July 2012

BioSupply Trends

Special Focus: VACCINES

Quarterly

Vaccine Innovation

Breakthroughs in Science and Technology

Influenza: Evolving Strains and Vaccines

Healthcare Legislation and Preventive Vaccines

Treating Immune Globulin Side Effects

Myths & Facts: Lyme Disease

Arriving Soon: Novel Quadrivalent Flu Vaccines — Page 50

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

The Power to Control VWD

www.wilateusa.com

I **will** use only high purity VWF/FVIII for my patients with VWD*

I **will** expect reliable dosing and monitoring from a balanced, 1:1 ratio of VWF and FVIII

I **will** demand proven clinical efficacy for acute bleeding in both adult and pediatric patients

I **will** choose the first double virus inactivated VWF/FVIII

***The resulting specific activity of wilate is ≥ 60 IU VWF: RCo and ≥ 60 IU FVIII activities per mg of total protein.**

The clinical relevance of this data has not been established

I **will** help my patients take control of VWD

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

For more information, please contact us:

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To report suspected adverse reactions,
Contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

Important safety information:
wilate® is contraindicated for individuals with a history of anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapies. FVIII activity should be monitored to avoid sustained excessive FVIII levels. wilate® is made from human plasma. The risk of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease agent, cannot be completely eliminated. The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions. Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors to VWF).

Please see Brief Summary of Prescribing Information, and additional information, on adjacent page.

Print Date 6/12. WIL-004-PAD

octapharma

For the safe and optimal use of human proteins

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Wilate safely and effectively. See full prescribing information for Wilate.

Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human), Powder for Solution, for Intravenous Use Only. Initial U.S. Approval: 2009

INDICATIONS AND USAGE

- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is also not indicated for Hemophilia A

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

CONTRAINDICATIONS

- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reaction
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients
- Theoretical risk of infectious agents transmission as the product is made from human plasma

ADVERSE REACTIONS

The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.**

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

Type of Hemorrhages	Loading Dosage (IU VWF:RCo/kg BW)	Maintenance Dosage (IU VWF:RCo/kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12 – 24 hours*	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12 – 24 hours*	VWF: RCo and FVIII activity through levels of >50%

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

NDC Number	Size	Protein Amount
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

HOW SUPPLIED/STORAGE AND HANDLING

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.

Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstitute the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.

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U.S. License No. 1646

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For the safe and optimal use of human proteins

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Features

Special Focus: Vaccines

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Up Front

BioTrends Watch

BioFocus

BioSources

Immunization: An Era of Innovation

VACCINES HAVE PLAYED a significant and transformative role in our world, eradicating diseases that once killed millions. But overall the work is far from complete. As we celebrate our third year in publication, we begin by exploring innovations in vaccine research and technology. One of the more intriguing aspects of current research involves DNA vaccines, a technique that utilizes genetically engineered DNA to improve immune response. Researchers believe this method may hold the potential for battling both chronic and infectious diseases.

Of course, some diseases in the United States and other developed nations have increasingly been viewed as "historical" due to their extremely low rates of infection. Meningitis is one such disease, and while the incidence rate is low, bacterial meningitis remains a life-threatening disease that claims several hundred lives annually. Our Update on Meningitis feature spotlights the causes, symptoms and treatments for this rare but lethal disease, with inoculation remaining the best means of defense.

One of the most devastating diseases of the 20th century is acquired immune deficiency syndrome (AIDS). By 2015, it is estimated that 60 million people will have died of AIDS, but hope is on the horizon. Scientists have reported a successful HIV vaccine regimen that includes a DNA priming vaccine, followed by an attenuated poxvirus vaccine booster; clinical trials are promising, with a Phase IIb DNA vaccine now on its way to efficacy trials.

Also in this issue, our patient profile takes a more personal look at HIV/AIDS. Improved medications and treatment options have flipped the tables on this once-fatal disease, resulting in significantly lowered mortality rates. Now, clinicians are tasked with helping patients not only adhere to treatment plans, but also navigate the emotional and social implications of living long-term with HIV. This month's profile looks at the stigmas and challenges of this disease from both a patient and provider perspective.

A vaccine issue would not be complete without a feature on influenza. Influenza: Past, Present and Future examines the strides and the setbacks since the infamous 1918 influenza pandemic claimed the lives of 50 million worldwide. While getting an annual flu vaccine remains the best way to prevent the spread of flu, the sad reality is that tens of thousands of people in the U.S. still succumb to flu-related complications each year. Those of us on the frontline recognize that more education, communication and effort are needed to help dispel common flu vaccine myths and ensure pandemic history does not repeat itself.

Beyond vaccines, biopharmaceuticals like intravenous immune globulin (IG) are both innovative and amazing in their ability to restore quality of life for patients living with chronic illness. Although it's one of the safest biological products available, IG can present a whole host of unwanted side effects. The article Understanding and Treating IG Side Effects explores what patients and caregivers can expect during and after immune globulin infusions, and discusses possible treatment changes to mitigate side effects and their impact.

Finally, reimbursement remains high on everyone's list of hot topics. Our article The ACA's Impact on Vaccine Administration and Reimbursement discusses the many ways in which healthcare professionals who provide preventive vaccines will be affected by recent legislation.

We hope you find this issue insightful and helpful to you and your colleagues.

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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Alzheimer's Research Receives More Funding

With as many as 5.1 million Americans currently suffering from Alzheimer's, as well as a projected 13.2 million Alzheimer's patients by 2050, the federal government has devoted new funding for research. In January 2011, President Obama signed the National Alzheimer's Project Act, a statute that addresses the medical and social complications connected with the disorder. The new law calls for a synchronized and aggressive nationwide Alzheimer's disease plan of action to accomplish five goals: prevent and effectively treat Alzheimer's disease by 2025; enhance care quality and efficiency; expand patient and family support; enhance public awareness and engagement; and improve data to track progress. The law also establishes an Advisory Council on Alzheimer's Research, Care and Services, which assembles some of the country's leading authorities on Alzheimer's disease to advise on the progression of the national plan.

In February, President Obama committed even more funds for Alzheimer's disease research. This includes making $50 million available now for innovative Alzheimer's research and increasing funding by $80 million in the 2013 fiscal year budget. Included in the $130 million total investment (which is more than 25 percent more than the current annual Alzheimer's research investment) is $26 million for "caregiver support, provider education, public awareness" and the enhancement of data organization. ❖

States Urged to Prepare for Health Insurance Exchanges

With the looming deadline to create health insurance exchanges, states are being encouraged to do all they can this year to prepare for their successful launch in 2014. Health insurance exchanges were created under the Affordable Care Act to function as a marketplace for health insurance consumers, providing them with options for health coverage. The goals of the exchanges are to offer a variety of qualified health plans and provide information and educational services to help health insurance buyers understand their choices. States will have the option to establish one or more state or regional exchanges; to partner with the federal government to run the exchange; or to merge with other state exchanges. If a state elects not to participate in an exchange, the federal government will create the exchange in the state.

Although the law's most important changes will not take effect until 2014, states and health insurers must prepare to sign up a projected 32 million people on Medicaid and private insurance. Yet,

states are still missing critical information from the federal government, such as key pieces of direction, from what various insurance exchange options will look like to which benefits must be included in health plans.

This year, the main concern for states is to create the exchanges, through which small businesses and individuals can buy health coverage starting in 2014. On Jan. 1, 2013, the U.S. Department of Health and Human Services (HHS) will confirm which states will be prepared to run exchanges on their own. For a state to achieve accreditation, it must pass laws to fund the ongoing processes of an exchange. While the federal government will offer initial financial support for the establishment of exchanges, states will have to budget for those fees once they are under way. HHS can issue a provisional certification for those states that are making headway but need additional time.

While some states are advancing toward exchange creation, most are unsure, and a few have decided to pull away from the idea altogether. Initially, the only other option to a state exchange was a total federal unit, but HHS has offered to join with states so that they can preserve general control of an exchange while giving certain responsibilities to the federal government. ❖

New Texas Law for Meningitis Vaccine

In May, the Texas Legislature passed Senate Bill 1107, a law that requires new college students to provide proof of receiving a bacterial meningitis vaccine 10 days prior to the start of classes. The updated 2011 law is an expansion of the 2009 law that required only students who were living on campus to receive a vaccine. The revised requirements will apply to all incoming students at the college and university levels, whether they are transfer or returning students, including those who live off campus.

Part of the new legislation will require private and independent institutions of higher education to assign a department to obtain proof from students that ensures they have received an initial bacterial meningitis vaccination or booster dose. If a student is not able to get vaccinated by the time classes begin, the law will allow for a 10-day extension after classes start.

With the cost of the vaccine as much as $300 if the student is not insured, there is concern some students won't be able to afford it. To address this, the Lone Star College System (LSCS) has joined with the Central Care Community Health Center (CCCHC) to offer $10 bacterial meningitis vaccinations for its nearly 6,000 LSCS students. ❖

Federal Court to Reconsider Genetics Patents

On March 26, the U.S. Supreme Court instructed the Federal Circuit Court of Appeals to reconsider its July 2011 decision to uphold patents held by Myriad Genetics. This decision is due to a new precedent that was set when Prometheus Laboratories, a small diagnostics company, was unable to patent the connection between optimum drug dosage and the way it metabolizes in a person's body. According to the Supreme Court, the Myriad Genetics' "patent claims at issue here effectively claim the underlying laws of nature themselves." As such, it concluded, "the claims are consequently invalid."

The two Myriad patents at issue are concerning genes BRAC1 and BRAC2. Patients with inherited mutations in these genes have a greater chance of acquiring breast cancer or ovarian cancer. Myriad has created a genetic exam called the BRACAnalysis test, which enables doctors to pinpoint patients with the greatest risk of developing cancer. If patients are confirmed to have a high cancer risk, then their physicians can take steps to help minimize that risk by prescribing preventive medical treatments.

With the Myriad patents hanging in the balance, biotechnology companies are concerned about the future of innovation. They say patent protection is a required motivation to encourage new technologies. Yet, academic researchers have conventionally been motivated by science rather than revenue, so the lack of patents could result in increased research activity. ❖

Online Marketplaces Make Medicaid Eligibility Easier

Individuals applying for health coverage in the new online marketplace, which is required by the federal health law, will be immediately informed if they qualify for Medicaid or premium subsidies, according to the Centers for Medicare and Medicaid Services. Previously, individuals had to wait days or even weeks until their residential state could determine their eligibility.

Online marketplaces, known as insurance exchanges, are expected to become active in 2014. Exchanges have been given the choice to make a preliminary determination of eligibility for Medicaid while allowing state Medicaid agencies to make the ultimate assessment. They also will be required to use state and federal databases like those kept by Social Security and the Internal Revenue Service to help confirm applicants' income levels and other pertinent information to determine eligibility. ❖

CARLA SCHICK *is a staff writer for* BioSupply Trends Quarterly.

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Recently, the Centers for Medicare and Medicaid Services (CMS) assigned a new ICD-9 code for acquired hemophilia. What is the code, and how is it significant for the healthcare community?

The new International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for NovoSeven RT (Coagulation Factor VIIa [Recombinant]) to treat acquired hemophilia is 286.52. This code applies to dates of service on or after October 1, 2011.

According to a statement by Novo Nordisk, NovoSeven RT's manufacturer, "Previously, disorders involving circulating anticoagulants, including acquired hemophilia, were coded with the broad ICD-9-CM code 286.5 or 'hemorrhagic disorder due to intrinsic circulating anticoagulants.' This did not allow for the differentiation of the unique condition of acquired hemophilia from the more common lupus anticoagulant (LAC) and hyperheparinization conditions. In mid-2010, Novo Nordisk submitted a request to the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention, to generate unique codes for these three different conditions to facilitate ongoing quality assurance and postmarketing surveillance activities. The resulting ICD-9-CM update is an important step forward for the hemophilia community and further demonstrates Novo Nordisk's commitment to bringing attention to this sometimes deadly condition of acquired hemophilia."

For more information, visit the CMS website at www.cdc.gov/nchs/data/icd9/ICD-9-CMINDEXADDENDAfy12.pdf. ❖

Does Medicare reimburse the cost of nursing services when injectables are administered to a patient in his or her home?

Medicare reimbursement for nursing services is determined by the site of care. If a patient is homebound, and there is a medical reason why he or she is unable to self-administer and/or there is not a caregiver to teach him or her to self-administer, then Medicare will reimburse for those services provided by a Medicare-certified home health agency. Under these circumstances, there may be no cost to the patient. However, if durable medical equipment (DME) is required, a patient will be responsible for a 20 percent co-pay to cover the cost of the DME.

If a patient is not certified homebound and he or she does not have secondary insurance or a Medicare Advantage plan, then having a nurse administer injectables in the home is not covered. However, a patient who is not homebound can go to his or her doctor's office to have the injection administered, and the doctor will be reimbursed by Medicare. In this case, the doctor's office will let the patient know if he or she will be subject to a co-pay.

Per Medicare, homebound means 1) leaving the home isn't recommended because of the patient's condition, 2) the patient's condition keeps him or her from leaving home without help (such as using a wheelchair or walker, needing special transportation, or getting help from another person), or 3) leaving home takes a considerable and taxing effort.

A person deemed homebound may leave home for medical treatment or short, infrequent absences for nonmedical reasons, such as attending religious services. In addition, a homebound patient can still get home healthcare if he or she attends adult daycare, but that patient would get the homecare services in his or her home. ❖

Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

if you spot it, you can stop it

Name: Joseph Miller Age: 62 years

Model is used for illustrative purposes only.

Symptoms[1,2]:

- Arrives at the ER with spontaneous, severe gastrointestinal bleeding
- No prior history of bleeding

Labs[1,3]:

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests and additional testing ordered by the attending physician

Treatments[1]:

- Did not respond to treatments, including platelets and fresh frozen plasma

Diagnosis: ACQUIRED HEMOPHILIA

Joe has acquired hemophilia (acquired inhibitors), which can be very difficult to diagnose and is **fatal in more than 20% of all cases**.[4]

You can help patients like Joe by being aware of the red flags of acquired hemophilia and bringing them up to the physician.

When you see an unusual order of factor VIII (FVIII), ask some simple questions:

- What is the reason for your recent unusual order of FVIII?
- Do you have a patient with congenital hemophilia?
- Is bleeding under control?
- What diagnostic tests, such as an aPTT or a mixing study, have been performed?
- Was the aPTT prolonged?
- Have you consulted a hematologist?
- Have you considered acquired hemophilia?

Find out more about acquired hemophilia and treatment at **CoagsUncomplicated.com/Joe**.

References: 1. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94(4):566-575. **2.** Collins PW, Hirsch S, Baglin TP, et al; for UK Haemophilia Centre Doctors' Organisation. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877. **3.** Collins PW, Percy CL. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br J Haematol*. 2010;148(2):183-194. **4.** Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2009;20(7):517-523.

Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540 U.S.A.

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novo nordisk®

Product Recall

Cangene Recalls HepaGam B Product Lots

Cangene Corp. has issued a voluntary recall of the following finished product lots associated with one bulk lot of Hepatitis B Immune Globulin ([Human] HepaGam B > 312 IU/mL): 11006960, 11006961, 11107308, 11107359, 11107360, 11007107, 11007148 and 11007151. The recall is a result of post-marketing and literature reports of serious thrombotic adverse events associated with the administration of intravenous and subcutaneous immune globulin products (IVIG, SCIG) in a wide range of patient populations. Recently, coagulation factors, including activated factor XI, have been identified in IVIG batches associated with thrombotic events. Measurable levels of procoagulant (factor XIa) activity have been detected in HepaGam B.

This Class II recall is appropriate for situations in which use of, or exposure to, a product may cause temporary adverse health consequences or where the probability of serious adverse health consequences is remote. Safe levels of FXIa in immune globulin products are not known. These lots of HepaGam B have been found to contain dose levels of FXIa below, but approaching those administered in immune globulin product lots implicated in thromboembolic events.

Patients are advised to check all product labels against the list of affected lot numbers and to quarantine any impacted inventory. For information about how to return the product, call (877) 437-2426 in the U.S. and (877) 226-4363 in Canada. ❖

Research

Slow Release of IG May Delay Alzheimer's Disease

Recent studies conducted by Dr. Giulio Maria Pasinetti, Saunders Family chair and professor in neurology and psychiatry at Mount Sinai School of Medicine in New York, suggest that the divergent outcomes in Alzheimer's disease clinical studies of intravenous immune globulin (IVIG) may be due to differences in temporal administration and administered dosages.

Dr. Pasinetti and his team of investigators recently found that prolonged administration of human immunoglobulin in models of Alzheimer's disease, using a dose of immunoglobulin ~5-20-fold less than equivalent doses used in Alzheimer's disease patients, is effective at attenuating Alzheimer's disease-type cognitive dysfunction while promoting synaptic plasticity. "This experimental observation provides a rational basis for rectifying the inconsistency of study outcomes in Alzheimer's disease clinical trials with IVIG," said Dr. Pasinetti. "We now have the much needed information supporting the potential application of slow release of immunoglobulins delivered subcutaneously to delay the onset of Alzheimer's disease, even at presymptomatic stages of the disease."

Dr. Pasinetti hypothesizes that the slow release of immunoglobulins into the circulation and eventually into the brain for a protracted period of time may delay Alzheimer's disease dementia onset and eventually its progression through epigenetic changes in the downstream gene expression of C5a-mediated pCREB-C/EBP signaling components associated with modulation of synaptic plasticity and eventually learning and memory functions. ❖

Insurance

HHS Delays ICD-10 Compliance Date

The Department of Health and Human Services (HHS) is postponing the date set for certain healthcare entities to comply with International Classifications of Diseases (10th edition) diagnosis and procedure codes (ICD-10). ICD-10 codes, which will be required of entities covered under the Health Insurance Portability and Accountability Act (HIPAA) of 1996, provide more robust and specific data to help improve patient care and enable the exchange of healthcare data with other countries that have long been using ICD-10 codes. However, according to HHS Secretary Kathleen G. Sebelius, the department has "heard from many in the provider community who have concerns about the administrative burdens they face in the years ahead." So, it is working with the "provider community to re-examine the pace at which HHS and the nation implement these important improvements" to the healthcare system. The final rule adopting ICD-10 as a standard was published in January 2009, which set a compliance date of Oct. 1, 2013, a delay of two years from the compliance date initially specified in the 2008 proposed rule. On April 17, HHS published a proposed rule that covered entities must be in compliance with ICD-10 on October 1, 2014. ❖

Research

Smallpox Vaccine Extends Life in Cancer Trial

A genetically engineered smallpox vaccine, known as JX-594, reduced the risk of death for patients with advanced liver cancer by nearly 60 percent in a mid-stage study, which has prompted the launch of a later-stage trial. In the small 30-patient study, patients given a high dose of JX-594 lived for a median of 13.8 months compared with 6.7 months for patients treated with one-tenth of that dose. The main side effect of high doses of JX-594 was temporary flu-like symptoms. JX-594 is derived from a strain of the virus vaccinia, once commonly used to vaccinate children against smallpox.

A Phase IIb study, which will allow for more continuous dosing than in earlier studies, will compare JX-594 with standard care in 120 liver cancer patients who have stopped responding to Nexavar, also known as sorafenib, sold by Onyx Pharmaceuticals. These patients will be given an intravenous infusion of JX-594, followed by direct injections into the tumor. A Phase III head-to-head trial comparing JX-594 with Nexavar will be launched next. ❖

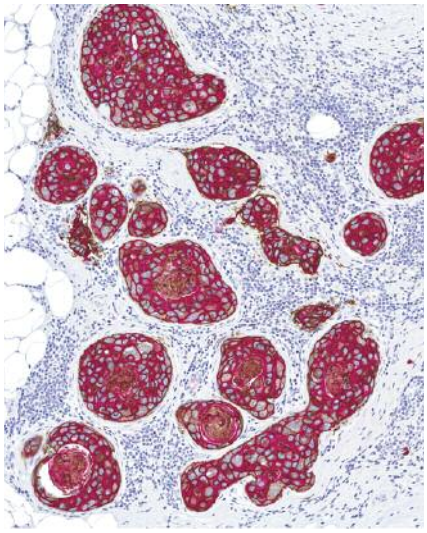
Vaccines

New Vaccine May Prevent Cancer

U.S. Army Col. George Peoples, chief of surgical oncology at the San Antonio Military Medical Center, says he has come up with a vaccine he thinks will prevent cancer. The NeuVax vaccine has begun Phase III clinical trials that will involve at least 700 breast cancer patients who will each receive one intradermal injection of NeuVax every month for six months. Once the first six months is up, the participants will then receive a booster inoculation every six months afterward. The goal: disease-free survival for participants at three years.

Peoples is the director for a cancer vaccine development program that he has been working on since the '90s. When he is not trying to find a cure for cancer, he is dispatched throughout the world to provide his surgical expertise for the military. "People who are in my field approach this by saying, yes, there are ways to treat cancer, but why wait and treat, why not try to prevent?" explains Peoples.

NeuVax, which utilizes the E75 peptide, is the result of nearly 20 years of research by Peoples and others. It parallels the development of the breast cancer drug Herceptin, which targets a protein called HER2/neu that is commonly



overexpressed in breast cancer patients. However, only 20 percent of breast cancer patients have a sufficient amount of HER2/neu in order for Herceptin to work. NeuVax is meant to aid those with breast cancer who have lower levels of HER2/neu expression — about 60 percent of breast cancer patients. The majority of other cancers express some levels of HER2/neu as well, which means NeuVax could prevent not just breast cancer, but a whole range of various other cancers. ❖

Research

Positive Results for Phase II Clinical Trial for ITP Patients

Symphogen has presented final Phase II data demonstrating that its recombinant polyclonal antibody drug candidate rozrolimupab exhibited a favorable safety profile and induced a rapid increase in blood platelets in patients with immune thrombocytopenia purpura (ITP). The Phase II study was an open-label, multicenter clinical trial evaluating the efficacy, safety and tolerability of rozrolimupab (SYM001) in adult RhD positive, non-splenectomized ITP patients. Results demonstrated that at 300 ug/kg, eight of 13 (62 percent) patients responded at day seven. The median time to respond was 59 hours, and the median duration of response was 14 days. The most common adverse events, mostly mild to moderate, were headache (18 percent), pyrexia (13 percent), chills (8 percent) and fatigue (8 percent). Four serious adverse events considered related to the drug were reported: decreased hemoglobin, extravascular hemolysis/dizziness and two cases of transient rise in D-dimer values without clinical symptoms. ❖

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Medicines

CSL's rVIIa-FP Granted Orphan Drug Designation

CSL Behring has been granted orphan drug designation (ODD) by the U.S. Food and Drug Administration (FDA) for its novel recombinant fusion protein linking coagulation factor VIIa with albumin (rVIIa-FP). The ODD is granted for the treatment and prophylaxis of bleeding episodes in patients with congenital hemophilia and inhibitors to coagulation factor VIII or IX. CSL Behring is developing this therapy in collaboration with its parent company CSL Limited.

