The organization's broad programs of research bring practical, science-based information to medical practitioners and to consumers and other healthcare purchasers.
www.ahrq.gov

ClinicalTrials.Gov

This registry of federally and privately supported clinical trials conducted in the United States and around the world gives individuals information about a trial's purpose, who may participate, locations and phone numbers for more details. The site's administrators suggest that the information be used in conjunction with advice from healthcare professionals.
www.clinicaltrials.gov

Department of Health and Human Services

This site includes healthfinder and human services information, research, policy and administration, employee information, news and public affairs and gateways.
www.dhhs.gov

Google Health

Google Health allows individuals to store their health information securely and privately with complete control over how it is used. Individuals can gather medical records from doctors, hospitals and pharmacies, organize health information in one place and share information securely with a family member, doctors or caregivers.
www.google.com/health

National Cancer Institute

This site includes information for patients, public and the mass media. It includes an international cancer information center, event calendar, intramural and extramural research, technology transfer and office of international affairs. Also on the site are comprehensive descriptions of the institute's research programs and clinical trials, and scientists will find detailed information on specific areas of research interest and funding opportunities.
www.cancer.gov

National Institutes of Health

The NIH is the primary federal agency for conducting and supporting medical research, and is responsible for making discoveries that improve health and save lives. The site includes information on health, grants, research, science, institutes and news.
www.nih.gov

National Library of Medicine

The NLM is the world's largest medical library with information on hot topics, general information, news, databases and electronic information sources, special information programs, research programs, and grants and applications.
www.nlm.nih.gov

WebMD

WebMD provides information about all types of health conditions, their symptoms and treatment modalities, as well as recommen-dations for healthy living. The site also contains daily health news and features, and individuals can sign up for one or more of the site's 30-plus newsletters or RSS feeds.
www.webmd.com

BioResearch

Summaries of up-to-date clinical research published in medical journals internationally.

Fibrinogen Concentrate Cuts Blood Loss in Cardiac Surgery

In a study of 170 patients undergoing coronary artery bypass graft (CABG) surgery (*Transfusion*, 2008 Oct;48:2152-8), investigators found that preoperative fibrinogen level independently predicted postoperative bleeding volume. Theorizing that boosting a low plasma fibrinogen content might improve hemostasis and reduce blood loss, they randomized 20 elective CABG patients with low preoperative fibrinogen levels (<3.8 g/L) to receive a prophylactic infusion of 2 grams of fibrinogen concentrate (Riastap, CSL Behring) or no infusion before surgery.

There were no clinically detectable adverse events associated with infusion of the fibrinogen product. Computed tomography revealed one subclinical vein graft occlusion in the fibrinogen (FIB) group. Mean blood loss was reduced by 32 percent in the FIB group (565 ± 150 vs. 830 ± 268 ml at 12 hours, p=0.010), with a correspondingly higher hemoglobin concentration at 24 hours post-surgery (11.0 +/- 1.2 vs. 9.8 +/- 0.8 g/dL, p=0.018). Prophylactic fibrinogen concentrate infusion did not influence global postoperative hemostasis as assessed by thromboelastometry, and there was no evidence of postoperative hypercoagulability. The authors called for larger studies to more fully document safety and to confirm efficacy of prophylactic fibrinogen treatment in cardiac surgery.

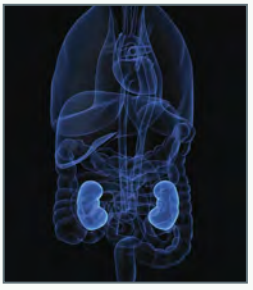
Karlsson, M, Ternström, L, Hyllner, M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Journal of Thrombosis and Haemostasis. *2009 Jul;102(1):137-44.*

Xyntha Pharmacokinetics Equal Full-Length Factor VIII

Xyntha (Wyeth Pharmaceuticals; BDDrFVIII) is a new B-domain deleted, plasma- and albumin-free recombinant factor VIII that has a pharmacokinetic profile equivalent to a full-length recombinant factor VIII, and it has demonstrated a good efficacy and safety profile in two studies involving a total of 204 patients with hemophilia A. A defined prophylaxis protocol in a patient population with pre-existing target joints showed that nearly half (45.7 percent) of patients had no bleeding episodes. Overall, a low-annualized bleed rate of 1.9 episodes was achieved; 92.5 percent of these hemorrhages required equal to or less than two infusions of BDDrFVIII.