The CSL Behring rVIIa-FP clinical program intends to demonstrate that an extended half-life rVIIa-FP will result in a requirement for fewer doses while providing adequate therapeutic response in patients who have hemophilia A and B with inhibitors.

"CSL Behring's albumin fusion technology uses albumin as the ideal recombinant genetic fusion partner for coagulation factor proteins because of its high tolerability, inherently long half-life, low potential for immunogenic reactions and known mechanism of clearance," said Russell Basser, MD, senior vice president Global Clinical R&D at CSL Behring. "CSL Behring's rVIIa albumin fusion protein is expected to exhibit a good tolerability profile and improved pharmacokinetics that may enable prophylaxis." ❖

Vaccine Update

A vaccine against **Alzheimer's disease**, known as a bapineuzumab jab, which is in the final phase of testing in more than 10,000 patients around the world, has been shown to prevent and, in some cases, reverse the buildup of amyloid protein, the substance that collects inside the brains of sufferers of several types of dementia. While the vaccine is not a cure, it is one of only two vaccines that have made it to the third and final stage of testing and holds promise for halting or reversing the effects of the disease.

Blue Cross Blue Shield is now covering the **human papillomavirus (HPV) vaccine** for males. The HPV vaaccine is approved by the U.S. Food and Drug Administration for teenage boys and men up to age 26.

Celldex Therapeutics' experimental vaccine for the most common type of **brain cancer** met the main goal of extending survival time for patients without a progression of the disease in a mid-stage trial. The vaccine rindopepimut, or CDX0110, is Celldex's lead product candidate.

Scientists at Dartmouth University have discovered a new process of personalizing vaccines to help **colorectal cancer** patients develop immune responses to their own tumors. The dendritic cell vaccine was used after patients had undergone surgical resection and metastatic tumors in order to prevent the growth of additional metastases.

Three major medical centers are now using three new vaccines to target and kill cancer. In a three-year study of an experimental vaccine called Prostvac-vf, 30 percent of patients with **non-small cell lung cancer** who got the vaccine were alive, while only 17 percent of those who got a placebo survived that long. A second vaccine recently approved by the Food and Drug Administration (FDA), Provenge, improved three-year survival of **prostate cancer** patients by nearly 40 percent. And a **breast cancer** vaccine is in the works at Cleveland College. All of these vaccines work by revving up the immune system.

Gardasil, the vaccine to prevent cervical cancer in girls, has been approved by the FDA as a vaccine to prevent **anal cancer**, a rare but growing diagnosis in the United States. The approval opens the way for the medication's maker, Merck and Co. Inc., to market the vaccine to boys and young men between the ages of 9 and 26.

Scientists in Dublin and Leicester have discovered how the body's immune system responds to infection caused by Streptococcus pneumoniae that will pave the way for more effective vaccines to fight against **pneumonia**, **meningitis** and **septicaemia**. They discovered that the bacterial toxin pneumolysin triggers an immune response by activating a recently discovered group of proteins, called the NLRP3 inflammasome. Once activated, the inflammasome provides protection against infection caused by this pathogen.

Researchers from Weill Cornell Medical College, New York, N.Y., have created a safe vaccine that combines bits of the common cold virus with a particle that mimics cocaine to prevent cocaine molecules from reaching the brain of mice, preventing any cocaine-related activity. They hope that it will not only work to treat **cocaine addiction**, but also heroin and nicotine addiction. ❖

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1. Marketing Research Bureau data, July 2011

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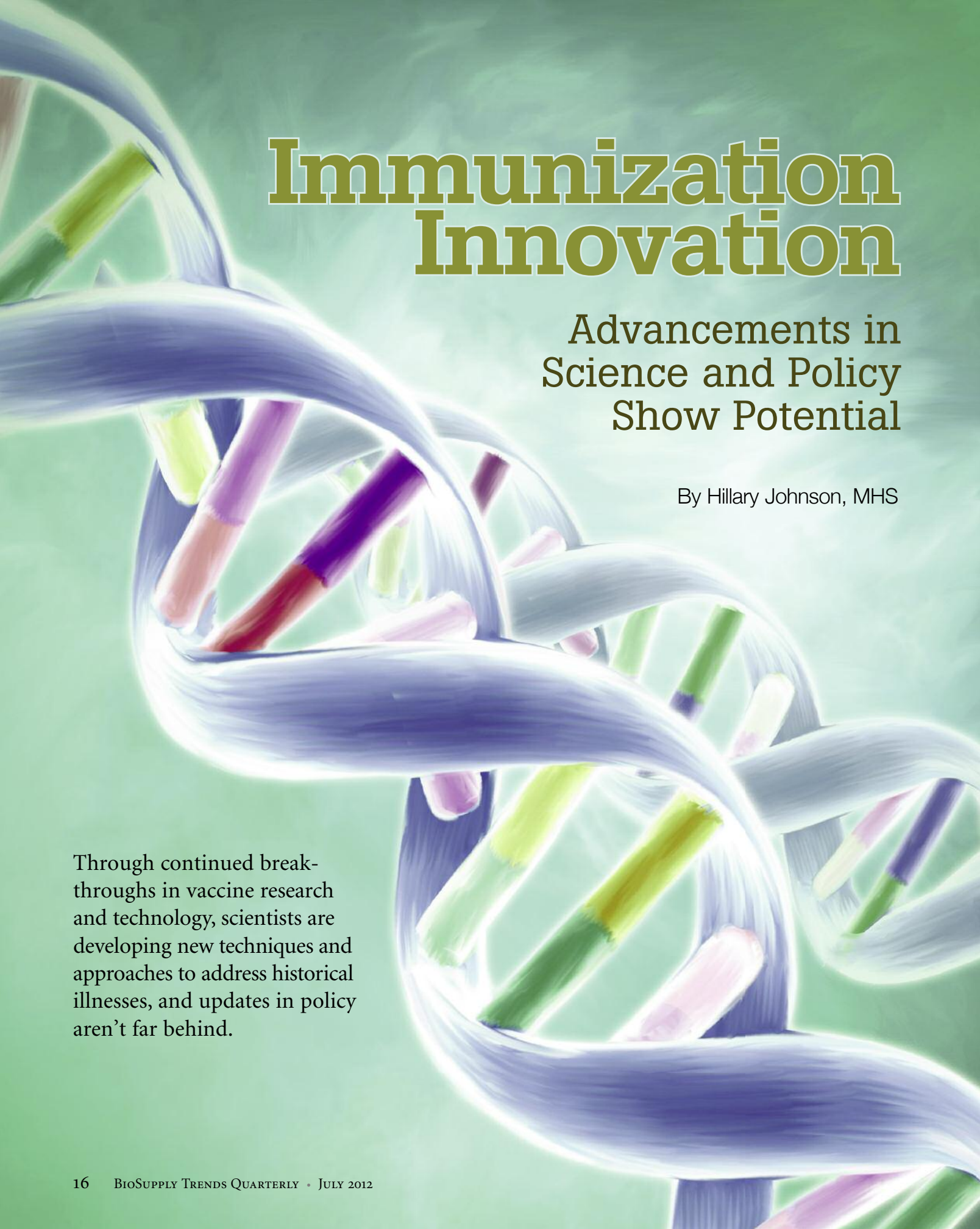

Immunization Innovation

Advancements in Science and Policy Show Potential

By Hillary Johnson, MHS

Through continued breakthroughs in vaccine research and technology, scientists are developing new techniques and approaches to address historical illnesses, and updates in policy aren't far behind.

To many in the United States, hand, foot and mouth disease (HFMD) is a common childhood viral illness that may include fever, rash on the hands and feet, and blisters inside the mouth. There is no vaccine, and it is not a reportable illness in the U.S. So why, then, has such a low-priority disease made headlines in early 2012 in four different U.S. states?

Between Nov. 7, 2011, and Feb. 29, 2012, the Centers for Disease Control and Prevention (CDC) received reports of atypical and more severe HFMD presentation in 63 cases across Alabama, California, Connecticut and Nevada. Subsequent virus strain sequencing in 24 of 34 patients tested showed coxsackievirus A6 (CVA6), an enterovirus associated with international outbreaks and more severe symptoms than the CVA16 strain typically seen in the U.S. Yet despite the genetic match to an international strain, epidemiological investigation was unable to confirm travel and directly link the cases to an imported source.[1]

Where did it come from? In spite of the blip on the radar, HFMD remains a rare disease in the U.S., although it is endemic in parts of Southeast Asia, where approximately two million children are affected annually, and more virulent strains pose potentially debilitating and even fatal risks.[2] Dr. Dan Stinchcomb, co-founder and CEO of global vaccine development company Inviragen Inc., describes HFMD as an emerging disease. "One of the dangers is that it could be a problem here," he tells the *Coloradoan* newspaper.[3]

And Dr. Stinchcomb would know. On March 12, Inviragen released results from its placebo-controlled, randomized Phase I trial of INV21, the company's highly purified virus particle vaccine against enterovirus 71 (EV71), a virulent strain of HFMD endemic to East Asia. The study showed INV21 was safe and well-tolerated, and it significantly increased EV71 immune responses in all individuals receiving the vaccine. Inviragen will proceed with Phase II clinical testing shortly.[2]

HFMD represents one of many diseases with potential to benefit from recent breakthroughs in vaccine science. From enhancements in DNA research, to innovations in the manufacturing process, even the most routine diseases are meriting a second look. And partnerships between government, academia and industry are leading government officials to re-examine vaccine policies and recommendations as well, hoping to catch up with the science.

Advances in Global Health

With an increasingly mobile global population and renewed attention to the potential for global infectious disease pandemics, everyone stands to benefit from breakthroughs in the global health arena.

Cholera. PaxVax Corp. made news in March with the U.S. Food and Drug Administration's (FDA) acceptance of its investigational new drug application for a cholera vaccine in the U.S. PXVX-0200, already approved and marketed in six other countries, is the only single-dose oral cholera vaccine worldwide, and provides immunity in as few as seven days, compared with other drugs that can take several weeks. PaxVax hopes to initiate Phase III trials shortly, and because the FDA classifies cholera as a "neglected tropical disease," it believes they may qualify for a priority review voucher.[4]

Previously, there was a cholera vaccine manufactured and marketed by Wyeth Laboratories Inc. approved by the FDA in 1952. However, in September 2001, the FDA revoked the license for that cholera vaccine (a heat-phenol inactivated form) at the request of the manufacturer.

Malaria. While the malaria parasite's crescent shape was first observed under a microscope in 1880, a viable vaccine has still remained elusive to researchers. But through modern high-end imaging techniques, University of Melbourne researchers believe they are one step closer to identifying a target for potential vaccine development. The team recently reported in the *Journal Of Cell Science* that, by using 3D Structured Illumination Microscopy and Cryo Electron Microscopy, they have discovered that malaria uses a "scaffold" of special proteins to form a banana shape before sexual reproduction. Researchers believe they may have found a new target in these "scaffold" proteins for a potential malaria vaccine.[5]

From enhancements in DNA research, to innovations in the manufacturing process, even the most routine diseases are meriting a second look.

Vical Inc. recently announced its development of a potential DNA vaccine targeted at interrupting the malaria parasite life cycle as well. Initial test results published in the journal *Vaccine* describe the transmission-blocking DNA vaccine candidate as expressing the Plasmodium vivax malaria parasite protein Pvs230. Mosquitoes fed with malaria-infected human red blood cells incubated with serum from vaccinated mice successfully produced anti-Pvs230 antibodies and experienced a statistically reduced infection rate and number of parasites. Further study is expected.[6]

The Promise of DNA Vaccines

Many researchers are looking to DNA vaccines to improve immune responses to some of our most significant health challenges. DNA vaccines work by injecting genetically engineered DNA, which is absorbed into the body's cells. The DNA contains coding for synthesizing a pathogen's antigenic proteins, enabling the body's cells to then create and display these proteins on their surface, alerting the immune system and triggering a response. Researchers believe this method holds potential for both chronic and infectious diseases, and various clinical trials have been performed or are ongoing. To improve immune response to DNA vaccines, many researchers also are examining new delivery technologies, formulations and prime-boost strategies.[7] Although no DNA vaccines have yet achieved market licensure, research in the areas of influenza, HIV and even herpes simplex virus have recently made headlines.

Influenza. Influenza creates a unique challenge for scientists engaged in vaccine research. Because of influenza's high propensity for mutation, each year the World Health Organization tries to predict the most likely dominate strains to come, and it directs seasonal vaccine manufacturers to focus their energies on those strains. Because these vaccines typically focus on the surface proteins, which vary across strains, vaccines must be altered and repeated each year to ensure maintained immunity.[8] (MedImmune LLC just announced the FDA's approval of its first quadrivalent seasonal influenza vaccine that contains four distinct vaccine strains. See story on page 50.) Research in the area of a universal influenza vaccine, which focuses on core proteins shared across influenza strains, also may benefit from a DNA vaccine approach.

Cancer vaccine efficacy faces limitations due to the low immunogenicity of cancer antigens.

Two recent Phase I clinical studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) report enhanced immune response to an H5N1 avian influenza vaccine in healthy adults first primed with a DNA vaccine expressing a gene for a key H5N1 protein. Some volunteers in the experiment receiving the prime-boost vaccine regimen also demonstrated production of broadly neutralizing antibodies (an early, yet significant finding for universal influenza vaccine research).[9]

HIV. Scientists at Emory University and GeoVax Labs Inc. have reported a successful vaccine regimen that includes a DNA priming vaccine, followed by an attenuated, poxvirus vaccine booster expressing HIV proteins, in the prevention of simian immunodeficiency virus (SIV) in nonhuman primates. (SIV is the nonhuman primate version of HIV.) The DNA prime vaccine co-expresses both HIV proteins and the normal immune response initiating protein GM-CSF (enhancing the ability to elicit SIV blocking antibodies before the virus enters cells). GeoVax reports that initial Phase I and IIa clinical trials of a similar first generation DNA vaccine (without the GM-CSF expression) showed "excellent" safety and reproducible vaccine responses in more than 400 HIV-negative people, helping to fast-track this second-generation DNA vaccine (expressing GM-CSF) to Phase IIb efficacy trials in people at high risk of HIV exposure. These trials are part of the National Institutes of Health HIV Vaccine Trials Network.[10]

Herpes simplex virus. At the 5th Vaccine and ISV Annual Global Congress in Seattle in October, DNA vaccine development company Coridon Pty Ltd announced it had successfully completed preclinical efficacy testing of its prototype herpes simplex virus 2 (HSV-2) vaccine, with results showing the vaccine was 100 percent effective in protection against HSV-2 infection in animals. Coridon plans to initiate preclinical safety studies shortly.[11]

The Challenges of Cancer

One of the major challenges facing the immune system centers around identification of cancer cells themselves as harmful. Subsequently, the FDA has, to date, approved only one cancer treatment vaccine (for men with metastatic prostate cancer) and two types of cancer-preventing vaccines: a vaccine against hepatitis B virus (which can lead to liver cancer) and a vaccine against human papillomavirus (HPV) types 16 and 18 (which can lead to cervical, anal, vaginal and vulvar cancers).[12] What is exciting is that, in October 2011, the Advisory Committee on Immunization Practices (ACIP) voted to expand recommended routine use of the HPV vaccine Gardasil to males ages 9 to 26 years, ensuring equal protection across genders.[13]

Melanoma. Cancer vaccine efficacy faces limitations due to the low immunogenicity of cancer antigens. Researchers are, therefore, looking to strategies for enhancement. The Mayo Clinic in Rochester, Minn., recently reported success in training mouse immune systems to eradicate skin cancer through the use of a genetic combination of human melanoma cell DNA and vesicular stomatitis virus (VSV). By utilizing a highly immunogenic virus such as VSV (a cousin of the rabies virus), scientists were able to increase the visibility of the cancer antigens by the immune system, as well as improve immune response. "The immune system now thinks it is being invaded by the viruses, which are expressing cancer-related antigens that should be eliminated," explains Dr. Richard Vile. The Mayo Clinic hopes to initiate human clinical studies in the next two to three years.[14]

Breast cancer. At their April 2012 annual meeting, the American Association for Cancer Research (AACR) chose to highlight results from the Generex Biotechnology Corp.'s ongoing Phase II clinical trial of AE37, an immunotherapeutic vaccine to prevent relapse in patients with a history of breast cancer. The vaccine utilizes the company's Ii-Key Hybrid technology platform to modify fragments of antigens and increase their immunogenicity. The resulting peptide vaccine contains a fragment of the HER2 protein (a highly potent cancer-expressing protein). Key findings from the clinical trials indicate that patients receiving AE37 develop an increase in circulating T cells in their blood and a reduction in T regulatory cells (known to hamper immune response). According to Dr. Elizabeth Mittendorf, principal investigator for the trial, these data suggest that patients receiving AE37 have a lower rate of relapse. "These studies help us to understand at a mechanistic level how the vaccine is working and on a more general level what hallmarks to look for in developing successful cancer immunotherapy," she explains.[15]

Technological Advances Beyond the Needle

Some currently innovative approaches to vaccines lie in looking beyond the syringe itself.

Needle-free. Researchers at the University of Saskatchewan believe the first successful respiratory syncytial virus (RSV) vaccine may require going "needle-free." RSV, a major cause of respiratory illness in young children, can lead to particularly bad sequelae in young infants, including pneumonia or bronchiolitis or, rarely, death. The challenge with any vaccine among the youngest infants is finding that delicate balance between inoculating a child early on before they are exposed to disease, and ensuring circulating maternal antibodies do not eliminate the vaccine before the child's own immune system is able to develop an immune response. By delivering the RSV vaccine intranasally and avoiding the needle, the vaccine then initiates the immune response in the mucous membranes of the nose and lungs before maternal antibodies in the blood are able to inactivate the vaccine. Pan-Provincial Vaccine Enterprise Inc. is backing the research through Phase I clinical trials.[16]

The path to better public health is paved with research and technological achievements, but governments also hold a significant piece of the pie.

Electrical currents. At the University of Oslo as well, researchers are finding that not all vaccine components must come from the needle. Their DNA vaccine studies do not require adjuvants to incite an immune response. Instead, they have developed a new technology that applies an electrical current to the injection site immediately after an injection of DNA code. It is this electrical pulse that results in skin cells absorbing the DNA and initiating the DNA-coded response — production of what they call Vaccibody molecules. This proprietary vaccine platform increases the antibody and T-cell responses, and could potentially be applied to a plethora of different diseases, as long as targeted antigens have a protein structure.[17]

Bar coding. Clinicians and patients at the point of care all will benefit from recent advancements in bar coding technology and updates to FDA requirements addressing vaccine labeling and documentation. In 2004, the FDA published guidance requiring industry to use linear bar coding containing National

Drug Code (NDC) information on all vaccine products.[18] But space constraints in the capacity of linear bar codes mean additional information such as expiration date and lot number cannot be included and must be recorded manually by the administering clinician into a patient record in order to meet requirements of the National Childhood Vaccine Injury Act of 1986. An updated August 2011 FDA guidance[19] allows for manufacturers to request a linear bar code waiver in favor of alternative symbologies such as 2D bar codes, which can store significantly more data.

With a simple scan, clinicians can interface with electronic medical records and immunization registries, reducing staff time spent on documentation and improving data accuracy. Staff also will benefit from advancements in vaccine inventory reconciliation and improved patient safety. Accurate electronic tracking of vaccine lot numbers will help identify safety concerns with specific lots, allow for ease in patient identification in the case of supply recall, and significantly improve vaccine adverse events tracking.[20] The CDC is currently engaged in a 2D vaccine bar coding pilot project among 10 CDC immunization grantees and two vaccine manufacturers, Sanofi Pasteur (for use with Menactra and pediatric DT vaccines) and GlaxoSmithKline (for use with adult Havrix vaccine).[21]

Building a Future Together

The path to better public health is paved with research and technological achievements, but governments also hold a significant piece of the pie. Challenges experienced during delays of the 2009 H1N1 pandemic vaccine production have highlighted the need to move beyond traditional egg-based production technology, and to accelerate where possible the vaccine development, manufacturing and administration processes — a priority for the U.S. government as well. A 2011 report from the U.S. Government Accountability Office finds that from 2005 to March 2011, the Department of Health and Human Services (HHS) and the Department of Defense (DOD) have cumulatively awarded nearly $2.1 billion for the development of alternative vaccine technologies (such as cell-based and recombinant technologies and adjuvants research). The report also examines challenges to development and licensure identified by stakeholders, including high research and development costs and insufficient FDA guidance documents, and it outlines proactive HHS steps to address these issues.[22]

Moving forward. HHS has made its plans for improvement known, and it is working to enhance the FDA's staff expertise and to facilitate the review of licensing applications for new influenza vaccines using alternative technologies.[23] The FDA continues to engage stakeholders on multiple levels, particularly through its Vaccines and Related Biological Products Advisory Committee (VRBPAC).

The VRBPAC meeting on February 29 of this year specifically addressed the challenges associated with licensure pathways of pandemic influenza vaccines, as well as the limitations in demonstrating pandemic vaccine effectiveness (a requirement for licensure). Quite simply, in order for a pandemic influenza vaccine to be licensed, the applicant must demonstrate data that support both safety and effectiveness. While it is possible to evaluate the safety and immunogenicity of a pandemic influenza vaccine candidate in a pre-pandemic period, it is not feasible for manufacturers to conduct clinical endpoint efficacy studies when the pandemic strain is not yet circulating. The committee seemed open to allowing inferred effectiveness of a pandemic influenza vaccine from the efficacy of a previously approved seasonal influenza vaccine made by the same manufacturer and process.[24] Stay tuned for further developments and guidance.

Yet It All Comes Back to Utilization

Of course, even when all the pieces come into play and modern medicine is able to tackle a significant health problem through achievements in immunization, sometimes the biggest challenge is making use of the resources we have — an issue the Indiana State Health Department knows all too well following a measles outbreak in February. The city of Indianapolis, host to the 2012 Super Bowl, made national headlines this year when it was discovered a highly infectious individual with measles had attended several activities at the nonticketed Super Bowl Village[25] (a three-block outdoor festival in downtown Indianapolis with estimated attendance in the hundreds of thousands). While the state was not able to directly

link any of its subsequent 16 confirmed cases that month to exposure at the Super Bowl Village, the entire episode highlights the multiple opportunities for disease transmission in public settings, and the importance of maintaining high measles-mumps-rubella (MMR) vaccine coverage rates to protect U.S. citizens from measles importations and transmissions both domestically and abroad.

There is room for improvement: Data from the National Immunization Survey indicate that nearly one in 10 children has not received the MMR vaccine by age 19 months to 35 months.[26] (ACIP recommends the first MMR vaccination at 12 months.) Efficacy data show that more than 95 percent of people receiving even just the first MMR will develop immunity to all three diseases.[27]

States are phasing in grade-specific school entry vaccination requirements, and recently the National Association of County and City Health Officials published a policy statement in support of eliminating personal belief exemptions for immunization requirements for childcare and school attendance (the brief did not address religious or medical exemptions).[28] On the whole, state and federal agencies seem poised and ready to engage in continued stakeholder dialogue and to accommodate advancements in research. Time will tell if immunization coverage rates and vaccine regulatory approval processes for vaccines will reap the benefits. ❖

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References

1 Centers for Disease Control and Prevention. Notes from the Field: Severe Hand, Foot, and Mouth Disease Associated with Coxsackievirus A6 — Alabama, Connecticut, California, and Nevada, November 2011–February 2012. *Morbidity and Mortality Weekly Report* 2012; 61(12);213-214. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/mm6112a5.htm?s_cid=mm6112a5_w.

2. Inviragen. Inviragen Hand, Foot and Mouth Disease Vaccine Generates Immune Responses in 100% of Study Participants [press release], Mar. 12, 2012. Accessed at www.inviragen.com/press/INV21%20top-line%20Phase%201%20US%20edition.pdf.

3. Magill, B. Inviragen Vaccine for Hand, Foot and Mouth Disease Ready for Next Test. *The Coloradoan*, Mar. 14, 2012. Accessed at www.coloradoan.com/article/20120314/BUSINESS/203140329/Inviragen-vaccine-hand-foot-mouth-disease-ready-next-tes.

4. Purlain, T. PaxVax Announces Progress on Single-Dose Oral Cholera Vaccine. *Vaccine News Daily*, Mar. 20, 2012. Accessed at vaccinenewsdaily.com/vaccine_development/318266-paxvax-announces-progress-on-single-dose-oral-cholera-vaccine/.

5. University of Melbourne. Malaria Parasite Goes Bananas Before Sex. ScienceDaily, Feb. 14, 2012. Accessed at www.sciencedaily.com /releases/2012/02/120214100940.htm.

6. Vical. Novel Transmission-Blocking Malaria DNA Vaccine Candidate Uses Vical's Vaxfectin Adjuvant [press release]. Distributed by GlobeNewswire, Mar. 28, 2012. Accessed at www.marketwatch.com/story/novel-transmission-blocking-malaria-dna-vaccine-candidate-uses-vicals-vaxfectinr-adjuvant-2012-03-28.

7. Liu, MA. DNA Vaccines: An Historical Perspective and Review to the Future. *Immunological Reviews*, 2011, Vol. 239: 62-84.

8. Centers for Disease Control and Prevention. Selecting the Viruses in the Seasonal Influenza (Flu) Vaccine. Questions & Answers. Accessed at www.cdc.gov/flu/professionals/vaccination/ virusqa.htm.

9. NIH/National Institute of Allergy and Infectious Diseases. Priming with DNA Vaccine Makes Avian Flu Vaccine Work Better: Proof of Concept for Universal Influenza Vaccine. ScienceDaily, Oct. 3, 2011. Accessed at www.sciencedaily.com/releases/2011/10/111003195258.htm.

10. Emory University. HIV/AIDS Vaccine Shows Long-Term Protection against Multiple Exposures in Non-Human Primates. ScienceDaily, Mar. 7, 2012. Accessed at www.sciencedaily.com/releases/2012/03/120307185131.htm.

11. Coridon. Coridon Demonstrates 100% Protection against Herpes Simplex Virus 2 using DNA Vaccine [press release]. Oct. 11, 2011. Accessed at www.coridon.com/files/Coridon_HSV-2_Vaccine_Announcement_11_October_2011.pdf.

12. National Cancer Institute. Cancer Vaccines. Accessed at www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines.

13. Centers for Disease Control and Prevention. Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males — Advisory Committee on Immunization Practices (ACIP), 2011. *Morbidity and Mortality Weekly Report* 2011; 60(50);1705-1708.

14. Mayo Clinic. Mayo Clinic Researchers Building Melanoma Vaccine to Combat Skin Cancer [press release]. Mar. 19, 2012. Accessed at www.mayoclinic.org/news2012-rst/6765.html.

15. Doheny, K. Early Study Hints That Breast Cancer Vaccine Might Work. *U.S. News & World Report*, Apr. 2, 2012. Accessed at health.usnews.com/health-news/news/articles/2012/04/02/early-study-hints-that-breast-cancer-vaccine-might-work.

16. University of Saskatchewan. Researchers Close In on Vaccine to Protect Babies. ScienceDaily, Mar. 29, 2012. Accessed at www.sciencedaily.com/releases/2012/03/120329101301.htm.

17. University of Oslo. Targeted DNA Vaccine Using an Electric Pulse. ScienceDaily, Jan. 30, 2012. Accessed at www.sciencedaily.com/releases/2012/01/120130093649.htm.

18. Bar Code Label Requirement for Human Drug Products and Biological Products: A Rule by the Food and Drug Administration. 69 Fed. Reg. 9120 (2004). Accessed at https://www.federalregister.gov/articles/2004/02/26/04-4249/bar-code-label-requirement-for-human-drug-products-and-biological-products#p-3.

19. Food and Drug Administration. Guidance for Industry: Bar Code Label Requirements — Questions and Answers, August 2011. Accessed at www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM267392.pdf.

20. 2D Barcode Vaccine Manufacturers Forum. (2012). Accessed at www.2dbarcodepilot.com/manuindex.php.

21. Gerlach, K. Barcoding: An Overview and Progress Update [presentation]. 2012 National Immunization Conference, Wednesday, Mar. 28, 2012. Accessed at cdc.confex.com/cdc/nic2012/webprogram/Paper30223.html.

22. U.S. Government Accountability Office. Influenza Vaccine. Federal Investments in Alternative Technologies and Challenges to Development and Licensure. GAO-11-435, Jun 27, 2011. Accessed at www.gao.gov/assets/330/320154.pdf.

23. The Vaccines and Related Biological Products Advisory Committee (VRBPAC). February 29, 2012 Committee Meeting Transcript. Accessed at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM296459.pdf.

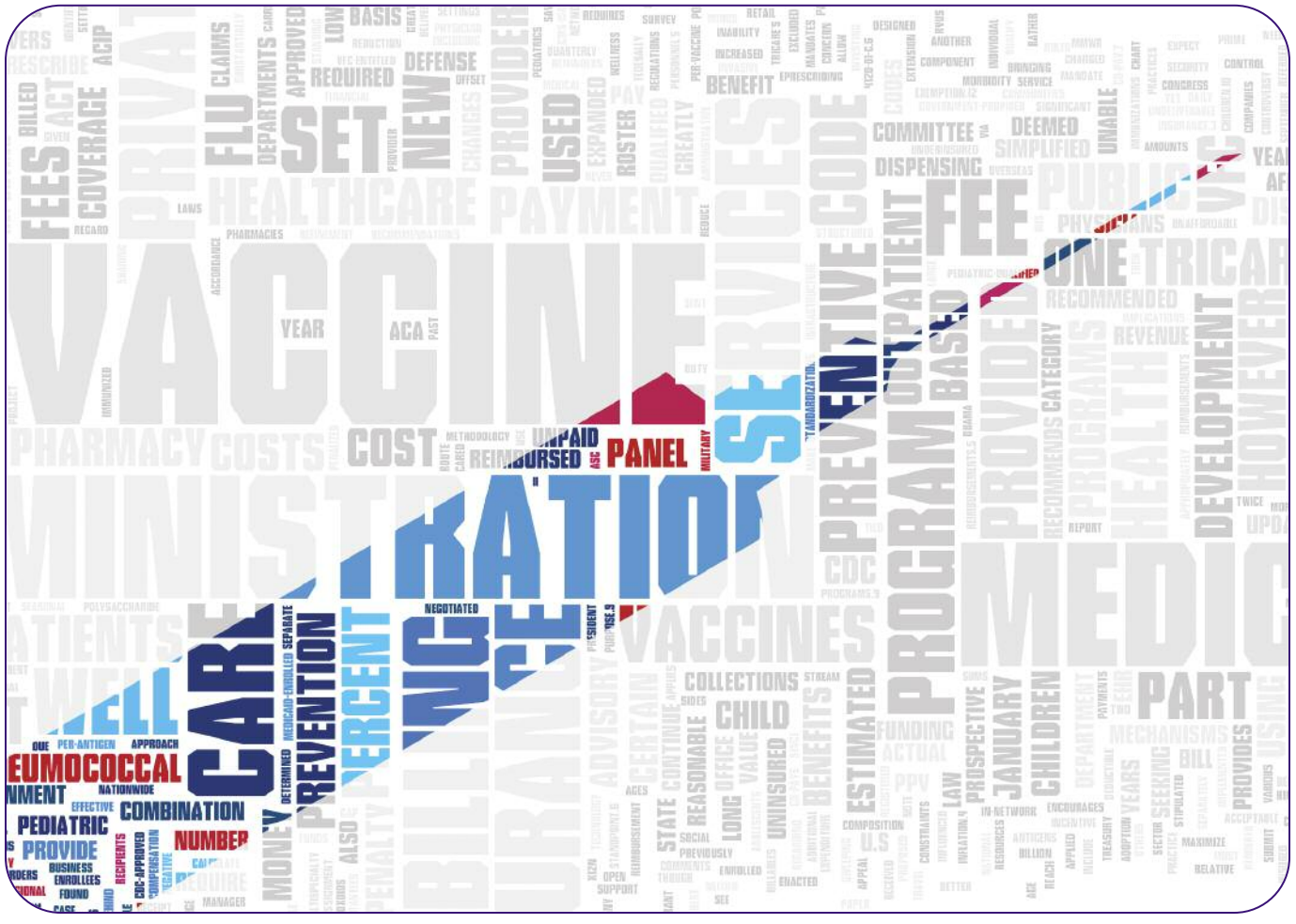
24. The Vaccines and Related Biological Products Advisory Committee (VRBPAC). February 29, 2012 Committee Meeting Summary Minutes. Accessed at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm288695.htm.

25. Indiana State Department of Health. 16 Confirmed Cases of Measles in Central Indiana [press release]. Feb. 24, 2012. Accessed at www.in.gov/activecalendar/EventList.aspx?fromdate=2/1/2012&todate=2/29/2012&display=Month&type=public&eventidn=53452&view=EventDetails&information_id=107209.

26. Centers for Disease Control and Prevention. National and State Vaccination Coverage Among Children Aged 19-35 Months. United States, 2010. *Morbidity and Mortality Weekly Report* 2011, 60(34);1157-1163. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a2.htm?s_cid=mm6034a2_w.

27. Centers for Disease Control and Prevention. Measles — Q&A about Disease & Vaccine. Accessed at www.cdc.gov/vaccines/vpd-vac/measles/faqs-dis-vac-risks.htm.

28. National Association of County and City Health Officials. Eliminating Personal Belief Exemptions from Immunization Requirements for Child Care and School Attendance. Statement of Policy. Approved by NACCHO Board of Directors July 2011. Accessed at www.naccho.org/advocacy/positions/loader.cfm?csModule=security/getfile&PageID=204056.



The ACA's Impact on Vaccine Administration and Reimbursement

By Amy Scanlin, MS

Healthcare professionals who provide preventive vaccines to patients will be affected in many ways, including an increase in patients, as well as changes in billing and reimbursement.

The Affordable Care Act enacted by President Obama in 2010 not only provides sweeping coverage for Americans who are uninsured or underinsured, but it has implications for healthcare providers as well. The regulations set forth by the U.S. Departments of Health and Human Services (HHS), Labor and the Treasury require that any individual or family enrolled in a new health insurance plan on or after September 23, 2010, be provided the recommended preventive services without a deductible, co-payment or co-insurance. By 2013, the number of Americans who will qualify for these

benefits is estimated to be 78 million, and it is estimated that 88 million overall will eventually benefit from the new policy.

This preventive care access, without co-pays or cost sharing (as long as the care is provided by an in-network provider), now mandates Advisory Committee on Immunization Practices (ACIP) recommended vaccines.[1] The ACIP, an independent advisory panel, makes these recommendations to the U.S. Centers for Disease Control and Prevention (CDC), and in the past, it has greatly influenced the vaccine coverage provided by both private and public insurers. The new mandate will require increased funding, though the cost expenditure is expected to be offset by savings with disease prevention.

Congress has appropriated large sums of money to fund these initiatives, including $1 billion in funding for wellness and prevention programs, with $300 million of that money set aside for the Section 317 immunization program,[2] which provides federal money to vaccine infrastructure programs at the federal, state and local levels.

What does this mean for healthcare providers? They will see an increase in the number of patients seeking preventive care, a change in how they can bill for that care, as well as changes in how care is reimbursed by government and private insurance.

Outpatient Settings

It is estimated that Medicaid covers between 40 percent and 90 percent of patients seeking immunizations, and private insurance covers 7 percent to 55 percent.[3] To maximize an immunization's reach, the ACA recommends that only government-provided vaccines be used for Medicare patients, and private-purchase vaccines be used for those with private insurance carriers for both the billing of the vaccine itself, as well as the administration fee. This approach is designed to preserve government resources for those with public insurance, as well as open a revenue stream from patients with private insurance.[3]

It was found in a 2001 survey that 70 percent of health departments did not bill private insurance for the administration and delivery of vaccines,[3] which means a significant loss in revenue, especially since Medicare payment updates lag behind medical inflation.[4] However, under the ACA, appropriately billed immunization services will be reimbursed by both private and public insurance, and administrative standardizations such as using roster billing, chart reminders and standing orders may substantially reduce the administration costs of delivery.

The roster billing methodology was developed to allow for simplified billing of the influenza vaccine and pneumococcal polysaccharide vaccine (PPV), and it does not provide for office services or any other administration fees. With these rosters, one claim can be submitted to Medicare daily for all flu and PPV vaccine recipients, provided two or more Medicare beneficiaries are immunized. Both paper billing (a separate CMS-1500 claim form must be submitted) and electronic billing (using HIPAA-adopted ASC X12N 837 claim standard) are acceptable to submit for Medicare Part B reimbursements.[5]

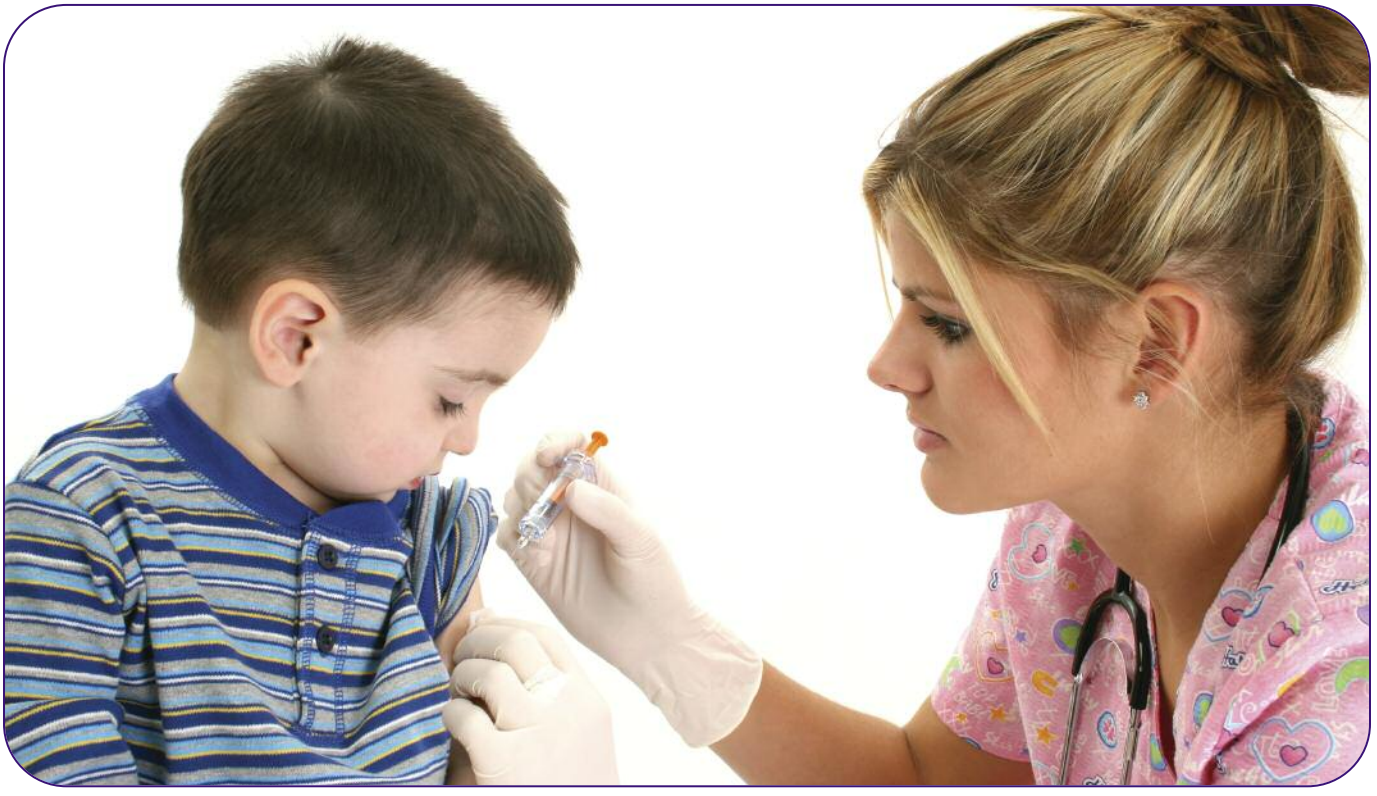
The Centers for Medicare and Medicaid Services (CMS) has approved Medicare reimbursement for only a few outpatient services deemed to be a reasonable cost, one of which is the flu vaccine. Yet, because of the fluctuations in composition of the flu vaccine from year to year, the CMS is unable to set a prospective payment because those fluctuations in yearly costs could make the vaccine unaffordable to hospitals and outpatient service centers and, thus, undeliverable from a business standpoint.[6] However, because CMS pays for the flu vaccine at a reasonable rate, it does not fall under the set Outpatient Prospective Payment System (OPPS) rates. And, the flu vaccine, which falls under the Category 1 CPT code set (which identifies the services rendered), will continue in 2012 as code 4120-01-C.[6] Category 1 CPT vaccine codes are updated twice yearly and implemented in the January and July quarterly updates.

By 2013, the number of Americans who will receive these benefits is estimated to be 78 million.

Department of Defense Pharmacy Benefits Expanded

The Department of Defense recently authorized Tricare retail network pharmacies to administer all Tricare-approved vaccines, in accordance with state laws, in the pharmacy setting, bringing Tricare in line with policies of many insurance companies. Previously, only three vaccines — seasonal influenza, H1N1 and the pneumococcal vaccines — were authorized. Now, Tricare basic and prime enrollees are authorized to receive CDC-approved vaccines as published in the *Morbidity and Mortality Weekly Report* (MMWR) for those ages 6 months and older, as well as vaccines required for overseas travel as part of active duty military personnel's assignment.

Tricare also expanded the vaccines approved by Medicare Part B, which was limited to invasive pneumococcal disease, hepatitis B and influenza. As part of Tricare's pharmacy benefit, the claims processing of vaccine administration will be greatly simplified. Because the negotiated fee by the Tricare pharmacy benefits manager is lower than that of the nationwide administration fee for Medicare Part B vaccines, the patient will have a $0 co-pay.[7]



Pediatrics

CMS revised the reporting of immunization administration for pediatric patients in order to better align with the evolving best practice model of delivering combination vaccines. Effective January 1, 2011, the reporting and payment for these services was structured on a per-antigen basis rather than a per-vaccine (combination of toxoids) basis as it was in prior years.

Further, based on negative comments regarding this CMS ruling's proposed work, CMS referred CPT codes 90460 and 90461 (immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health professional; each additional vaccine/antigen component) to the multispecialty refinement panel for further review. That panel ruled at work relative value units (RVUs) — used to calculate compensation for physicians using a set formula tied to various services — of 0.17 for CPT Code 90460 and 0.15 for CPT code 90461.[8]

The National Vaccine Advisory Committee (NVAC) recommends that the CDC provide support for the development of billing mechanisms for insured children and adolescents who are cared for in the public sector, as well as technical assistance for the development of these billing mechanisms. It also encourages that any reimbursements received be reinvested in local immunization programs.[9] The CDC is investing funds for the development of billing programs, which are in development in certain communities, through a Billables Grant Project. In 2011, the Affordable Care Act Prevention and Public Health Fund provided $13 million in 2011 to grantees for this purpose.[9]

CMS revised the reporting of immunization administration for pediatric patients in order to better align with the evolving best practice model of delivering combination vaccines.