Only three subjects (1.5 percent) developed de novo inhibitors, which were low-titer and transient in nature. A Bayesian analysis further documented the absence of neoantigenicity for BDDrFVIII. "This extensive dataset demonstrates the safety and efficacy of BDDrFVIII for hemophilia A," the authors concluded.

Recht, M, Nemes, L, Matysiak, M, et al. Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII. Haemophilia, *2009 Jul;15(4):869-80.*



Rituximab Plus IVIG for Kidney Allograft Rejection

While acute antibody-mediated rejection (AMR) of transplanted kidneys relies mainly on plasmapheresis or immunoadsorption, no available studies address treatment of chronic AMR. Researchers, then, looked at four kidney allograft recipients suffering from chronic AMR, extending from one to 27 years post-transplant, who were treated with a combination of rituximab and intravenous immunoglobulin (IVIG) and showed improved function.

Treatment with rituximab and IVIG improved kidney allograft function in all four patients, with reductions of donor-specific antibodies in two of the four. However, one patient experienced an acute rejection episode 12 months after this treatment, and another had severe, possibly rituximab-associated lung toxicity. This Swiss team concluded that rituximab/IVIG may be a useful strategy for the treatment of chronic AMR, but further randomized multicenter studies are needed to establish its efficacy and safety profile.

Fehr, T, Rüsi, B, Fischer, A, et al. Rituximab and intravenous immunoglobulin treatment of chronic antibody-mediated kidney allograft rejection. Transplantation, *2009 Jun 27;87(12):1837-41.*

IVIG May Lower Risk of Alzheimer's in Elderly

Amyloid beta peptide (A) plaques are a consistent finding at autopsy in brain tissue of persons with Alzheimer's disease (AD). Due to the discovery of lower titers of antibodies directed

against the amyloid beta peptide in patients with AD than in healthy individuals, a number of human studies are currently in progress using IVIG or anti-A monoclonal antibodies to treat mild to moderate AD. Researchers examined a national physician claims database of 20 million patients over age 65 to learn whether the use of IVIG in the usual care of non-AD conditions is associated with a reduction in risk of subsequent diagnosis with AD and related disorders (ADRD).

A total of 847 patients were identified who received at least one infusion of IVIG. Their claims records were observed for a minimum "post-index period" of 731 days to measure ADRD incidence. Results were compared with 84,700 control patients matched for age and other risk factors for ADRD who never received IVIG. Overall, 2 percent of patients treated with IVIG were diagnosed with ADRD in the post-index period, compared with 4.1 percent of untreated controls ($p = 0.002$). This disparity was maintained across three age intervals: 0.6 percent vs. 2.2 percent for age 65 to 74 ($p = 0.021$); 3.7 percent vs. 6.2 percent for age 75 to 84 ($p = 0.062$); and 5 percent vs. 12 percent for age greater than 84. A five-year incidence model predicts that 2.8 percent of IVIG-treated cases will be diagnosed with ADRD compared with 4.8 percent of untreated controls — a 42 percent lower risk. The authors cautioned that data derived retrospectively from claims may not adequately control for ADRD risk differences between the study cohorts.

Fillit, H, Hess, G, Hill, J, et al. IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders. Neurology, *2009 Jul 21;73(3):180-5.*

TPE Permits Kidney Transplantation

Because of the shortage of cadaveric donor kidneys and varying frequencies of each major blood group, more than 4,000 U.S. patients die annually waiting for a kidney transplant. In a review of 46 cases, a team at Johns Hopkins Hospital has documented that therapeutic plasma exchange (TPE) with 5% albumin replacement reduced ABO titers sufficiently to permit transplants of ABO-incompatible (ABO-I) kidneys.