Administration Fees

The CMS deemed in 1994 that lower administration fees should be set for the Vaccines For Children (VFC) program. It further stipulated in the Social Security Act, Section 1928(c)

(2) (C) (ii), that administration fees may be charged for qualified pediatric vaccines under the VFC program as long as that fee "in the case of a federally vaccine-eligible child does not exceed the costs of such administration (as determined by the Secretary based on actual regional costs for such administration)."[10] However, a vaccine-eligible child may not be denied a pediatric-qualified vaccine due to inability to pay the administration fee. Administration fee caps are for VFC children only and not for those who fall under private insurance programs.

One note of concern to physicians with regard to the receipt of Medicare payments is the new ePrescribing penalty that took effect January 1, 2012.

Another rule by the CMS in 2012 requires that vaccine administration fees, which are billed separately from the dispensing of a vaccine, be excluded from cost-sharing reductions in the coverage gap, or actual cost minus dispensing and administration fees.[11] Providers administering vaccines under the VFC program should use code 90460. Code 90461 is used for a vaccine with multiple antigens and should be given a $0 value for a child covered under the VFC program. This applies to both Medicaid-enrolled and non-Medicaid-enrolled VFC-entitled children.[10] And, providers may not send unpaid vaccine administration bills to collections should a parent be unable to pay. However, an unpaid office visit fee may be sent to collections.

Medicare ePrescribe Penalty

One note of concern to physicians with regard to the receipt of Medicare payments is the new ePrescribing penalty that took effect January 1, 2012. This penalty states that those who do not successfully participate in the ePrescribe program and who have not successfully applied for an extension or exemption will be penalized with a 1 percent payment reduction for *all* Medicare claims based on the 2012 fee schedule amounts.

Certain exemptions include being registered to participate in the Medicare or Medicaid Electronic Health Record (EHR) Incentive Program in which the adoption of certified EHR technology was required by October 1, 2011, as well as others. And, there is no appeal process to this request for exemption.[12]

Preventive Healthcare Needed for All

The changes to the new healthcare law continue to unfold, and one can expect controversy on both sides based on perception of the law. One thing is certain, however: The need to care for those who have financial constraints, some severe, has never been greater. As such, preventive care provided to those who are under- and uninsured will enable preventive healthcare for all.[3] ❖

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References

1. Newsroom Factsheet: The Affordable Care Act and Immunization. Healthcare.gov. Accessed at www.healthcare.gov/news/factsheets/2010/09/affordable-care-act-immunization.html.
2. American Medical Association. Current Topics in Advocacy: American Recovery and Reinvestment Act of 2009 (ARRA). Accessed at www.ama-assn.org/ama/pub/advocacy/current-topics-advocacy/additional-advocacy-topics/american-recovery-and-investment-act.page?.
3. Centers for Disease Control and Prevention. Billables Project for Health Department Immunization Services Reimbursement. Accessed at www.cdc.gov/vaccines/spec-grps/prog-mgrs/billables-project/default.htm.
4. American College of Physicians. Coding and Billing for Internists' Services: Challenges and Opportunities. Accessed at www.acponline.org/running_practice/practice_management/payment_coding/coding.
5. American College of Physicians. Running a Practice: Payment Coding and Billing of Vaccines. Accessed at www.acponline.org/running_practice/practice_management/payment_coding/coding/billvaccines.pdf.
6. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medicare and Medicaid Programs: Hospital Outpatient Prospective Payment; Ambulatory Surgical Center: Rules and Regulations (PPV) vaccines, Payment; Hospital Value-Based Purchasing Program; Physician Self-Referral; and Patient Notification Requirements in Provider Agreements. Federal Register, Vol. 76, No. 230, page 74,328, Wednesday, Nov. 30, 2011.
7. Department of Defense, Office of the Secretary. Civilian Health and Medical Program of the Uniformed Services (CHAMPUS)/TRICARE: Inclusion of Retail Network Pharmacies as Authorized TRICARE Providers for the Administration of TRICARE Covered Vaccines, Rules and Regulations. Federal Register, Vol. 76, No. 134, Wednesday, Jul. 13, 2011, Page 41,063.
8. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Medicare Program: Payment Policies Under the Physician Fee Schedule, Five-Year Review of Work. Federal Register, Vol. 76, No. 228, Monday, Nov. 28, 2011, Page 73,154.
9. Centers for Disease Control and Prevention. Billables Project for Health Department Immunization Services Reimbursement: Developing Mechanisms for Billing. Accessed at www.cdc.gov/vaccines/spec-grps/prog-mgrs/billables-project/default.htm.
10. Centers for Disease Control and Prevention. Billables Project for Health Department Immunization Services Reimbursement: Vaccines Program Administration Fees. Accessed at www.cdc.gov/vaccines/programs/vfc/projects/faqs-doc.htm#admfees.
11. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medicare Program, Payment Policies Under the Physician Fee Schedule, and Other Revisions to Part B CY 2012. Federal Register, Vol. 76, No 138, Tuesday, Jul. 19, 2011.
12. American College of Physicians. Act Now to Avoid the Medicare ePrescribing Penalty That Starts January 1, 2012. Accessed at www.acponline.org/running_practice/technology/eprescribing/avoid-erx-penalty-tip.pdf.

Kogenate® FS:

The brand you know with

Kogenate® FS with BIO-SET® offers:

- *Grab & Go* packaging contains materials necessary for safe and fast reconstitution

- BIO-SET® reconstitution system with user-friendly features
- Wide range of vial sizes for flexibility in preparing your dose
- Small diluent volumes make reconstitution fast and easy

250 IU	500 IU	1000 IU	2000 IU	3000 IU
2.5-mL Diluent			5.0-mL Diluent	

Ask your doctor if **Kogenate® FS** is right for you.

- **INDICATIONS**
  Kogenate® FS, antihemophilic factor (recombinant), is a recombinant factor VIII treatment indicated for the control and prevention of bleeding episodes and peri-operative management in adults and children (0-16 years) with hemophilia A. **Kogenate® FS** is also indicated for routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no preexisting joint damage.

Bayer HealthCare
Pharmaceuticals

the convenience you need

Kogenate® FS can be stored at room temperature (up to 77°F) **for up to 1 year***

*Store Kogenate® FS at 36°F to 46°F for up to 30 months from the date of manufacture. Within this period, Kogenate® FS may be stored for a period of up to 12 months at temperatures up to 77°F. The starting date of room temperature storage should be clearly recorded on the unopened product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature (up to 12 months) or the expiration date on the product vial, whichever is earlier.

For more information, visit **kogenatefs.com**.

IMPORTANT SAFETY INFORMATION

The most serious adverse reactions are systemic hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to AHF. The most common adverse reactions observed in clinical trials were inhibitor formation in previously untreated or minimally treated patients, skin-associated hypersensitivity reactions, infusion site reactions, and central venous access device (CVAD) line-associated infections.

Kogenate® FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

For important risk and use information, please see brief summary of Prescribing Information on the following page or visit **kogenatefs.com/prescribing-information.jsp**.

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.

Kogenate® FS

antihemophilic factor (recombinant)

with BIO-SET®

needleless reconstitution system

Real Life...Real Protection

Kogenate FS (Antihemophilic Factor [Recombinant] Formulated with Sucrose) For Intravenous Use, Lyophilized Powder for Reconstitution with BIO-SET, a needle-less self-contained reconstitution system

Initial U.S. Approval: 1993

BRIEF SUMMARY - CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

Kogenate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

1.2 Peri-operative Management

Kogenate FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

1.3 Routine Prophylaxis in Children with Hemophilia A with No Pre-existing Joint Damage

Kogenate FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.

Kogenate FS is not indicated for the treatment of von Willebrand's disease.

4 CONTRAINDICATIONS

Kogenate FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to Kogenate FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Kogenate FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed. *[See Warnings and Precautions (5.4).]*

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic-type hypersensitivity reactions including anaphylaxis have been reported with Kogenate FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Discontinue Kogenate FS if symptoms occur and seek immediate emergency treatment.

Kogenate FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests.[6] Inhibitors have been reported following administration of Kogenate FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed.*[See Warnings and Precautions (5.4).]*

5.4 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated. *[See Dosage and Administration (2).]*
- Monitor for development of factor VIII inhibitors. Perform assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of Kogenate FS. Use Bethesda Units (BU) to titer inhibitors.
  - If the inhibitor is less than 10 BU per mL, the administration of additional Kogenate FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.

Adequate hemostasis may not be achieved if Inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Kogenate FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF.

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in previously untreated patients (PUPs) and minimally treated patients (MTPs), skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for intravenous administration.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Kogenate FS (0.1%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 3 below.

Table 3 Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of ≥ 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01

SOC = System Organ Class

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with pediatric PUPs and MTPs, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Kogenate FS (0.3%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 4 below.

Table 4 Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of ≥ 4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)[a]	N/A
General Disorders and Administration Site Conditions	Infusion site reactions	4 (6.6)	0.04

SOC = System Organ Class

a) *Denominator for *de-novo* inhibitors is N=60, since one patient had a pre-existing inhibitor.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study with pediatric MTPs treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced adverse events over the study duration. Adverse events were not assessed for their relationship with Kogenate FS.

Table 5 Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, Catheter removal	19 (59)	18[a] (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)

SOC = System Organ Class

a) Three patients from the enhanced episodic arm had catheter removal.

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a pre-existing inhibitor. In the other 72 patients, followed over 4 years, no de-novo inhibitors were observed.

In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer[1] (>5BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the Joint Outcome Study with Kogenate FS,[5] de-novo inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients

developed high titer[1] (>5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Kogenate FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Kogenate FS, cases of serious allergic/ hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates.

The following table represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Table 6 Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion site reaction Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity reactions

SOC = System Organ Class

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with Kogenate FS. It is also not known whether Kogenate FS can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Kogenate FS should be used during pregnancy only if clinically needed.

8.2 Labor and Delivery

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. Kogenate FS should be used only if clinically needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Kogenate FS is administered to nursing mothers. Kogenate FS should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients. Children in comparison to adults present higher factor VIII clearance values and thus lower recovery of factor VIII. This may be explained by differences in body composition[7] and should be taken into account when dosing or following factor VIII levels in such a population. *[See Clinical Pharmacology (12.3).]* Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage. *[See Clinical Studies (14.3).]*

8.5 Geriatric Use

Clinical studies with Kogenate FS did not include patients aged 65 and over. Dose selection for an elderly patient should be individualized.

13 NONCLINICAL TOXICOLOGY

Preclinical studies evaluating Kogenate FS in hemophilia A with mice, rats, rabbits, and dogs demonstrated safe and effective restoration of hemostasis. Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effect for Kogenate FS in laboratory animals.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with Kogenate FS to assess its mutagenic or carcinogenic potential and impairment of fertility. Kogenate FS has been shown to be comparable to the predecessor product with respect to its biochemical and physiochemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, the predecessor product and Kogenate FS would be expected to have equivalent mutagenic and carcinogenic potential.

The predecessor product did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation with the predecessor product in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that the predecessor product did not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed due to the immune response to heterologous proteins in all non-human mammalian species.

17 PATIENT COUNSELING INFORMATION

See Patient Product Information and Instructions for Use

Advise patients to report any adverse reactions or problems following Kogenate FS administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions have been reported with Kogenate FS. Warn patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.
- In clinical studies with Kogenate FS, a 15% incidence of inhibitor development was observed in PUPs/MTPs and zero de-novo inhibitors were observed with the PTPs. Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their healthcare provider prior to travel. While traveling advise patients to bring an adequate supply of Kogenate FS based on their current regimen of treatment.

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Influenza

Past, Present and Future

The flu virus has claimed millions of lives. Examining past outbreaks, researching strain mutations and monitoring global epidemic statistics may help us better predict and possibly prevent future pandemics.

By Trudie Mitschang

It was a pandemic unlike any other. The 1918-19 influenza outbreak at the end of World War I killed more people than the Great War itself, claiming the lives of as many as 50 million men, women and children. The Spanish flu has been called the most devastating epidemic in recorded world history, with more people dying of influenza in a single year than in four years of the black death bubonic plague.[1] A global disaster of this magnitude is hard to imagine today, especially when so many people view the flu as little more than a very bad cold. History, unfortunately, contradicts that cavalier point of view. And when it comes to flu, experts believe history may have a tendency to repeat itself.

Understanding Influenza

Influenza, commonly known as the flu, is actually a general name given to any one of a number of viruses that can cause serious illness. There are three types of the flu: influenza A, B and C — each one with its own viral strain that replicates and changes independently from the other types. Seasonal strains of human influenza change constantly, which is why people can catch the flu multiple times. It is also why the flu shot is the only vaccination that is continually updated; influenza is a rare type of virus that is constantly mutating.

Each year, a certain strain becomes prevalent and strikes, typically between the months of October and March, a time period now referred to as flu season. When a flu outbreak occurs in one country or region, it is referred to as an epidemic, whereas outbreaks around the world are called pandemics. Because of the global nature of our world today and the speed and frequency of international air travel, the likelihood of another great pandemic is not farfetched; a flu strain that originates in China, for example, could land in New York in less than a day's time, infecting everyone en route.

Large-scale events that create a draw for tourists are a concern for those who study flu outbreaks. A recent report suggests that the 2012 Summer Olympic Games pose an extreme threat for a serious flu outbreak within the United Kingdom as an extra 5.3 million tourists descend upon the area. The report, which was conducted by global risk research firm Maplecroft, revealed that such a large influx of visitors during the summer months coupled with an increase in the use of public transportation will exacerbate the already significant risk to this particular region of the world.[2]

A Viral Link to the Past

The flu virus mutates and changes each year, but many researchers believe the specific strain that wreaked worldwide havoc in the mid-1900s may have birthed a viral dynasty with ramifications that can still be seen today. According to scientists from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, it may even be linked to the now infamous H1N1 outbreak of 2009. In an article published online by the *New England Journal of Medicine*, authors Anthony S. Fauci, MD, Jeffery K. Taubenberger, MD, PhD, and David M. Morens, MD, argue that we have lived in an influenza pandemic era since 1918, and they go on to describe how the H1N1 virus that circled the globe in 2009 was merely another manifestation of the same viral family that killed millions nearly a century ago.[3] "The 1918-1919 influenza pandemic was a defining event in the history of public health," said Dr. Fauci, director of NIAID and a co-author of the study. "The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for nine decades."[4]

The study went on to explain that all flu viruses have eight genes, including two that are coded to produce the proteins hemagglutinin (H) and neuraminidase (N) that allow the virus to enter a host cell and spread from cell to cell. There are 16 H subtypes and nine N subtypes, making 144 possible HN combinations. But only three — H1N1, H2N2 and H3N2 — observed to date are fully adapted for infecting humans. Other combinations such as the H5N1 bird flu virus have only occasionally infected small numbers of humans. "The eight influenza genes can be thought of as players on a team: Certain combinations of players may arise through chance and endow the virus with new abilities, such as the ability to infect a new type of host," said study co-author David Morens. "That is likely what caused the 1918 pandemic."

The Fight Against Flu

From a public health perspective, the flu has become easier to manage in recent decades. Improved healthcare conditions, greater understanding of the virus itself, more sophisticated means of communicating the risks of flu and, of course, the creation of the flu vaccine all have contributed to this achievement.

When it comes to flu, experts believe history may have a tendency to repeat itself.

The influenza virus was first identified in the early 1930s, and scientists developed a working vaccine by the 1940s, which was used on soldiers during World War II. At the time of the great pandemic during the first World War, the flu virus and its means of transmission were not familiar to the medical community, and there was no such thing as a vaccine. By 1957, the time of the next major flu outbreak, doctors had developed an arsenal of vaccines and were able to alert the public to the risks of not being vaccinated. Casualties were still high — 70,000 people in the U.S. alone.[5]

The next large flu outbreak in 1968 was known as the Hong Kong flu. Thanks to ample supplies of vaccines and public compliance to get vaccinated, only 34,000 people died in the U.S. as a result.[6] These declining mortality rates may have contributed to the growing public sentiment that the flu is not that deadly, but the appearance of several new flu strains in recent years — including the H5N1 "avian flu" strain in the late 1990s — illustrates the challenges faced annually by researchers trying to track, contain and develop vaccines for the ever-changing virus known as influenza.

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IMPORTANT SAFETY INFORMATION

INDICATION

Fluzone Intradermal vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 18 through 64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

SAFETY INFORMATION

The most common local and systemic adverse reactions to Fluzone Intradermal vaccine include erythema, induration, swelling, pain, and pruritus at the vaccination site; headache, myalgia, and malaise. Other adverse reactions may occur. Fluzone Intradermal vaccine should not be administered to anyone with a severe allergic reaction (eg, anaphylaxis) to any vaccine component, including egg protein, or to a previous dose of any influenza vaccine. The decision to give Fluzone Intradermal vaccine should be based on the potential benefits and risks, especially if Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine. Vaccination with Fluzone Intradermal vaccine may not protect all individuals.

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

CPT®[a] Code: 90654

[a] CPT = Current Procedural Terminology is a registered trademark of the American Medical Association.

Fluzone Intradermal vaccine is manufactured and distributed by Sanofi Pasteur Inc.

To order Fluzone Intradermal vaccine or learn more about the Fluzone Vaccine Partners Program, please log onto **VaccineShoppe.com** or call **1-800-VACCINE** (1-800-822-2463).

References: 1. Laurent PE, Bonnet S, Alchas P, et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. *Vaccine*. 2007;25:8833-8842. **2.** Immunization Action Coalition. Administering vaccines: dose, route, site, and needle size. http://www.immunize.org/catg.d/p3085.pdf. Accessed November 8, 2011.

SANOFI PASTEUR

Fluzone® Intradermal (Influenza Virus Vaccine)
2011-2012 Formula

℞ only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATION AND USAGE

Fluzone Intradermal vaccine is an inactivated influenza virus vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Fluzone Intradermal is approved for use in persons 18 through 64 years of age.

DOSAGE AND ADMINISTRATION

Dosage and Schedule

The dose, schedule, and route of administration for Fluzone Intradermal is presented in Table 1.

Table 1: Fluzone Intradermal

	Dose/Route	Schedule
18 through 64 years of age, any vaccination status	0.1 mL/Intradermal	1 dose

Administration

Inspect Fluzone Intradermal microinjection system visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered.

Gently shake the microinjection system before administering the vaccine.

1. Remove Needle Cap: Remove the needle cap from the micro-injection system.

2. Hold Microinjection System Between Thumb and Middle Finger: Hold the system by placing the thumb and middle finger only on the finger pads, the index finger remains free. Do not place fingers on the windows.

3. Insert Needle Rapidly and Perpendicular to the Skin: Insert the needle perpendicular to the skin, in the region of the deltoid, in a short, quick movement.

4. Inject Using the Index Finger: Once the needle has been inserted, maintain light pressure on the surface of the skin and inject using the index finger to push on the plunger. Do not aspirate.

5. Remove Needle from Skin and Activate Needle Shield by Pushing Firmly on Plunger: Remove the needle from the skin. Direct the needle away from you and others. With the same hand, push very firmly with the thumb on the plunger to activate the needle shield. You will hear a click when the shield extends to cover the needle.

DOSAGE FORMS AND STRENGTHS

Suspension for injection is supplied in a single-dose prefilled microinjection system, 0.1 mL, for adults 18 through 64 years of age.

CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or to a previous dose of any influenza vaccine is a contraindication to administration of Fluzone Intradermal.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated.[1] If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone Intradermal should be based on careful consideration of the potential benefits and risks.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Altered Immunocompetence

If Fluzone Intradermal is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone Intradermal may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Adults 18 through 64 years of age were randomized to receive Fluzone Intradermal or Fluzone (year 2008-2009 formulation) in a multi-center trial conducted in the US. The trial was open-label for administration route. The safety analysis set included 2855 Fluzone Intradermal recipients and 1421 Fluzone recipients. Table 2 summarizes solicited injection-site reactions and systemic adverse events reported within 7 days post-vaccination via diary cards. With the exception of pain, solicited injection-site reactions were more frequent after vaccination with Fluzone Intradermal compared to Fluzone. Nine percent of Fluzone recipients and 49% of Fluzone Intradermal recipients had an injection-site reaction present beyond Day 3 post-vaccination. Approximately 20% of subjects in both groups had a solicited systemic adverse event present beyond Day 3 post-vaccination.

Table 2: Frequency of Solicited Injection-Site Reactions and Systemic Adverse Events Within 7 Days After Vaccine Injection, Adults 18 Through 64 Years of Age

	Fluzone Intradermal (N[a]=2798-2802) Percentage			Fluzone (N[a]=1392-1394) Percentage		
	Any	Grade 2[b]	Grade 3[c]	Any	Grade 2[b]	Grade 3[c]
Injection-site reactions						
Erythema	76.4	28.8	13.0	13.2	2.1	0.9
Induration	58.4	13.0	3.4	10.0	2.3	0.5
Swelling	56.8	13.4	5.4	8.4	2.1	0.9
Pain	51.0	4.4	0.6	53.7	5.8	0.8
Pruritus	46.9	4.1	1.1	9.3	0.4	0.0
Ecchymosis	9.3	1.4	0.4	6.2	1.1	0.4
Systemic adverse events						
Headache	31.2	6.4	1.5	30.3	6.5	1.6
Myalgia	26.5	4.6	1.5	30.8	5.5	1.4
Malaise	23.3	5.5	2.2	22.2	5.5	1.8
Shivering	7.3	1.5	0.7	6.2	1.1	0.6
Fever[d]	3.9	0.6	0.1	2.6	0.4	0.2

[a] N is the number of vaccinated subjects with available data for the events listed.

[b] Grade 2 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥2.5 cm to <5 cm; Injection-site pain and Injection-site pruritus: sufficiently discomforting to interfere with normal behavior or activities; Fever: >100.4°F to ≤102.2°F; Headache, Myalgia, Malaise, and shivering: interferes with daily activities.

[c] Grade 3 - Injection-site erythema, Injection-site induration, Injection-site swelling, and Injection-site ecchymosis: ≥5 cm; Injection-site pain: incapacitating, unable to perform usual activities; Injection-site pruritus: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism; Fever: >102.2°F; Headache, Myalgia, Malaise, and Shivering: prevents daily activities.

[d] Fever - Any Fever indicates ≥99.5°F. The percentage of temperature measurements that were taken by oral or axillary routes, or not recorded were 99.9%, <0.1%, and 0.1%, respectively for Fluzone Intradermal; and 99.6%, 0.0%, and 0.4%, respectively for Fluzone.

Within 28 days post-vaccination, a serious adverse event was reported by 10 (0.4%) Fluzone Intradermal recipients and 5 (0.4%) Fluzone recipients. Within 6 months post-vaccination, a serious adverse event was reported by 47 (1.6%) Fluzone Intradermal recipients and 20 (1.4%) Fluzone recipients. No deaths were reported during the 6 months post-vaccination. Throughout the study, one reported serious adverse event was considered to be caused by vaccination: a pruritic rash on the extremities and torso that began 48 hours after receipt of Fluzone Intradermal and resulted in hospitalization and treatment with an antihistamine and steroids.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B. Fluzone Intradermal should be used during pregnancy only if clearly needed.

Pediatric Use: Safety and effectiveness of Fluzone Intradermal in persons <18 years of age have not been established.

Geriatric Use: Safety and effectiveness of Fluzone Intradermal in persons 65 years of age and older have not been established.

CLINICAL STUDIES

Immunogenicity of Fluzone Intradermal in Adults

Adults 18 through 64 years of age were randomized to receive Fluzone Intradermal or Fluzone (year 2008-2009 formulation) in a multi-center trial conducted in the US. The trial was open-label for administration route. For immunogenicity analyses, there were 2581 participants who received Fluzone Intradermal and 1287 participants who received Fluzone in the per protocol analysis set. Hemagglutination inhibition (HI) antibody geometric mean titers (GMTs) following Fluzone Intradermal were non-inferior to those following Fluzone for all three strains. (See Table 3) Seroconversion rates following Fluzone Intradermal were non-inferior to those following Fluzone for strains A (H1N1) and A (H3N2), but not for strain B. (See Table 4) At 28 days following vaccination with either Fluzone or Fluzone Intradermal, the percentages of subjects with a serum HI antibody titer of at least 1:40 ranged from 87% to 92%, depending on the influenza strain.

Table 3: Non-inferiority of Fluzone Intradermal Relative to Fluzone by HI Antibody GMTs at 28 Days Post Vaccination, Adults 18 through 64 Years of Age

	GMT		GMT Ratio (95% CI)	Non-inferior[a]
Influenza Strain	Fluzone Intradermal N=2573-2579	Fluzone N=1283-1285	Fluzone GMT divided by Fluzone Intradermal GMT	
A (H1N1)	193.2	178.3	0.92 (0.85; 1.01)	Yes
A (H3N2)	246.7	230.7	0.94 (0.85; 1.03)	Yes
B	102.5	126.9	1.24 (1.15; 1.33)	Yes

[a] Pre-defined criterion for non-inferiority: The upper bound of the two sided 95% CI of the ratio of GMTs (Fluzone divided by Fluzone Intradermal) is <1.5.

Table 4: Non-inferiority of Fluzone Intradermal Relative to Fluzone by HI Antibody Seroconversion at 28 Days Post Vaccination, Adults 18 through 64 Years of Age

	Seroconversion[a] %		Difference (95% CI)	Non-inferior[b]
Influenza Strain	Fluzone Intradermal N=2573-2578	Fluzone N=1283-1285	Fluzone minus Fluzone Intradermal	
A (H1N1)	61.2	60.5	-0.69 (-3.97; 2.56)	Yes
A (H3N2)	75.3	74.8	-0.55 (-3.49; 2.31)	Yes
B	46.2	54.2	7.99 (4.64; 11.31)	No

Note: As defined in the study protocol:

[a] Seroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:40 or a minimum 4-fold increase for participants with pre-vaccination titer ≥1:10.

[b] Pre-defined criterion for non-inferiority: The upper bound of the two sided 95% CI of the difference in seroconversion rates (Fluzone minus Fluzone Intradermal) is <10%.

REFERENCE

1. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med.* 1998;339(25):1797-1802.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Fluzone Intradermal microinjection system does not contain latex.

Single-dose prefilled microinjection system, 0.1 mL, package of 10 (does not contain latex) – NDC 49281-703-55.

Storage and Handling

Store Fluzone Intradermal refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone Intradermal contains killed viruses and cannot cause influenza. Fluzone Intradermal stimulates the immune system to produce antibodies that help protect against influenza, but does not prevent other respiratory infections. Annual influenza vaccination is recommended. Instruct vaccine recipients and guardians to report adverse reactions to their healthcare provider and contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE) and/or VAERS at 1-800-822-7967. Inform the patient about the Sanofi Pasteur Inc. pregnancy registry, for Fluzone Intradermal as appropriate.

Product information as of May 2011.

Manufactured by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

Printed in USA

MKT24534

6044-6045-6046-6109

An Evolving Challenge

Because of the evolving nature of the flu, developing an effective vaccine each year is no small task. Each year, a global network of scientists are tasked with surveying flu virus mutations and making vaccine recommendations.

The World Health Organization (WHO) holds two vaccine strategy meetings annually, one for the Northern Hemisphere (in February) and one for the Southern Hemisphere (in September). As soon as the organization announces which influenza subtypes should be targeted by the vaccine, medical labs go to work developing strain-specific vaccines. As one might imagine, production schedules are tight and leave little room for error — the FDA must approve the vaccine by the spring, the vaccine must be in production by August and be ready to be administered in September through December, giving people enough time to develop immunity before flu season is in full swing.

Today's influenza vaccine contains three strains of the virus, as determined by the World Health Organization (WHO), and researchers labor to stay one step ahead of the constantly mutating bug. For the 2012-13 flu season, the vaccine was reformulated with two new flu strains.[7] Each year, public service campaigns encourage people to get vaccinated; current Centers for Disease Control and Prevention (CDC) guidelines advise everyone 6 months of age and older to get a flu vaccine annually.

A Historical Look at Pandemic Flu

Spanish Flu, 1918–1919

- Illness from the 1918 flu pandemic, also known as the Spanish flu, came on quickly. Some people felt fine in the morning but died by nightfall.
- Approximately 20 percent to 40 percent of the worldwide population became ill.
- An estimated 50 million people died.
- Nearly 675,000 people died in the United States.

Asian Flu, 1957–1958

- In February 1957, a new flu virus was identified in the Far East. Immunity to this strain was rare in people younger than 65.
- Vaccine production began in late May 1957 and was available in limited supply by August 1957.
- By December, the outbreak ebbed but resurged in January of 1958.
- Although not as devastating as the 1918 pandemic, about 69,800 people in the United States died.
- The elderly had the highest rates of death.

Hong Kong Flu, 1968–1969

- In early 1968, a new flu virus was detected in Hong Kong. The first cases in the U.S. were detected as early as September 1968.
- The number of deaths between September 1968 and March 1969 was 33,800, making it the mildest flu pandemic in the 20th century.
- The flu hit hardest in December when schoolchildren were on vacation, leading to a decline in flu cases.
- Improved medical care and antibiotics effective for secondary bacterial infections were available, minimizing fatalities.

H1N1, 2009–2010

- In the spring of 2009, a new flu virus spread quickly across the U.S. and the world. The first case of H1N1 (swine flu) was diagnosed on April 15, 2009.
- By April 21, the Centers for Disease Control and Prevention (CDC) began work on a vaccine. On April 26, the U.S. government declared a public health emergency.
- A total of 74 countries were affected by the pandemic.
- During the outbreak, 80 million people were vaccinated against H1N1.
- The CDC estimates that 43 million to 89 million people contracted the virus.
- There were between 8,870 and 18,300 H1N1-related deaths.

Source: Pandemic Flu History. Flu.gov. Accessed at www.flu.gov/pandemic/history/index.html.

When you consider how far we've come from the fearful days when flu was an indiscriminate killer and no protection existed, it seems odd that each year tens of thousands of people still die from flu-related complications in the U.S. While there may be many extenuating reasons for these statistics, the sad fact remains that many people still avoid getting a flu vaccine. Studies show young healthy adults are chief among the population groups who skip immunization because they feel they are not at high risk, they think that the vaccine doesn't work, and/or they believe that getting the flu vaccine will make them sick. Clearly, more education, communication and effort are needed to help dispel some of these common myths surrounding flu vaccination to ensure pandemic history does not repeat itself.

For years, infectious disease experts have warned of an influenza virus that could infect 40 percent of the world's population.

The 1970s Swine Flu Scare

The ability of a virus to breed panic was perfectly illustrated when the emergence of a flu-like illness at Fort Dix, N.J., in the late 1970s became public knowledge. Federal researchers isolated a flu virus with the same H1N1 antigenic signature as the Spanish flu. Thirteen soldiers became seriously ill, and one young man died.

While hindsight is 20/20, at the time of the outbreak, the CDC recommended a massive vaccination campaign in an effort to protect the American public. The effort was initially successful, and within 10 weeks, 40 million Americans were inoculated. Unfortunately, public health officials had little time to revel in the achievement, as reports of temporary paralysis and death linked to the vaccine began to emerge. By January 1977, more than 500 cases of Guillain-Barré syndrome were counted, along with 25 deaths.[8]

To add insult to injury, the potentially deadly pandemic never really materialized, and the public backlash against government-recommended flu vaccines created skepticism about flu vaccine efficacy that continues to this day.

Pandemic Predictions: Fact or Science Fiction?

For years, infectious disease experts have warned of an influenza virus that could infect 40 percent of the world's population. Some now believe that the H5N1 virus, also known as the avian flu, could become that deadly strain. The catastrophe such a pandemic could pose has been compared to the 1918-19 Spanish flu, with the possibility of H5N1 being even more lethal.

Since it was discovered in China in 1997, the H5N1 has mutated, becoming stronger and more deadly. But whether the relentless virus ever becomes capable of being transmitted from human to human on a wide scale remains to be seen.[9] The fear of this unknown creates much unease among those whose job is to predict pandemic outbreaks.

The threat of bioterrorism is also a concern, with many in the scientific community wanting to limit the release of information garnered from studies about H5N1, lest it fall into the wrong hands. In a correspondence addressing the topic earlier this year, Michael Osterholm, director of the Center for Infectious Disease Research and Policy, which studies bioterrorism threat, stated that even if H5N1 was not spread in human populations, a terrorist group might try to infect pigs, devastating local livestock industries because people would fear infection from eating them (despite the fact that viruses are not transmitted this way).[10] "I can't think of a worse scenario than having H5N1 virus circulating widely in swine with a critical reassortment likely to occur and human transmission not far off," Osterholm said.

Developing countermeasures to hold back the flu is an even more complicated challenge to today's scientists than it was to their predecessors. Much is dependent on our current strategies and continued vigilance against the virus that has the potential to bring about global disaster.[3] ❖

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

References

1. Stanford University. The Influenza Pandemic of 1918. Accessed at virus.stanford.edu/uda.
2. Maplecroft. Flu Pandemics Likely to Spread Fastest in Travel Hub U.K., But Country Has One of the Highest Capacities to Contain Diseases — Global Study. Accessed at maplecroft.com/about/news/influenza_pandemic_risk_index.html.
3. Spanish Flu Created a Viral Dynasty — Study. Keyt.com, May 3, 2012. Accessed at www.keyt.com/health/49504497.html.
4. National Institutes of Health, Dynasty: Influenza Virus in 1918 and Today. NIH News, Jun. 29, 2009. Accessed at www.nih.gov/news/health/jun2009/niaid-29.htm.
5. 1957 Asian Flu Pandemic. GlobalSecurity.org. Accessed at www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1957.htm.
6. 1968 Hong Kong Flu. GlobalSecurity.org. Accessed at www.globalsecurity.org/security/ops/hsc-scen-3_pandemic-1968.htm.
7. FDA Panel Recommends Strains for 2012-2013 Flu Vaccine. RX-s.net. Accessed at rx-s.net/weblog/more/fda-panel-recommends.
8. A Century of Flu Pandemics. Nieman Foundation. Accessed at www.nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/AHistoryOfPandemics/ACenturyOfFluPandemics.aspx#swineflu.
9. What Is Bird Flu? News Medical. Accessed at www.news-medical.net/health/What-is-Bird-Flu-(H5N1).aspx.
10. Emspak, J. Controversial Bird Flu Paper Explains Potential of Pandemic. Mother Nature Network, May 2, 2012. Accessed at www.mnn.com/green-tech/research-innovations/stories/controversial-bird-flu-paper-explains-potential-of-pandemic.

FAMILIES FIGHTING FLU (FFF) is a nonprofit, 501(c)(3) volunteer-based advocacy organization dedicated to protecting the lives of children by helping to increase annual influenza vaccination rates among families. Our members include families whose children have suffered serious medical complications or died from influenza, as well as health care practitioners and advocates committed to flu prevention.

Share in our mission to protect all children against influenza and save lives.

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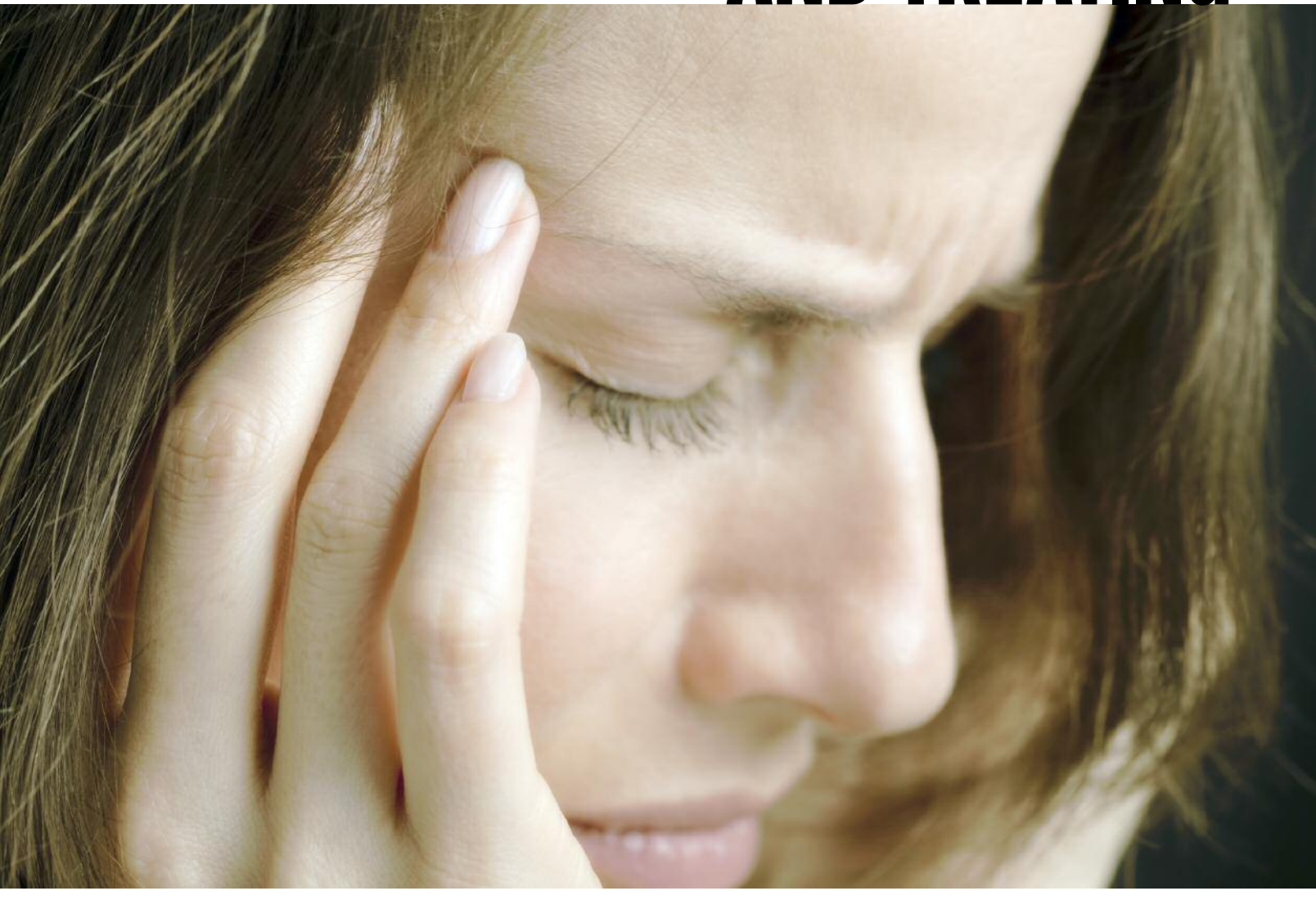
By Ronale Tucker Rhodes, MS, and Kris McFalls

UNDERSTANDING AND TREATING



Knowing what side effects, from mild to serious, to expect during and after immune globulin infusions can prepare patients and their caregivers for treatment changes to mitigate their impact.

IG SIDE EFFECTS

It makes most people chuckle: A television commercial touts the benefits of a wondrous new drug; the patient is smiling and laughing, obviously enjoying a newfound healthy lifestyle while spending time with family and friends. Then, the announcement: "Side effects include …" Wow, the viewer thinks, no thanks!

The truth is that there is nothing funny about a drug's side effects — especially when it comes to a life-sustaining drug like immune globulin (IG). IG patients either undergo the treatments or they forgo them, which brings on far worse consequences than those caused by side effects. Fortunately, many IG patients never experience any effects, and while those who do often think they are having a severe reaction, by definition, the reaction is typically a moderate or mild side effect. And, the good news is that in almost all cases, the effects can be controlled or even eliminated.

Side Effects Defined

Side effects, also referred to as adverse drug reactions (and considered one and the same by the U.S. Food and Drug Administration [FDA]), are those that are expected, although undesired, and are listed on the package insert for each medication. Mild or moderate side effects typically occur due to the manner in which the treatment is administered, and they can be managed. Serious side effects, on the other hand, also can be a result of the components of the drug itself and result in hospitalization or prolongation of an existing hospitalization and can be life-threatening.

The Mayo Clinic has an exhaustive list of side effects available at www.mayoclinic.com/health/drug-information/DR601705/DSECTION=side-effects. Most of these effects often can be eliminated by stopping the infusion temporarily and then restarting at a lower infusion rate, and even by switching the treatment modality.

Mild and Moderate Side Effects and Treatments

Mild and moderate side effects of intravenous IG (IVIG) are headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension. Headaches and their more severe form, migraines, tend to be one of the more common side effects. Patients can overcome both forms of headaches by treating with antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids both before and after an infusion. In addition, hydrating before, during and after an infusion can help alleviate these discomforts.

Other forms of treatment also can be tried. For example, a patient just beginning IVIG treatments experienced a mild migraine the day following her first treatment. As a further preventive measure, she increased hydration and took Tylenol before her next two treatments. Regardless, on her third treatment, she experienced a severe migraine lasting three days. For her next infusion, her doctor ordered a small dose of prednisone to be taken the day before the infusion, the day of the infusion and the day after the infusion. In addition, the rate of the infusion was decreased. With these treatment adjustments, the patient still experienced occasional mild headaches, but she no longer had migraines.

In another instance, a patient experienced severe migraines following IVIG infusions. The patient was given Tylenol, Benadryl and steroids, as well as a migraine prophylaxis, prior to treatment, but the headache symptoms persisted. Different formulations of IVIG 5% and 10% were then tried, but the migraines continued. So, the patient switched to subcutaneous IG (SCIG), which has eliminated the problem, and no premedications are needed.

Mild or moderate side effects typically occur due to the manner in which the treatment is administered and can be managed.

For SCIG patients, the most common side effects include headaches and local irritation (redness, swelling, itching, blanching) at the needle site. Some reactions, especially for

patients new to SCIG therapy, are expected, and most decrease with time once the body becomes accustomed to the therapy. For patients bothered by reactions, applying ice or heat to the needle sites can help decrease some of the symptoms. Using a topical anesthetic cream 30 to 60 minutes prior to starting the infusion also can be helpful. Patients with persistent symptoms should explore needle placement as a possible cause. If the needle is not properly placed, it is possible that some of the fluid is leaking into surrounding tissue rather than into the subcutaneous space. Patients also can try using a dry needle insertion technique. Typically, the IG product is filled to the end of the needle before it is inserted. With this method, patients are more likely to experience local reactions. However, rather than priming all the way to the tip of the needle, patients can try filling the needle with the IG product just short of the tip and then inserting the needle. A provider experienced in SCIG therapy should be able to help patients troubleshoot and eliminate possible causes of site reactions. However, in some cases, patients are simply unable to tolerate the side effects of SCIG and need to switch back to IVIG treatment.

Serious Side Effects and Treatments

Serious side effects are rare, and most can be reduced by screening the patient for factors predisposing them to complications.[2] Serious side effects can include acute renal failure, thrombosis, Stevens-Johnson syndrome, serum sickness, aseptic meningitis and anaphylaxis. The most severe form of IG-related headache comes from aseptic meningitis, and some studies show that patients with a history of migraines appear to be more susceptible to aseptic meningitis, yet other studies do not. Symptoms, which are severe and similar to meningitis, usually begin a few hours after treatment but can occur up to two days later. They can include severe headache, neck stiffness, photo sensitivity, chills, nausea, vomiting, fever and painful eye movement. Although cerebrospinal fluid (CSF) can show increased white blood cells and proteins, cultures are generally negative, thus resulting in the aseptic diagnosis.[1] Treatment to prevent aseptic meningitis includes antihistamines, NSAIDs, steroids both before and after an infusion and adding concomitant hydration.

Anaphylaxis, a rapidly progressing, life-threatening allergic reaction, can be a side effect of both IVIG and SCIG. Anaphylactic reactions may require administration of corticosteroids and antihistamines, and in very severe cases, administration of epinephrine.[3]

Side effects are rare, and most can be reduced by screening the patient for factors predisposing them to complications.

A case in point: One patient who experienced anaphylaxis is a child named Julia. At 7 months old, Julia was diagnosed with pertussis, despite having been vaccinated. Julia's health

Alphanate®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

FACTORS FOR HEALTH

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First FVIII/VWF product in the US stable for 3 years, up to the expiration date printed, when stored at or below 77°F (25°C). Do not freeze.

Please see brief summary of Alphanate® Full Prescribing Information below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Alphanate Antihemophilic Factor/von Willebrand Factor Complex (Human) safely and effectively. See Full Prescribing Information for Alphanate.