In the study, all patients received a mean of 6.2 pretransplantation and 5.0 posttransplantation TPE procedures, with low-dose infusion of CMVIg (CytoGam, CSL Behring) following each procedure. CMVIg is a potent immunomodulator that is thought to suppress de novo antibody production. There was excellent allograft performance in all patients and no episodes of hyperacute rejection or graft loss from antibody-mediated rejection. TPE reduced mean AHG phase ABO titers from 64 to eight prior to transplantation; titers remained very low three to six months after transplantation. One-year graft survival was 100 percent. TPE treatments resulted in minimal complications. A combination of TPE and CMVIg is now a mainstay of the institution's ABO-I renal transplantation program.

Tobian, AAR, Shirey, RS, Montgomery, RA, et al. Therapeutic plasma exchange reduces ABO titers to permit ABO-incompatible renal transplantation. Transfusion, *2009 Jun;49(6):1248-54.*

Pregnant Women at Higher Risk from H1N1 Flu Complications

The U.S. Centers for Disease Control and Prevention (CDC) believes that pregnant women might be at increased risk for complications from the current pandemic H1N1 influenza virus outbreak, based on reports by 13 states of cases and hospitalizations between April 15 and May 18, 2009. Of 34 confirmed or probable cases of pandemic H1N1 in pregnant women reported during that period, 11 women were admitted to the hospital. Between April 15 and June 16, six deaths in pregnant women were reported to the CDC; all had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation.

The estimated rate of admission in these pregnant women during the first month of the H1N1 outbreak was higher than it was in the general population (0.32 per 100,000 pregnant women vs. 0.076 per 100,000 U.S. population at risk). The CDC suggested that these findings lend support to its current recommendation to promptly treat pregnant women with H1N1 infection with anti-influenza drugs.

Jamieson, DJ, Honein, MA, Rasmussen, SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet, *2009 Jul 28 [Epub ahead of print].*

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gamunex®

immune globulin intravenous (human), 10%
caprylate/chromatography purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.

GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified) 10% Liquid Preparation

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

GAMUNEX is an immune globulin intravenous (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Hyperproteinemia, increased serum viscosity and hyponatremia occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome has been reported with GAMUNEX and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough.
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea.
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever.

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- The passive transfer of antibodies may interfere with the response to live viral vaccines.
- The passive transfer of antibodies may confound the results of serological testing.

USE IN SPECIFIC POPULATIONS

- In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse GAMUNEX at the minimum infusion rate practicable.
- Pregnancy: no human or animal data. Use only if clearly needed.

Talecris BIOTHERAPEUTICS

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08939392/08939393-BS
Revised: October 2008

The PROOF is everywhere you look

GAMUNEX is the IGIV therapy supported by robust clinical trials

- Proven efficacy and safety in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]
- The most clinically studied liquid IGIV, with >600 patients and >4100 infusions[2]

The most common drug-related adverse reactions observed at a rate ≥5% were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions observed in clinical study subjects receiving GAMUNEX were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post study drug infusion and was not considered drug related (in ITP).

*CIDP=chronic inflammatory demyelinating polyneuropathy; PI=primary humoral immunodeficiency; ITP=idiopathic thrombocytopenic purpura.

References: 1. Data on file. Talecris Biotherapeutics, Inc. **2.** GAMUNEX® [package insert]. Research Triangle Park, NC: Talecris Biotherapeutics; 2008.

Important Safety Information—Gamunex, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP). Gamunex is contraindicated in individuals with known anaphylactic or severe systemic response to Immune Globulin (Human).

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV. Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Gamunex is made from human plasma. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease, cannot be totally eliminated. There is also the possibility that unknown infectious agents may be present in such products.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see adjacent page for brief summary of GAMUNEX full Prescribing Information.

Evidence based. Patient proven.

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