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])
Sterile, lyophilized powder for injection

For Intravenous Use Only

Initial U.S. Approval: 1978

INDICATIONS AND USAGE

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

CONTRAINDICATIONS

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients have been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

ADVERSE REACTIONS

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.
- Labor and Delivery: No human or animal data. Use only if clearly needed.
- Nursing Mothers: No human or animal data. Use only if clearly needed.
- Pediatric Use: Clinical trials for safety and effectiveness in pediatric hemophilia A patients have not been conducted. The hemostatic efficacy of Alphanate has been studied in 20 pediatric subjects with VWD 18 years of age and under. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo.
- Geriatric Use: No human or animal data. Use only if clearly needed.

For more information: **Grifols Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

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deteriorated so rapidly that she was sent by ambulance to a hospital where she stayed for nearly three weeks. At age 5, she was diagnosed with a primary immune deficiency, and at age 6, IVIG treatments were started. Unfortunately, her infusion days rarely went smoothly. From the beginning, Julia was plagued with flu-like symptoms, and by age 9, she experienced severe migraines lasting three days. Doctors treated Julia with Benadryl and prednisone prior to her infusions, as well as with intravenous Benadryl during her infusions. In addition, the rate of infusions was slowed down so much that they took eight hours to complete. When Julia was 13, doctors suggested subcutaneous infusions in hopes of giving Julia her lifesaving IG without risking her life. This worked; Julia was soon free of the side effects that plagued her with every treatment.

Anaphylactic and anaphylactoid reactions to IVIG therapy are relatively rare, but they can occur in any patient at any time.

Anaphylactic and anaphylactoid reactions (both referred to as anaphylaxis) are life-threatening events that result from an overreactive and misdirected immune response to a substance that is viewed by the body as foreign (an antigen). An anaphylactic reaction is an acute fatal, or potentially fatal, hypersensitivity reaction that requires the patient to be sensitized and their reaction mediated through immunoglobulin E (IgE) antibodies. An anaphylactoid reaction doesn't need the presence of IgE antibodies for a hypersensitivity reaction to occur. Thus, an anaphylactic reaction occurs only after the patient has been previously exposed at least once to the antigen and is sensitized. And, it can occur following a single, first-time exposure to certain agents in nonsensitized patients.[4]

Anaphylactic and anaphylactoid reactions to IVIG therapy are relatively rare, but they can occur in any patient at any time. Some IgA-deficient patients produce certain IgA antibodies that can increase the potential for anaphylaxis. For those patients, it is prudent to use an IVIG product that has a very low IgA content. Alternatively, many patients who experience anaphylaxis have had good success by switching their route of infusion from intravenous to subcutaneous.[4]

Documenting and Reporting Side Effects

Both the FDA and European regulatory authorities are encouraging patients and healthcare professionals to report adverse drug reactions so that any unknown serious side effects, such as those that occurred with Vioxx, can be discovered more quickly. (Vioxx and related pain medications were taken off the market in 2004 because they caused dangerous heart problems in some people.) The purpose of documenting and reporting these effects is to prevent future injuries for patients. Of particular importance to the FDA are suspected adverse drug reactions for a new drug (i.e., within three years of entry to market) and suspected severe adverse drug reactions for any drug, no matter when the drug entered the market.[5]

The FDA also requires many manufacturers of newly licensed drugs to perform post-marketing risk management (pharmacovigilance studies) to collect information on adverse reactions in a more proactive manner. Additional information on serious adverse drug reactions and instructions for reporting an adverse drug reaction to the FDA can be obtained at www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

Benefits Outweigh Risks

IG is one of the safest biological products available, and although severe side effects have been reported, they are rare. The good news is that almost all side effects can be safely controlled and often eliminated altogether. And, with the growing number of diseases being treated today with IG, as well as the stringent testing and reporting standards mandated by the FDA, patients who rely on this lifesaving treatment can rest assured that they can be safely treated. ❖

RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine, and* **KRIS MCFALLS** *was previously the full-time patient advocate for* IG Living *magazine, written for patients who depend upon immune globulin products and their healthcare providers.*

Sources

1. Gamunex Prescribing Information. Accessed at www.gamunex.com/media/Gamunex_Prescribing_Info.pdf.
2. Duhem, C, Dicato, MA, and Ries, F. Side-effects of intravenous immune globulins. *Clinical & Experimental Immunology*. 1994: 97 (Suppl 1), 79-83.
3. Siegel, J. Case Management of the Challenging IgG Patient: Clinical Considerations for the Most Effective and Safe Therapy. Breakfast symposium, National Home Infusion Association (NHIA) Meeting, March 1-5, 2009.
4. Limmer, DD, Mistovich, JJ, and Krost, MS. Anaphylactic and Anaphylactoid Reactions: Prehospital Pathophysiology. EMSResponder.com. Accessed at publicsafety.com/article/article.jsp?id=2165&siteSection=6.
5. VA Center for Medication Safety and VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel (November 2006). Adverse Drug Events, Adverse Drug Reactions and Medication Errors: Frequently Asked Questions. Accessed at www.pbm.va.gov/vamedsafe/Adverse%20Drug%20Reaction.pdf.

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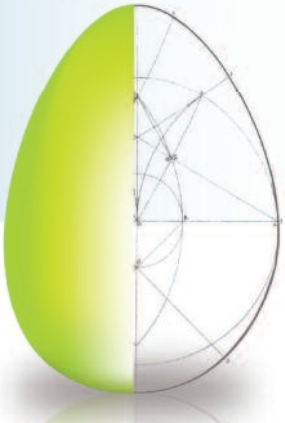

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Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott- Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion).

Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to treatment with Privigen. Closely monitor patients for hemolysis and hemolytic anemia. Risk factors for hemolysis include non-O blood group, underlying inflammation, and high doses. Carefully consider relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload.

Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

Please see brief summary of full prescribing information on following pages.

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com www.Privigen.com PVG10-11-0014a 6/2012

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]*).**

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (*see Warnings and Precautions [5.1]*).

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]*). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (*see Boxed Warning*, *Dosage and Administration [2.3]*).

5.3 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.[2-4] 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.

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 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]).*

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as 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 thromboembolic events.[5]

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen (*see Adverse Reactions [6]*) and other human immune globulin products. Discontinuation of 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. 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, but negative culture results. 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 test (DAT) (Coombs' test) result and hemolysis.[7-9] Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[10] Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following can be associated with risk of hemolysis: high doses (eg, ≥ 2 g/kg), whether given either as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state.[11,12] Hemolysis has been reported following administration of IGIV for indications including ITP AND PI.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a 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 following treatment with IGIV products, including Privigen.[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. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) 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

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

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. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen 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; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule

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 an infusion 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%). 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: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, *Irrespective of Causality*

Adverse Event (Excluding Infections)	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0)†	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, 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 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).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (*see Dosing and Administration [2.3]*). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

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 infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

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 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle, *Irrespective of Causality (Two consecutive daily infusions)*

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

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 that 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; these cases resolved uneventfully.

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 adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

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

- **Infusion Reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *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 DAT (Coombs' test)
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

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Myths and Facts:

Lyme Disease

Discussion about this rare disease continues to grow as patients increasingly look to LD to explain their symptoms, physicians fail to diagnose or misdiagnose, and myths continue to unfold.

By Ronale Tucker Rhodes, MS

Lyme disease (LD) is a rare and mysterious disease, increasingly talked about by both physicians and patients. Dr. Robert Schoen, a rheumatologist and internist and a clinical professor of medicine at Yale University School of Medicine, says that all practicing physicians — both in areas of the country where LD is and isn't highly endemic — are seeing patients who have questions about the disease. Indeed, he says, "We probably see more patients who have questions about the disease than who actually have Lyme disease."[1]

While manifestations of LD were first reported in the medical literature in Europe in 1883, it wasn't until 1975 that LD was described following an outbreak of apparent juvenile arthritis, preceded by a rash, among residents of Lyme, Conn. Today, it is the most commonly reported vector-borne illness (an illness caused by an infectious microbe that is transmitted to people by bloodsucking arthropods) in the U.S.[2] LD is one of 1,200 diseases listed in the National Organization for Rare Disorder's *Rare Disease Report Abstract*, and in 2009, it was the fifth most common infectious nationally notifiable disease.[3] Since 1982, more than 150,000 cases have been reported to the Centers for Disease Control and Prevention (CDC).[2] But it is believed that far many more cases go unreported.

Unfortunately, many patients often believe they have LD when their symptoms are really something else. And, many physicians frequently fail to diagnose and misdiagnose LD. While LD has been directly responsible for fewer than two dozen deaths, if left untreated or inadequately treated, neurologic, cardiac or joint abnormalities may occur.[2] For these reasons, it's extremely important for both patients and physicians to understand the facts about this disease.

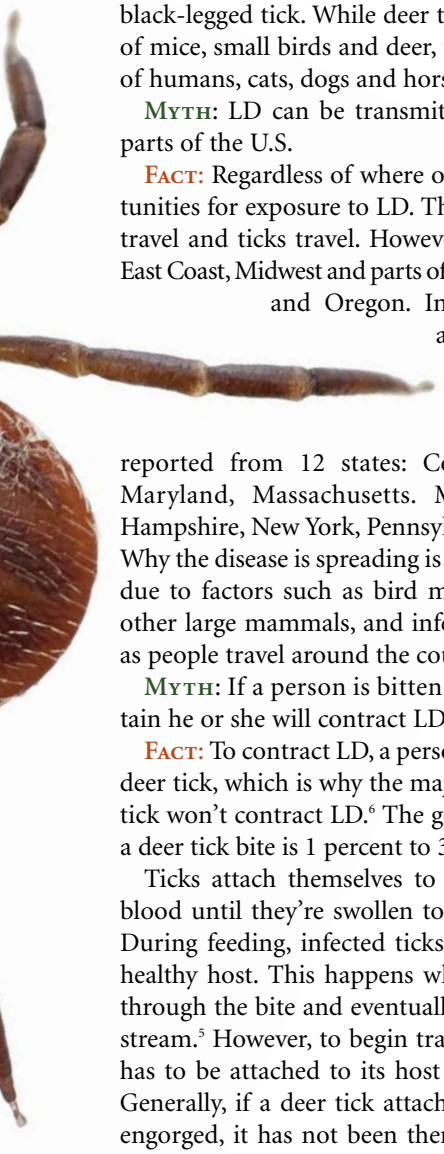
Separating Myth from Fact

Myth: Any tick bite can cause LD.

Fact: LD bacteria are carried primarily by deer ticks, which are brown and often no bigger than the head of a pin, making them nearly impossible to detect. The LD spirochete (a long, spiral-shaped bacterial cell), Borrelia burgdorferi, infects other species of ticks, but it is known to be transmitted to humans and other animals only by deer ticks and the related Western black-legged tick. While deer ticks typically feed on the blood of mice, small birds and deer, they also can feed on the blood of humans, cats, dogs and horses.[4]

Myth: LD can be transmitted to humans only in certain parts of the U.S.

Fact: Regardless of where one lives, there are many opportunities for exposure to LD. This is because people travel, pets travel and ticks travel. However, LD is most prevalent in the East Coast, Midwest and parts of the coasts of northern California and Oregon. In fact, LD is spreading slowly along and inland from the Upper East Coast, as well as in the Upper Midwest.[2] In 2010, 94 percent of LD cases were reported from 12 states: Connecticut, Delaware, Maine, Maryland, Massachusetts. Minnesota, New Jersey, New Hampshire, New York, Pennsylvania, Virginia and Wisconsin.[3] Why the disease is spreading is unclear, but it is suspected to be due to factors such as bird migration, mobility of deer and other large mammals, and infected ticks dropping off of pets as people travel around the country.[2]



Myth: If a person is bitten by a deer tick, it is almost certain he or she will contract LD.

Fact: To contract LD, a person must be bitten by an infected deer tick, which is why the majority of people bitten by a deer tick won't contract LD.[6] The general risk of LD infection after a deer tick bite is 1 percent to 3 percent.[4]

Ticks attach themselves to a host and feed on the host's blood until they're swollen to many times their normal size. During feeding, infected ticks can transmit the bacteria to a healthy host. This happens when the bacteria enter the skin through the bite and eventually make their way to the bloodstream.[5] However, to begin transmitting the spirochete, a tick has to be attached to its host approximately 36 to 48 hours. Generally, if a deer tick attached to the skin has not become engorged, it has not been there long enough to transmit the bacteria.[2]

Myth: LD can be transmitted through means other than being bitten by a tick.

Fact: It is believed by some that LD can be transmitted by blood transfusions, physical contact and breast milk. However, while the bacteria are capable of living in blood samples, people infected with LD are not allowed to donate blood. And, breast milk has never been found to sustain the bacteria. Indeed, there has never been a documented case of the LD bacteria being transmitted through breast milk or physical contact.[4] Unfortunately, despite these facts, fear, ignorance and Internet rumors continue to expand on these myths. Postings on one newsgroup read: "I think Lyme is also a STD [sexually transmitted disease]" and "I've talked to many couples who claim they transmitted to each other through sexual contact. I believe I gave it to my wife."[6]

Myth: The symptoms of LD are easy to detect.

Fact: The signs and symptoms of LD are variable and usually involve more than one system, most often the skin, joints and nervous system.[5] However, early symptoms of LD can be mild and easily overlooked.

The first symptom is usually an expanding rash known as erythema migrans (EM), or bull's-eye rash, which is believed to occur in 80 percent to 90 percent of all LD cases. An EM rash usually (but not always) radiates from the site of the tick bite, appears either as a solid red expanding rash or blotch or as a central spot surrounded by clean skin that is in turn ringed by an expanding red rash (that looks like a bull's-eye), appears an average of one to two weeks after disease transmission, has an average diameter of 5 to 6 inches, persists for about three to five weeks, may or may not be warm to the touch and is usually not painful or itchy. An EM rash typically appears at the site of the tick bite, usually in areas where the body creases such as the armpit, groin, back of the knee and nape of the neck. However, the rash is not restricted to these areas. And, in brown-skinned or suntanned patients, an EM rash can be harder to identify because of the decreased contrast between normal skin tones and the red rash; instead, a dark, bruise-like appearance is more common.[2]

Today, LD is the most commonly reported vector-borne illness in the U.S.

Other symptoms such as joint pain, chills, fever and fatigue will occur around the time the rash appears, although these symptoms may not seem serious enough to require medical attention. In addition, they may be brief, and as the LD spirochete continues spreading through the body, they may recur as a broader spectrum of symptoms as the disease progresses. A number of other symptoms also may develop, including severe fatigue and a stiff, achy neck, and the peripheral nervous system may become involved causing

tingling or numbness in the extremities or facial palsy (paralysis). More severe and potentially debilitating symptoms of later-stage LD may occur weeks, months or, in a few cases, years after a tick bite. These include severe headaches, painful arthritis, swelling of joints, cardiac abnormalities and central nervous system involvement leading to cognitive (mental) disorders.[2]

Myth: Most patients diagnosed with LD recall being bitten by a tick and/or having a rash.

Fact: Fewer than 50 percent of patients with LD recall a tick bite, and in some studies of culture-proven infection with the Lyme spirochete, this number is as low as 15 percent.

Additionally, fewer than 50 percent of patients with LD recall any rash. This is because while EM is considered classic, it is not the common dermatologic manifestation of early localized Lyme infection. More common are atypical forms of the rash.[7]

Myth: Diagnosing LD is subjective and not based on serology (blood work).

Fact: In the first month after infection, blood tests are not reliable and often result in false results for diagnosing LD because antibody levels are too low. This is true even in the absence of an EM rash. Instead, physicians typically ask detailed questions about a patient's medical history, perform a physical exam and diagnose on the basis of symptoms and evidence of a tick bite. However, as the disease progresses, blood tests are more reliable.[2,4]

The general risk of LD infection after a deer tick bite is 1 percent to 3 percent.

Myth: Screening tests for LD are always reliable.

Fact: Blood tests to confirm a diagnosis of LD can be reliable only after the disease has progressed and the body has developed antibodies. The CDC recommends the enzyme-linked immunosorbent assay (ELISA) and the Western blot tests. The ELISA test, which is used most often to detect LD, and the Western blot test detect antibodies to the LD bacteria. However, because they sometimes produce false-positive results, they are not used as the sole basis for a diagnosis, but instead are used to confirm a diagnosis.[2,5] According to the International Lyme and Associated Diseases Society (ILADS), the ELISA test misses 35 percent of culture-proven LD, when, by definition, a screening test should have at least 95 percent sensitivity.[4]

A third test, the polymerase chain reaction, helps to detect bacterial DNA in fluid drawn from an infected joint. It's not as effective for detecting infection of blood or urine; instead, it is used for people who may have chronic Lyme arthritis, and it also may be used to detect persistent infection in the cerebrospinal fluid of people who have nervous system symptoms.[5]

Myth: If living or vacationing in an area prone to deer ticks, there is little one can do to prevent contracting LD.

Fact: There are many things individuals who are living or visiting in tick-infested areas can do to protect against LD. The first is to avoid contact with soil, leaf litter and vegetation as much as possible. Those spending time outdoors should learn how to identify what a deer tick looks like.[2] They should also wear long pants and sleeves, use insect repellents, check themselves afterward for ticks, and if a tick is found, they should know how to remove it with tweezers. In addition, those who live in tick-infested areas should tick-proof their yards by clearing brush and leaves where ticks live and keeping woodpiles in sunny areas. Last, people should never assume they are immune to LD. Even those who have previously been infected with LD can get it again.[5]

Myth: There is a vaccine to prevent LD.

Fact: In 1998, the U.S. Food and Drug Administration licensed the first vaccine for LD called Lymerix. The vaccine, intended for at-risk individuals between the ages of 15 and 70 years, was given in three separate injections, and it appeared to be effective in preventing infection. Unfortunately, after years of pre-license clinical trials and three years of commercial sales, GlaxoSmithKline pulled the vaccine off the market in 2002 citing poor sales and a projected low demand. There also were several lawsuits filed against the company by individuals who claimed the vaccine caused adverse events. However, repeated studies failed to find any evidence of specific adverse events associated with Lymerix.[6]

Myth: While LD can be treated, it is often difficult to cure.

Fact: The majority of LD patients recover completely. LD in its early stages (within the first few weeks after initial infection) is almost always cured when treated with oral antibiotics. Doxycycline, amoxicillin and ceftin are the three oral antibiotics most highly recommended. Those treated after the first three weeks also will likely fully recover, but the cure rate decreases the longer treatment is delayed. Unless neurological or severe cardiac abnormalities are present, oral antibiotics are still the recommended course of treatment. A study reported in the *New England Journal of Medicine* showed that a four-week course of oral doxycycline is just as effective in treating late LD, and much less expensive, than a similar course of intravenous Ceftriaxone.

Treating late-stage LD patients is more complicated and, in some cases, standard antibiotic treatment regimens are ineffective. In this small percentage of cases, intravenous antibiotic

treatment may be indicated. And while the disease may persist for months or even years in these patients, they will eventually experience slow improvement and resolution of persisting symptoms.[2]

Myth: LD cannot be overtreated.

Fact: A small number of patients with LD continue to experience symptoms such as muscle aches and fatigue; however, the cause of these symptoms is unknown. It's possible that certain LD patients become predisposed to develop an autoimmune response that contributes to their symptoms.[5] And, while treatment of late-stage LD has become a matter of considerable debate, there is no scientific evidence to support the long-term use of antibiotics. Indeed, it is ill-advised due to adverse side effects.[2]

Myth: Lyme disease can be effectively treated by regimens other than antibiotics.

Fact: Antibiotics are the only appropriate treatment for LD. Unfortunately, some LD patients have been treated with inappropriate and ineffective regimens. These include malariotherapy, an injection of blood containing the malaria parasite, which is considered far more dangerous than the common case of LD; intracellular hyperthermia therapy in which a chemical such as 2,4-dinitrophenol (a metabolic poison that can result in severe weight loss and even death) is administered; hyperbaric oxygen therapy, an experimental treatment for some infectious diseases and one that is not recommended by the Infectious Diseases Society of America; colloidal silver, which has been touted as a cure for many diseases without any studies proving so; and rife machines, electromagnetic frequency devices from the 1930s that supposedly cure LD by matching the disease's radio-like frequencies.[6]

In addition, some alternative medicine practitioners prescribe Bismacine, an injectable compound, which the FDA warns consumers and healthcare providers against. Bismacine, also known as Chromacine, contains high levels of the metal bismuth, and while it can be used safely in some oral medications for digestive conditions, it's not approved for use in injectable form or as a treatment for LD. In fact, it can cause bismuth poisoning, which may lead to heart and kidney failure.[5]

Myth: The fetuses of pregnant women with LD are at increased risk for fetal malformation or adverse events during pregnancy if the mother is treated for the disease.

Fact: While many expectant mothers worry about the effects of treatment on the fetus, there have been no cases of treatment harming the fetus, and all cases of congenital LD clear shortly after birth. The reality is that mothers who refuse treatment put their children at higher risk of serious infection. There are documented cases of babies dying shortly after birth from the LD bacteria.[4]

Myth: LD patients can suffer long-term effects especially if undetected in its early stages.

Fact: It is rare for patients to suffer long-term effects. However, if LD is left untreated, it can cause chronic joint inflammation (Lyme arthritis), particularly of the knee; neurological symptoms such as facial palsy and neuropathy; cognitive defects such as impaired memory; and heart rhythm irregularities.[5]

Antibiotics are the only appropriate treatment for LD.

Myth: LD is a chronic illness.

Fact: Individuals who do continue to experience chronic fatigue and muscle aches believe it is caused by LD that has turned into chronic LD. However, no bacterial infection has been found in these patients after the initial infection is eliminated, and chronic symptoms experienced after LD have never been proved to be related to LD.[4]

Dispelling the Myths Now

Scientists are continuing to conduct research to find new ways of preventing and treating LD. While there is no vaccine to prevent LD today, in the future, there may be vaccines that can provide immunity to not just the pathogen but also the vector (its salivary glands, for example). In addition, interesting new tests are being developed that are more sensitive at the beginning of the infection. But, in the long run, the healthcare profession is going to be limited by science as it is for a number of other infections. Therefore, it's important to understand the clinical features of LD, as well as the myths and facts that abound.[1] ❖

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

References

1. Schoen, RT. What's New in Lyme Disease? ConsultantLive.com. Accessed at www.consultantlive.com/display/article/10162/1828834.
2. Centers for Disease Control and Prevention. Lyme Disease Data. Accessed at www.cdc.gov/lyme/stats/index.html.
3. American Lyme Disease Foundation. Lyme Disease. Accessed at www.aldf.com/lyme.shtml.
4. Lyme Help. Lyme Disease Symptoms, Treatment and Lyme Disease Info. Accessed at www.lymehelp.org/lyme-disease-myths.htm.
5. Mayo Clinic. Lyme Disease. Accessed at www.mayoclinic.com/health/lyme-disease/DS00116.
6. McSweegan, E. Lyme Disease: Questionable Diagnosis and Treatment. Quackwatch. Accessed at www.quackwatch.com/01QuackeryRelatedTopics/lyme.html.
7. International Lyme and Associated Diseases Society. Basic Information about Lyme Disease. Accessed at www.ilads.org/lyme_disease/about_lyme.html.

Quadrivalent Flu Vaccines: Four Means More Protection

By Keith Berman, MPH, MBA, and Luke Noll

AHEAD OF EACH flu season, experts at the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO) isolate the influenza virus strains thought to be potentially the most virulent and supply them to manufacturers so they can prepare enough vaccine to distribute ahead of the fall-through-spring flu season. Trying to identify which of many antigenic variants will ultimately account for the bulk of infections and disease is a challenging and imperfect science. But evolutionary biology has added another important dimension to the game. Decades ago, there was only one influenza A strain (A/H3N2) and one B strain, and flu vaccines were "bivalent" — meaning they contained killed virus of each of the two strains. Then, in the mid-1970s, a second A strain (A/H1N1) emerged. By 1977, the vaccines industry transitioned to a "trivalent" flu vaccine (TIV) containing both A strains and the lone B strain. Today's inactivated or live attenuated flu vaccines are still all trivalent with two A strains and one B strain.

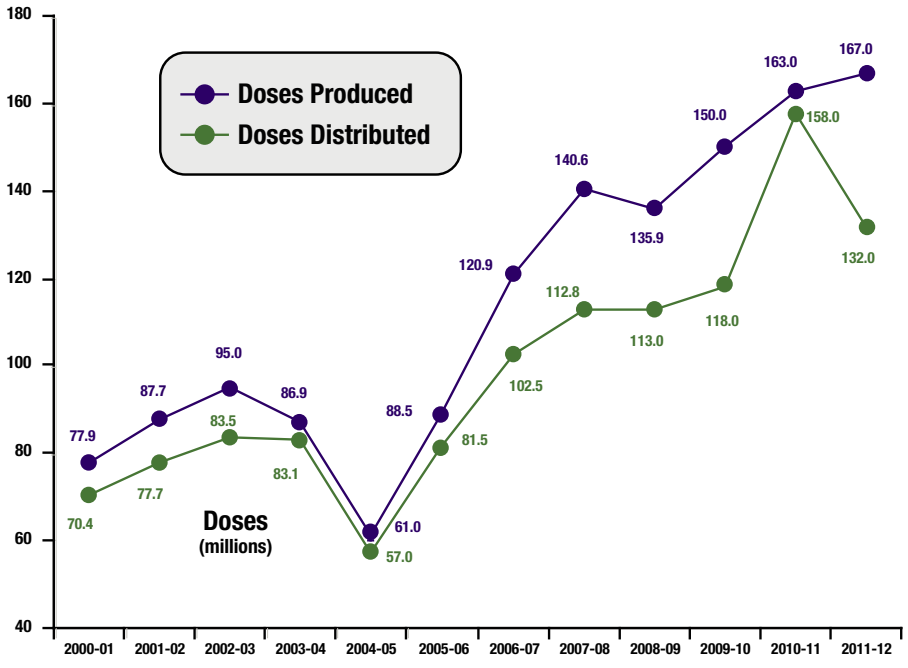
The evolutionary saga continued: In 1985, an entirely new lineage of the influenza B virus emerged. This new "Victoria" lineage was first isolated outside of China[1] and soon joined and co-circulated with the long-standing "Yamagata" B lineage. For a couple of years in the late 1980s, Victoria displaced Yamagata as the dominant cause of influenza B virus infections globally; then it receded in the 1990s as Yamagata reasserted itself as the predominant influenza B lineage.

But over the last decade beginning with the 2001-02 flu season, Victoria B viruses have again co-circulated with the Yamagata lineage in North America. "It looks like we're stuck with two lineages for the time being," said Dr.

Anthony Fiore, an epidemiologist at the Centers for Disease Control and Prevention's (CDC's) Influenza Division.[2] For the FDA and WHO experts, this has created the daunting task of trying to choose the lineage to include in the vaccine that they believe is likelier to predominate and spread to the U.S. Unfortunately, they've gotten it right just five times over those 10 years — no better than flipping a coin. Over the other five flu seasons, far more significant outbreaks occurred with the B lineage not selected for inclusion in flu vaccines supplied to the public. Discussion soon turned to the prospect of producing a four-strain — or "quadrivalent" — flu vaccine (QIV) that includes both the Yamagata and Victoria lineages to enhance its potential protective benefit.

But given the substantial variation in the influenza B attack rate from one season to the next, how much added benefit can be expected of a QIV that covers both lineages? While influenza B causes disease in all age groups, it accounts for an outsized proportion of deaths in children and young adults. From the 2004-05 through 2010-11 seasons, influenza B accounted for 22 percent to 44 percent of reported influenza deaths in children up to 18 years of age — and 34 percent of deaths overall.[3] "Influenza B strains are an important issue with regard to illness, particularly in children," notes Dr. Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases.[4] But influenza B also accounts for many hospitalizations and deaths in adults as well. The CDC recently quantified the potential health impact of a QIV in relation to the standard TIV. Its analysis suggested that administration of QIVs in the U.S. during the 2001-02 through 2008-09 seasons would have cumulatively yielded approximately 2.1 million fewer cases of influenza, 20,000 fewer hospitalizations and 1,200 fewer deaths.[5]

Figure 1. Doses of Seasonal Influenza Vaccine Produced and Distributed for the U.S. Market, 2000-2011



Today's inactivated or live attenuated flu vaccines are still all trivalent with two A strains and one B strain.

The Will and Now the Way

While discussion about including a second B lineage in the seasonal flu vaccine began some years ago, a critical impediment stood in the way: lack of adequate manufacturing capacity to produce a QIV and still make enough doses in total to meet projected demand.

While cell culture-based flu vaccines may be just around the corner, today all U.S.-licensed flu vaccines are still produced by inoculating embryonated chicken eggs — millions or tens of millions of them in a single facility — with live influenza virus. Highly specialized processes and automated equipment are needed to facilitate mass inoculation, harvesting and vaccine purification on this vast scale over a tight four- to five-month production cycle. Just a handful of manufacturers possess the requisite expertise. Yet even they are challenged by the demands of

attempting to expand each phase of production without risking contamination or other untoward events that can result in the loss of an entire bulk vaccine harvest.

From the 2001-02 through the 2005-06 flu seasons, fewer than 100 million doses of seasonal flu vaccine were produced and distributed in the U.S. (Figure 1). With the exception of the 2004-05 season, when a production problem created a vaccine supply shortage, the supplied quantities of flu vaccine tracked fairly closely with market demand. Because each embryonated egg is inoculated with only a single live virus strain, adding a second B lineage to produce QIVs during that period would have had the counterproductive effect of reducing the total number of doses that could be manufactured and supplied to the market.

For the first time, the vaccines industry finds itself with the capacity to inoculate many millions more eggs to produce large stocks of QIVs without jeopardizing its ability to make enough doses to satisfy market demand.

But since 2005-06, flu vaccine manufacturing capacity has dramatically expanded — a direct byproduct of avian and swine flu outbreaks that prompted the U.S. government to help industry improve preparedness for a potential global flu pandemic. As Figure 1 illustrates, both the produced and distributed doses of seasonal flu vaccine began to climb in the 2005-06 season. But available manufactured doses — more than 160 million over the last two flu seasons — have now outpaced market demand, clearly a reflection of the industry's much-expanded capacity. If WHO projections prove accurate, the approval of novel cell culture-based flu vaccines may further boost global production capacity of all flu vaccines by more than 50 percent, to around 1.7 billion doses.[6] For the first time, then, the vaccines industry finds itself with the capacity to inoculate many millions more eggs to produce large stocks of QIVs without jeopardizing its ability to make enough doses to satisfy market demand.

The Quadrivalents Are Coming!

In February, the FDA approved MedImmune's new live attenuated intranasal flu vaccine, FluMist Quadrivalent, for immunization against both subtypes of influenza A and B. MedImmune says it plans to discontinue production of its current trivalent FluMist vaccine ahead of the 2013-14 season and exclusively supply FluMist Quadrivalent, which is approved for vaccination of persons age 2 through 49 years.

Several other QIVs are likely to be approved in time for the 2013-14 flu season, including two from GlaxoSmithKline and one from Sanofi Pasteur (Table 1). As one would expect, the added influenza B lineage is fully immunogenic and does not interfere with the antibody-generating response to the other influenza antigens already included in these products. But unlike MedImmune, both companies plan to introduce the new QIV version together with their current TIV products.

Additionally, Novartis Vaccines is developing both egg-based and cell culture-based QIVs. The company recently reported findings from a European study evaluating both an adjuvanted and a non-adjuvanted QIV in children 6 years to less than 36 months of age.[7]

Questions Ahead for Policymakers and Suppliers

For the 2013-14 flu season, and likely for several seasons beyond, the U.S. flu vaccine supply will be a combination of TIV and QIV products. This situation will raise important new questions for public health policymakers, as well as for flu vaccine manufacturers and distributors that must try to match the mix of products and customer demand.

• *Advisory Committee on Immunization Practices (ACIP)*. Most immediately, this circumstance will create some interesting questions for the CDC's ACIP, whose recommendations guide seasonal flu vaccine ordering decisions. ACIP must decide which type of seasonal flu vaccine to recommend in the context of an approaching 2013-14 flu season where QIV products will account for only a small proportion of the overall flu vaccine supply.

The question initially, then, is: Will ACIP recommend immunization with QIV only for children at the highest risk for serious influenza B-related complications to optimize its accessibility for those who stand to benefit the most? Or, will ACIP decide to take a noncommittal position, as it did in response to the introduction of a high-dose TIV preparation (Fluzone High-Dose; Sanofi

Table 1.
Approved and Development-Stage Quadrivalent Influenza Vaccines (QIVs)

Approved:

Product/Supplier	Status
FluMist Quadrivalent (MedImmune)	*February 2012:* Approved by FDA for administration to persons aged 2 to 49 years. Will be available for 2013-14 flu season; MedImmune expects to replace all trivalent FluMist product with FluMist Quadrivalent.

Investigational:

Product/Manufacturer	Status
QIV products (GlaxoSmithKline)	*March 2012:* Applied for U.S. approval of QIV version of Fluarix (0.5 mL prefilled syringes) for immunization of persons 3 years and older. GSK plans also to apply for approval of QIV version of FluLaval by the end of 2012. GSK expects to offer both TIV and QIV products in the 2013-14 flu season.
Fluzone Quadrivalent (Sanofi Pasteur)	*May 2012:* Comparative safety/immunogenicity data presented from Phase III study in >4,300 children aged 6 months to 8 years. Immunogenicity of QIV in this Phase III study of >4,300 children was noninferior to TIV products for both A strains, and superior versus TIVs without the corresponding B lineage. *October 2011:* Broadly similar immunogenicity findings in a Phase II study in 675 subjects ≥65 years of age. A Phase III study in children and adults aged 9 to 60 years is currently ongoing. Sanofi Pasteur currently plans to phase in a limited supply of QIV for the 2013-14 flu season.
QIV products (Novartis Vaccines)	Developing egg-based and cell culture-based QIV products.

Pasteur) licensed for adults aged 65 years and older?[8] In that instance, clinical trial data have documented a significantly enhanced antibody response to high-dose TIV in older adults, but results of studies examining whether this translates into reduced illness or mortality are still pending.

• *Manufacturers*. Once a manufacturer secures approval to market its new QIV, on what basis should it decide whether and how many doses of its older TIV product should be produced and supplied? This delicate decision may involve the interplay of several factors, including ACIP recommendations relating to QIV versus TIV administration, production yield considerations, and potential market sensitivity to the higher price of QIV in relation to TIV.

• *Distributors*. No less interesting is the decision-making process that will face U.S. distributors that supply seasonal influenza vaccine to more than 220,000 sites of care, including more than 195,000 physician offices and clinics, as well as thousands of hospitals, long-term care facilities, pharmacies and other providers.[9] What will ACIP recommend? How will ACIP guidelines, the TIV-QIV pricing differential, initiatives to boost vaccination rates and other influencers translate into market demand for TIVs and QIVs? For each distributor, it all boils down to this question: In the midst of all these changes, how many doses of TIVs and QIVs should they commit to purchase?

Count On It: Quadrivalents Will Prevent Illness, Save Lives

For any given flu season, we know that the potential benefit in averted hospitalizations and deaths attained by adding the second B virus lineage to flu vaccines is essentially a matter of chance. In 2002-03, for example, B lineages accounted for an unusually high 43 percent of all cultured influenza infections, according to a CDC study cited

earlier.[5] But the Victoria lineage, which accounted for 99.6 percent of B virus picked up on virologic surveillance, was selected for inclusion in the flu vaccines administered that season. CDC estimated that addition of the second Yamagata B lineage in that year's flu vaccine would not have yielded any health benefits to the vaccinated population.

But CDC experts describe an entirely different picture for the 2007-08 flu season: B viruses accounted for 29 percent of all flu infections — nearly one-third. But this time, WHO and FDA virologists picked the wrong B lineage: Ninety-eight percent of identified cases with a B virus infection carried the Yamagata lineage, but that year manufacturers were given only the Victoria lineage to include in the vaccine. CDC's model estimates that nearly one million flu illnesses and a surprising 484 deaths could have been averted with the Yamagata lineage added as a fourth vaccine antigen. In the following 2008-09 season, the experts got it wrong again and included the Yamagata lineage, only to see the Victoria lineage predominate with 83 percent of B virus-induced infections. Had both lineages been in all flu vaccines, CDC estimates that 169 lives could have been saved.

One thing is clear: For many millions of people at risk for serious influenza B-related illness, this new class of QIVs will be a welcome — and potentially lifesaving — advance.

One thing is clear: For many millions of people at risk for serious influenza B-related illness, this new class of QIVs will be a welcome — and potentially lifesaving — advance over the annual coin flip that limits the protective value of our current generation of trivalent products. ❖

References

1. Chen, JM, Guo, YJ, Wu, KY, et al. Exploration of the Emergence of the Victoria Lineage of Influenza B Virus. *Archives of Virology*, 2007;152:415-22.
2. Roos, R. Experts Consider 4-Strain Flu Vaccine to Fight B Viruses. Centers for Infectious Disease Research and Policy News; 2009 Jan 16. Accessed 4/29/2012 at www.cidrap.umn.edu/cidrap/content/influenza/general/news/jan1609flub.html.
3. Ambrose, CS, and Levin, MJ. The Rationale for Quadrivalent Influenza Vaccines. *Human Vaccines and Immunotherapeutics*, 2012 Jan;8(1):1-8.
4. Dolgin, E. Four-Strain Flu Vaccines Coming to a Pharmacy Near You. *Nature Medicine*, 2012 Apr 5;18:471.
5. Reed, C, Meltzer, M, Finelli, L, et al. Public Health Impact of Including Two Influenza B Strains in Seasonal Influenza Vaccines. *Vaccine*, 2012;30:1993-8.
6. Kieny, M. World Health Organization. Overview of Global and Regional Influenza Vaccine Production Capacity. July 13, 2011. Accessed 5/21/2012 at who.int/influenza_vaccines_plan/resources/mpk_b.pdf.
7. Della Cioppa, G, Vesikari, T, Sokal, E, et al. Trivalent and Quadrivalent MF59-Adjuvanted Influenza Vaccine in Young Children: A Dose- and Schedule-Finding Study. *Vaccine*, 2011 Nov 3;29(47):8696-8704.
8. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *Morbidity and Mortality Weekly Report*, 2011 Aug 26;60(33):1128-32.
9. Health Industry Distributors Association (HIDA). 2010-2011 Influenza Vaccine Production and Distribution Market Brief.

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. Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

LUKE NOLL *is director of vaccine sales and corporate accounts at FFF Enterprises Inc.*

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Leading the Way in Vaccine Innovation

"I love vaccines; I believe fundamentally that vaccination is an instrument of public health and feel we have a very important responsibility to the greater good. I honestly believe we are engaged in a noble endeavor; vaccines save lives."

— Brent MacGregor, president, Novartis Vaccines, U.S.

by Trudie Mitschang

BRENT MACGREGOR stepped into his leadership role at Novartis Vaccines on January 1 of this year and, essentially, hit the ground running. With more than 16 years of global experience in an industry he describes as "vibrant and exciting," MacGregor joined Novartis from Sanofi Pasteur, where since 1995 he held leadership positions of increasing importance, including vice president of the influenza and pneumococcal franchise; managing director, Australia/New Zealand; and most recently, managing director, Japan. Beginning his career as a sales representative, MacGregor has extensive experience in the vaccines industry spanning roles in marketing, sales, strategic planning and general management in five different countries.

Clearly, he stands well prepared to lead Novartis into new spheres of influence and success. "For me, leadership is heavily behavioral — you have to lead by example in order to instill leadership skills in your team," says MacGregor. "I believe in a very collaborative approach that is extremely team-oriented. I also strongly believe people don't need to wait to be empowered; if you create a culture that is supportive, people will feel empowered to make decisions and offer meaningful contributions."

As someone who takes changes in stride, MacGregor is currently leading his entire regional vaccine team in a relocation from Cambridge, Mass., to the Novartis campus in East Hanover, N.J. Once there, he plans to build upon the current Novartis Vaccines culture, which he says promotes an entrepreneurial spirit coupled with an element of risk-taking that he thrives on. "What I hope to bring to the table as someone who has been in the industry a long time is a clear, concise view of what we're up against in terms of competition," he explains. "This culture suits me because I believe in a certain amount of risk-taking; we're not the biggest player in the industry, but we have an important contribution to make in U.S. public health."

"This culture suits me because I believe in a certain amount of risk-taking."

Making the Case for Vaccines

As the U.S. government struggles with the ever-increasing cost of healthcare, those in the vaccine industry are well positioned to argue that by promoting preventive vaccines, public health officials can avoid the high cost of treating disease later. But, as MacGregor acknowledges, it can sometimes be a difficult argument to convey: "There are many challenges we face within the industry, including the ebb and flow of the anti-vaccine movement. In a sense, we have become

victims of our own success because there has been such a significant reduction in certain infectious diseases, due to the overwhelming success of routine vaccination in the U.S., that some people don't see a reason to continue vaccinating. Ironically, they are ignoring the fact that diseases have diminished because vaccines work."

In recent years, vaccine complacency has been particularly pronounced when it comes to flu immunizations. With back-to-back flu seasons that were particularly mild, coupled with a perceived overreaction to the 2009 H1N1 pandemic, MacGregor says "flu fatigue" set in among individuals and healthcare providers. At a recent influenza conference, he noted that one of the ideas under consideration involves getting the five flu vaccine manufacturers in the U.S. to band together behind a single marketing message. "Instead of a fragmented approach, it may make sense to convey one key message that supports public health," he says. "With two new strains added to this year's vaccine, the timing may be right to help people understand the inherent risks associated with flu. The challenge is to raise awareness of the risks of the flu without scaring people."

Meeting Industry Demand

When it comes to meeting the changing demands of the industry, Novartis Vaccines is responding with improved options in the categories of flu and meningitis. With a long history of industry leadership in the areas of innovation and technology, the company is poised to continue blazing new trails. Currently, Novartis Vaccines is anticipating the opening of a new manufacturing facility located in Holly Springs, N.C. The facility is slated to begin commercial-scale operations in 2013, and will be the first-of-its-kind U.S. facility producing cell culture-based flu vaccines. "Cell culture-based flu vaccine production is essential in terms of reducing the flu vaccine industry's dependence on eggs," says MacGregor. "The opportunity to bring this innovative technology to the U.S. market, from a U.S.-based facility, is especially exciting."

In 2010, Novartis Vaccines launched Menveo, a vaccine to prevent meningococcal disease, the leading cause of bacterial meningitis. The culmination of 10 years of dedicated effort, Menveo represented an immunization milestone for millions of adolescents at risk for this often-deadly disease. Novartis Vaccines is actively working to expand the age indications for Menveo to make the vaccine available to patients as young as 2 months of age.

Also on the near-term horizon, MacGregor says the company's research and development team is targeting meningitis B, a disease that is particularly dangerous for children; there are approximately 1,200 new cases of meningitis B every year. Of those cases, one in 10 people die and another 15 percent are left with permanent disabilities such as limb amputation. "Clinical trials are promising, and we expect to launch a vaccine within the year, beginning with Canada and the U.K.," says MacGregor. "One of our goals is to become a much more impactful player when it comes to meningitis prevention; this vaccine would be a key component of that strategy."

Another initiative in the Novartis pipeline involves exploring the benefits of maternal immunizations. Currently in the preclinical trial phase, the study examines how vaccinating pregnant women can protect the mother against vaccine-preventable disease, while also passing those antibodies on to the unborn child. One of the diseases being studied is group B streptococcus, common and harmless in pregnant women, but life-threatening for newborns.

Novartis plans to achieve its ambitious goals by focusing on innovative solutions that will support both customers and key stakeholders.

A Promising Future

Always an advocate of specific and measurable goals, MacGregor says he aspires to elevate Novartis Vaccines from its current No. 5 spot among vaccine manufacturers in the U.S.; he has his sights set on reaching the No. 3 position in the coming years: "I want to bring an even greater contribution to U.S. public health; the pipeline we have currently is regarded as one of the most vibrant in the industry, so we have a solid foundation to build upon."

According to MacGregor, Novartis plans to achieve its ambitious goals by focusing on innovative solutions that will support both customers and key stakeholders. As far as his personal ambitions, MacGregor maintains that his passion for the industry is what inspires him daily: "I love vaccines; I believe fundamentally that vaccination is an instrument of public health and feel we have a very important responsibility to the greater good. I honestly believe we are engaged in a noble endeavor; vaccines save lives." ❖

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

HIV: A Patient's Perspective

Results from a routine physical permanently altered the course of Jacques Whitfield's life by revealing he was HIV positive. But for this patient-turned-advocate, promoting prevention has become his life's passion.

Jacques Whitfield was diagnosed with HIV at age 43, but today, due to dietary changes, exercise and adherence to his medication regimen, he is the picture of health.

IT WAS JUNE of 2007, but Jacques Whitfield remembers it vividly. The then-43-year-old attorney had recently come to terms with his homosexuality and was in the process of ending his marriage of 11 years. Optimistic about the future, he was just finishing a meal with his soon-to-be ex-wife when she reached into her purse and grimly handed him an envelope. Puzzled, Whitfield scanned the letter from his life insurance company, slowly absorbing the news that would forever change his life; he'd been exposed to the HIV virus. "It was like a movie scene where everything in the room suddenly disappears," he recalls. "In my mind, I saw the faces of all the friends I'd lost over the years to HIV/AIDS — I just couldn't believe I had become a statistic."

From Denial to Hope

Prior to his diagnosis, Whitfield's professional background included volunteer work in HIV/AIDS education, making him familiar with the symptoms and treatments associated with the virus. Like most people, however, he never thought it could happen to him. Healthy and symptom-free, Whitfield went into what he calls "HIV denial," shunning prescribed medications for over a year. The wake-up call came when he learned he was responsible for infecting someone else. "It's an indescribable guilt that will never go away," he says. "It's like the ultimate karma because the same thing was done to me."

Whitfield realized if he wanted to be around for the three children he was actively co-parenting, it was time to get in the game and fight. A short time later, he qualified for a Kaiser-sponsored HIV clinical trial. That's when his real journey as an HIV patient began. "Taking daily medication is a reminder that you are sick, and it is a lifetime commitment because if you are noncompliant, the virus can become transmuted and severely compromise your health," he explains. "Everything was fine until my insurance plan changed and I was no longer eligible for the trial. My viral load numbers escalated, I became depressed and fell out of treatment — that was a difficult time."

Eventually, Whitfield changed jobs and obtained the insurance coverage necessary to manage his disease. Whitfield acknowledges his situation is not the norm; few people have the insurance or the personal means to cover both HIV treatment and the pricey prescription medications needed to keep them alive. "I'm very appreciative of the position I'm in today because I can afford the medical care I need," he says. "For patients who don't have the means, it can be a matter of life and death."

Advocating for Education

It's been five years since Whitfield's diagnosis, and at 48, he appears the picture of health. Dietary changes, exercise and an adherence to his medication regimen help, as does a positive outlook. A busy single dad, he recently celebrated an anniversary with his partner of one year. The director of human resources development and personnel services for Yuba Community College District, he also is a board member and speaker for Sacramento's Center for AIDS Research, Education & Services (CARES), where he donates his time and energy speaking to as many as 5,000 high school and college students annually about the risks associated with various sexual behaviors. No longer saddled by shame, he's frequently applauded for his candor about his personal truths. "I believe in the power of transparency, and I refuse to live in fear, shame or condemnation," he says. "If sharing my story will help others avoid this path, then I will feel I've accomplished my life's purpose." ❖

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

HIV: A Physician's Perspective

Improved medications and lowered mortality rates have tasked providers with helping patients not only adhere to treatment plans, but also navigate the emotional and social implications of living long term with HIV.

Dr. J. Kevin Carmichael oversees the care of HIV-infected patients, as well as provides clinical support for physicians dealing with HIV in Tucson, Ariz.

AS CHIEF OF service at El Rio Special Immunology Associates (SIA) in Tucson, Ariz., Dr. J. Kevin Carmichael oversees the care of 1,250 HIV-infected patients and personally attends to almost 300. He also provides clinical support for area physicians dealing with HIV.

BSTQ: Tell us about your early work with HIV/AIDS.

Dr. Carmichael: I was in medical school from 1982 to 1986 in Miami, Fla., when HIV was first coming along and many doctors referred to it as "gay-related immune deficiency." As the epidemic unfolded, we saw more and more women and children infected. It was common back then to have kids living in the hospital because their parents had died and no one would adopt them because they were going to die too. It was a difficult time.

BSTQ: How have things changed?

Dr. Carmichael: In the '80s and early '90s, our work was largely about caring for dying people. Since 1996, it's been more about helping people living with HIV attain meaningful and healthy lives. Doctors who are getting into HIV treatment today have a different perspective. When I started, there were times when, no matter how much you wanted to, there was simply nothing you could do. People were really sick, and you could offer little hope.

BSTQ: How has HIV treatment evolved?

Dr. Carmichael: I believe the evolution of HIV treatment is the greatest medical success story in my lifetime. In 1995, 14 out of every 100 patients in our clinic died. As of this year, it is one out of 100. Complicated multipill regimens have been replaced by more combination formulations dosed once or twice daily. Highly Active Antiretroviral Therapy (HAART) has sufficient potency [so] that viral control is common and the development of viral resistance is significantly reduced. When you look at the majority of people who die from HIV today, it is often because they are not on treatment.

BSTQ: How much does HIV care cost?

Dr. Carmichael: On average, medications run $25,000 to $30,000 per year, plus the cost of lab work to monitor care. The largest expense in HIV care today is medication, compared to the old days when it was in-hospital care.

BSTQ: How do you encourage patient compliance?

Dr. Carmichael: We use the term adherence rather than compliance; it means the patient is making a decision to do something as opposed to doing something I'm asking them to do. My job is not to shake my finger and make you take your pills. My job is to convince you [that] the plan you and I came up with is in your best interest. The HIV virus replicates very rapidly, and if people don't take their medications on a consistent basis, the virus replicates in the presence of low levels of drugs, and drug-resistant virus results. We understand human nature; no one will be perfect. We ask patients to aim for 95 percent adherence and, in fact, the majority of our patients have undetectable viral loads.

BSTQ: What advice do you have for clinicians?

Dr. Carmichael: I think the biggest issue for general practitioners is not doing enough HIV testing. The current CDC [Centers for Disease Control and Prevention] guideline recommends all people ages 13 to 65 be checked annually, but testing is rarely offered because doctors are busy, have many issues to address, and can be reluctant to raise HIV testing for fear of offending patients. As physicians, I think we have an obligation to lead the discussion. I'd like to see us move toward a time when HIV testing is part of routine medical care. ❖

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

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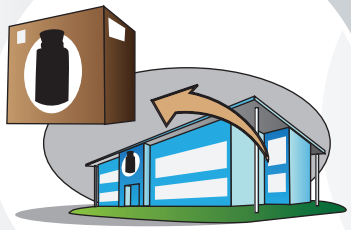

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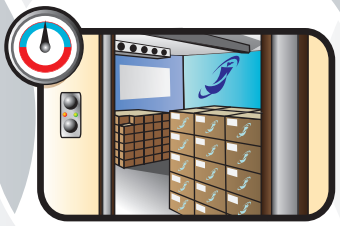

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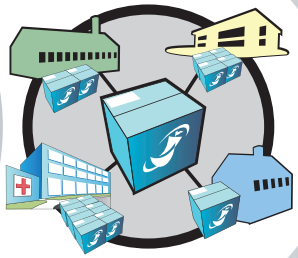

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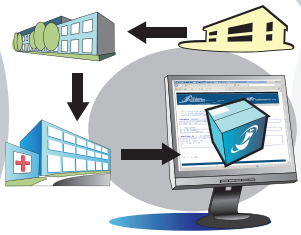

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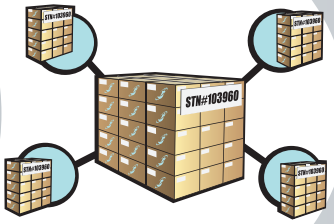

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Intravenous Immunoglobulin Protects Neurons Against Amyloid Beta-Peptide Toxicity: In Vitro and Murine Studies

Prompted by interest in its potential use for treatment of stroke and Alzheimer's disease, a multinational team of investigators exposed cultured neurons with intravenous immunoglobulin (IVIG) to evaluate its effect on downstream signaling pathways involved in neuronal cell death. In vitro treatment of neurons with IVIG reduced both simulated ischemia- and amyloid beta peptide-induced caspase-3 cleavage and phosphorylation of the cell death-associated kinases p38MAPK, JNK and p65.

Additionally, amyloid beta peptide-induced accumulation of the lipid peroxidation product 4-HNE was attenuated in neurons treated with IVIG. IVIG treatment also upregulated the apoptotic protein Bc12 in cortical neurons under a combination of ischemia-like conditions and exposure to amyloid beta.

In a model of focal ischemic stroke, treatment of mice with IVIG was shown to reduce neuronal cell loss, apoptosis and infarct size, and improved functional outcome. Together, these results indicate that IVIG acts directly on neurons to protect them against ischemic stroke and amyloid beta-induced neuronal apoptosis by inhibiting cell death pathways and by elevating levels of the anti-apoptotic protein Bc12, the authors concluded.

Widiapradja, A, Vegh, V, Lok KZ, et al. Intravenous immunoglobulin (IVIg) protects neurons against amyloid beta-peptide toxicity and ischemic stroke by attenuating multiple cell death pathways. Journal of Neurochemistry, *2012 Apr 12 [Epub ahead of print].*

Immunogenicity and Safety of Quadrivalent Live Attenuated Influenza Vaccine in Children

A randomized, double-blind study was conducted to demonstrate the immunologic noninferiority of an investigational quadrivalent live attenuated influenza vaccine (Q/LAIV) developed by MedImmune. Q/LAIV contains both of the influenza B virus lineages, in contrast to available trivalent vaccines that include only one of the two lineages that co-circulate each year. This trial compared the safety and immunogenicity of Q/LAIV with that of two trivalent LAIVs (T/LAIVs) in children from 2 years to 17 years of age.

Children were randomized 3:1:1 to receive Q/LAIV or one of two T/LAIV vaccines. Subjects aged 9 years to 17 years received one dose, and those aged 2 years to 8 years received two doses one month apart. Serum immune responses, measured as geometric mean titers (GMTs) of hemagglutination inhibition antibodies, were evaluated one month after the single dose or two-dose series.

Q/LAIV was found to be noninferior to T/LAIV: the upper bounds for all four 95% confidence intervals for the post-dose GMT ratios (T/LAIV divided by Q/LAIV) were ≤1.5, the predefined noninferiority margin. The overall seroresponse rates were also comparable between treatment groups. Adverse event rates for the three treatment groups were comparable excepting fever, which was more common after dose 1 in Q/LAIV subjects (5.1%) than in T/LAIV subjects (3.1%) between 2 years and 8 years of age.

Block, SL, Falloon, J, Hirschfield, JA, et al. The immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. The Pediatric Infectious Disease Journal, *2012 Mar 29 [Epub ahead of print].*

Biotest's Investigational 10% Liquid IVIG Assessed in Patients with PIDD

An investigational 10% liquid intravenous immunoglobulin (IVIG) product currently under U.S. regulatory review for marketing approval appears to be safe and effective for prophylactic treatment of patients with primary immunodeficiency disorders (PIDDs), according to a study involving 63 PIDD patients conducted at 15 U.S. clinical study sites. Developed by Biotest Pharmaceuticals, this product is manufactured from source plasma by Cohn-Oncley fractionation followed by ion exchange chromatography.

Patients ranging in age from 6 years to 75 years received a total of 746 infusions of Biotest-IVIG every three or four weeks. The mean dose per infusion was 500 mg/kg, with a range of 254 to 1,029 mg/kg. Fifty-two patients were treated with the product for at least 12 months. Two serious bacterial infections (SBIs) were observed, translating into a rate of 0.035 SBIs per person per year, which is well below the ≤1.0 SBI per patient-year target recommended by the U.S. Food and Drug Administration (FDA). Two patients were hospitalized for infection, producing a rate of 0.21 hospitalization days/patient/year. Just 2.28 work or school days/patient/year were missed due to infection; nearly two-thirds of patients did not miss a day of work or school.

The proportion of infusions with one or more temporally associated adverse events (TAAEs) was 27.7% (upper one-sided 95% confidence limit, ≤30.6%), significantly below the 40% limit recommended by the FDA. The IgG half-life for all patients was about 30 days, with significant variation among individuals. Throughout the study, however, all patients maintained an average serum IgG level above 500 mg/dL.

Wasserman, RL, Church, JA, Stein, M, et al. Safety, efficacy and pharmacokinetics of a new 10% liquid intravenous immunoglobulin (IVIG) in patients with primary immunodeficiency. Journal of Clinical Immunology, *2012 Mar 6 [Epub ahead of print]*

BioResources

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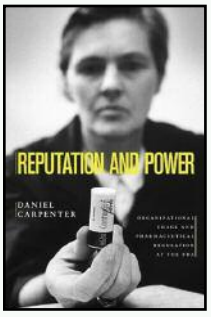

Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA

Author: Daniel Carpenter

Reputation and Power traces the history of U.S. Food and Drug Administration (FDA) regulation of pharmaceuticals, revealing how the agency's organizational reputation has been the primary source of its power, yet also one of its ultimate constraints. The author describes how the FDA cultivated a reputation for competence and vigilance throughout the last century, and how this organizational image has enabled the agency to regulate an industry as powerful as American pharmaceuticals while resisting efforts to curb its own authority. He also explains how the FDA's reputation and power have played out among committees in Congress, and with drug companies, advocacy groups, the media, research hospitals and universities, and governments in Europe and India. Carpenter shows how FDA regulatory power has influenced the way that business, medicine and science are conducted in the United States and worldwide. Along the way, he offers new insights into the therapeutic revolution of the 1940s and 1950s; the 1980s AIDS crisis; the advent of oral contraceptives and cancer chemotherapy; the rise of antiregulatory conservatism; and the FDA's waning influence in drug regulation today.

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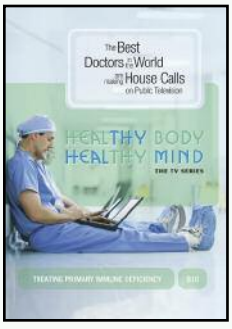

Treating Primary Immune Deficiency (Educational Use)

Treating Primary Immune Deficiency is part of the award-winning public television series "Healthy Body, Healthy Mind." The educational program describes primary immune deficiency — which is diagnosed in several hundred children each year, and which thousands of adults have, many of whom don't know it — and how it can successfully be treated or even cured. It also delves into new insights about the disease.The DVD is manufactured on demand, is for self-education use only and is prohibited from being used in any educational setting.

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Mobile Drug Labeling Tool

Sources: Skyscape and MedHand

MobilePDR is now available for mobile devices or smartphones. It is based on the Physicians' Desk Reference, the source for FDA-approved drug labeling information, and it is free to U.S. prescribers. Features include a comprehensive search feature, new drug labeling information, color images of medications and full prescribing information. Powered by Skyscape, the device is available for Android, BlackBerry, iPhone/iPod touch/iPad, Palm OS and Windows Mobile/Pocket PC/Smartphone. Powered by MedHand, the device is available for iPhone, iPod touch and iPad.

www.pdr.net

EHR Event Reporting System

Source: iHealth Alliance

An Electronic Health Record (EHR) Event Reporting System has been developed by the iHealth Alliance in collaboration with the U.S. Food and Drug Administration (FDA), the Agency for Healthcare Research and Quality (AHRQ) and the PDR Network. Using a standardized online form, EHRevent.org will collect information from physicians and other healthcare providers who work with EHRs, and it will create reports that medical societies, professional liability carriers and the FDA can use to help educate providers about possible challenges with these electronic systems. Reports will be kept confidential through PDR's designation as a patient safety organization. Only participating organizations will be able to access the reports, which will be used to better understand challenges with EHR adoption and improve EHR and patient safety. Data also will be used by the FDA to help evaluate issues related to EHRs and their use. EHRevent.org will be governed by the iHealth Alliance, with network operations provided by the PDR Network.

www.EHRevent.org

BioProducts

Extreme Climate Shipping Solution

Xtremotherm Extreme Exposure Systems provide a range of shipping solutions designed to protect critical patient sample payloads against degradation during periods of extreme temperature exposures that are common during shipment due to increasingly remote clinical sites. They are certified for time ranges from four hours to 38 hours at constant external temperatures of minus 30 degrees Centrigrade. At the extreme end of the product range is Xtremotherm-5, which utilizes proprietary patent-pending peak ratio algorithm technology that delivers the absolute optimal size for maximum performance.

Intelsius, (317) 452-4006, www.intelsius.com

Insulated Medicine Carry Cases

Thermotrek systems are a range of insulated patient carry cases designed for movement of temperature-sensitive medications either being tested in clinical trials or for approved and marketed medicines used by patients. The systems are qualified to maintain contents at the required temperature for up to 24 hours and are designed to ensure many months of use. The first two released Thermotrek cases are constructed with proprietary materials that provide a high level of resistance to tears or abrasions and provide stain- and water-resistance. Each case is ergonomically designed to have a minimum impact on the patient's daily life and enable comfortable transportation of medicine. In addition, the cases' discreet design keeps the contents confidential.

Intelsius, (317) 452-4006, www.intelsius.com

Immune System Sensor

An inexpensive new medical sensor, called an integrated microfluidics-waveguide sensor, has the potential to simplify the diagnosis of diseases ranging from life-threatening immune deficiencies to the common cold. For instance, instead of using the current trial-and-error method for diagnosing a runny nose, doctors could take a mucus sample from the patient in their office and measure the white blood cells present to determine if the cause is allergies, a sinus infection or simply due to the common cold. The sensor, which is about the size of an adult's thumbnail, counts cells in small samples of blood and other body fluids. It consists of a small, rectangular piece of glass impregnated with a strip of potassium ions that act as a "waveguide." To operate it, a patient's fluid sample is mixed with antibodies specific for the particular type of white blood cells to be measured. It has been invented by a team at the Stanford University School of Medicine led by Manish Butte, MD, PhD, who is an assistant professor of pediatrics at Stanford, a pediatric immunologist at Lucile Packard Children's Hospital and the senior author of a paper describing the sensor (published online March 7 in *Biomicrofluidics*). Butte developed the sensor because he wanted a better way to screen newborns for severe combined immunodeficiency. According to Butte, this would be "a low-cost way of counting cells [that] could provide point-of-care diagnosis and monitoring for immune disorders, allergies, infections, AIDS, cancer and other disorders." The prototype cost about $60 to build using off-the-shelf electronics components, but Butte says the per-unit cost would be lower if the sensors were manufactured in bulk. Although it is not yet available commercially, Stanford University has filed for a patent for the device, and the inventors are seeking a partner to commercialize the sensors.

The Lancet iPad App

This new app provides innovative, article-based navigation across all Lancet titles including *The Lancet*, *The Lancet Oncology*, *The Lancet Neurology* and *The Lancet Infectious Diseases*. Healthcare professionals can download articles for immediate or future use, either on or offline, share articles with colleagues, annotate articles, create alerts and bookmark favorites. It can be downloaded from the Apple iTunes store or by registering on *The Lancet* website.

The Lancet, (800) 462-6198, USLancetCS@elsevier.com

BioDashboard

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective July 1, 2012 through September 30, 2012.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+4% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$61.03	$62.20
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$68.59*	$68.59
GAMMAGARD LIQUID	Baxter BioScience	J1569	$77.06	$78.54
GAMMAGARD S/D	Baxter BioScience	J1566	$61.03	$62.20
GAMMAKED	Kedrion	J1561	$75.35	$76.80
GAMMAPLEX	Bio Products Laboratory	J1557	$74.59*	$74.59
GAMUNEX-C	Grifols	J1561	$75.35	$76.80
OCTAGAM	Octapharma	J1568	$67.13	$68.42
PRIVIGEN	CSL Behring	J1459	$68.76	$70.08

*ASP + 6% (pass-through drug)

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Indication	Size	Manufacturer
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter BioScience
GAMMAGARD S/D Lyophilized, 5% or 10%	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g	Baxter BioScience
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL	CSL Behring
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g	CSL Behring

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PIDD Primary immune deficiency disease

2012-2013 Influenza Vaccine

Administration Codes: G0008 (Medicare plans) 90471 (non-Medicare plans)
Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	Code
FLUZONE Intradermal	0.1 mL microinjection	Influenza virus vaccine, split virus, preservative free, for intradermal use	90654
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
AGRIFLU	0.5 mL prefilled syringe		
FLUARIX	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUMIST	0.2 mL nasal spray	Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age	90660
FLUZONE High-Dose	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLULAVAL			Q2036
FLUVIRIN			Q2037
FLUZONE			Q2038

GAMUNEX®-C

Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX-C, [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]

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 occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

----------INDICATIONS AND USAGE----------

GAMUNEX-C is an immune globulin injection (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. Have epinephrine 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.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may 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 (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

----------ADVERSE REACTIONS----------

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMUNEX-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia.

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 transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. Passive transfer of antibodies may confound serologic testing.

----------USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

Talecris BIOTHERAPEUTICS

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

08939771/08939782-BS
Revised: October 2010

The PROOF is everywhere you look

GAMUNEX-C has proven efficacy and patient outcomes in CIDP, PI, and ITP*[1]

Important Safety Information for GAMUNEX-C

Gamunex-C, Immune Globulin Injection (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).

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gamunex-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gamunex-C at the minimum concentration available and the minimum infusion rate practicable.

Gamunex-C is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

Gamunex-C is not approved for subcutaneous use in patients with ITP or CIDP. **Due to the potential risk of hematoma formation, Gamunex-C should not be administered subcutaneously in patients with ITP.**

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

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, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV.

The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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.

In clinical studies, the most common adverse reactions with Gamunex-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PI) and infusion site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies 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 immunodeficiency; ITP=Idiopathic thrombocytopenic purpura.

Reference: 1. Data on file, Grifols.

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-C full Prescribing Information.

gamunex®-C

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

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www.gamunex-c.com

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