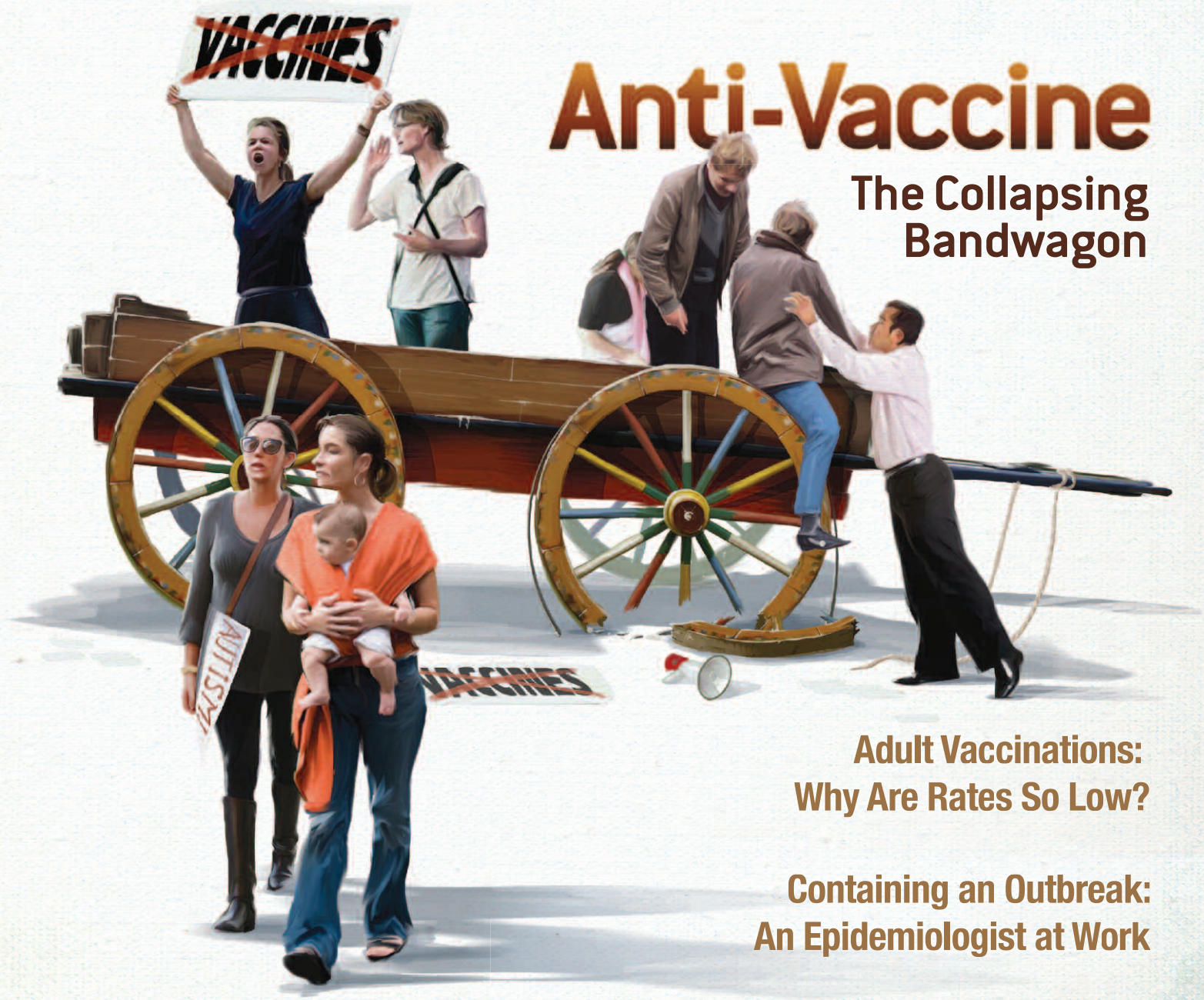
July 2014

BioSupply Trends

Special Focus: VACCINES

Quarterly



Anti-Vaccine
The Collapsing Bandwagon

Adult Vaccinations: Why Are Rates So Low?

Containing an Outbreak: An Epidemiologist at Work

How Healthcare Reform Affects Providers

The Changing Face of HIV

Myths & Facts: Skin Cancer

Novel Plasma Proteins for Major Cardiovascular Disorders — Page 48

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Protein Sciences CORPORATION

CPT Code 90673

Flublok (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok safely and effectively. See full prescribing information for Flublok available at www.Flublok.com.

INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

DOSAGE AND ADMINISTRATION

A single 0.5 mL dose for intramuscular injection.

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5mL single dose vials.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks.

ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (>37%); the most common (≥10%) solicited systemic adverse reactions were headache (>15%), fatigue (>15%) and myalgia (>11%).

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older.
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Revised: October 2013

Manufactured by:
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450
(203)686-0800 • www.proteinsciences.com

FB13017-1

www.Flublok.com

BioSupply Trends Quarterly

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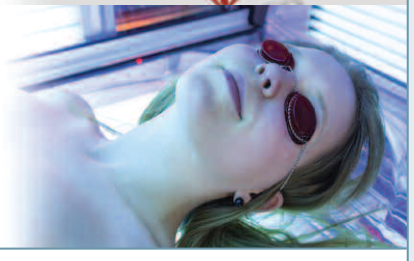
Features

Special Focus: Vaccines



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

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 41093 County Center Drive, Temecula, CA 92591

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

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Celebrating Five Years of BioSupply Reporting

IT'S HARD TO believe it's been five years since the first issue of *BioSupply Trends Quarterly* went to press. This publication was originally envisioned as an expanded edition of our BioSupply Trends bi-weekly e-newsletter, filled with up-to-date news, trends and perspectives impacting the biopharmaceuticals marketplace. Since its debut, *BioSupply Trends Quarterly* has won numerous awards for its in-depth content and outstanding cover designs, in addition to being named among the top-10 pharmaceutical magazines for 2010 by Cision U.S. Inc, a leading media relations firm.

This fifth anniversary issue puts a spotlight once again on the ever-evolving landscape of the vaccine industry. Since the year 2000, the vaccines market has nearly tripled, exceeding $17 billion globally. Long considered the most significant innovation of the 20th century, vaccines continue to play a significant role when it comes to addressing issues that include increased life expectancy, infectious disease outbreaks and childhood mortality in developing countries.

Ever since actress Jenny McCarthy became a poster mom for the anti-vaccine movement in 2008, a rising tide of highly vocal vaccine opponents has created a wave of public cynicism and distrust regarding vaccine efficacy and safety. Even though the now infamous *Lancet* study linking vaccines to autism has been publicly discredited, misinformation continues to abound. Our article "The Anti-Vaccine Movement: Where Are We Now?" explores this still volatile issue amid recent reports from the Centers for Disease Control and Prevention that the U.S. now has the most measles cases in 20 years, as well as the most cases since homegrown outbreaks were eliminated in 2000. As of May, the case count was 288 and growing.

As public health officials grapple with questions about containing outbreaks of highly infectious diseases like measles, the timely article "Containing an Outbreak: An Epidemiologist at Work" delves into the complex steps that must be taken from the moment an infectious disease is suspected, to the use of new mobile apps and GPS technologies that can help retrace the trail of infected patients and assist in disease intervention.

While the anti-vaccine movement has largely focused on childhood immunizations, the recommendations for adult vaccines have received far less attention from patients, physicians and the media. There are 17 vaccine-preventable diseases targeted by immunization recommendations across a person's lifespan, yet many of the new immunizations and booster vaccines for adults are often overlooked or ignored. With low adult vaccination rates resulting in thousands of deaths annually, our article "An Update on Adult Immunizations" looks at the need to increase education and awareness about this surprisingly high-risk group.

HIV/AIDS is another infectious disease that has confounded the medical establishment since it was first diagnosed in the early 1980s, fanning fears of a new and deadly plague. A lot has changed since a diagnosis of HIV was a guaranteed death sentence. And, as our article "The Changing Face of HIV" examines, the evolution of treatment and ongoing research seems to be moving us closer to a potential HIV vaccine and perhaps even a cure.

As a publisher, we look back with great pride on these past five years, and we will continue to make it our mission to provide you with timely, newsworthy and critical information impacting the biopharmaceuticals marketplace. As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and we welcome your comments.

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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CMS Issues Key Changes to Ensure High-Quality Care

The Centers for Medicare and Medicaid Services' 2015 rate announcement and final call letter for Medicare Advantage and Part D programs implements several policies that will ensure beneficiaries have access to high-quality, high-value and low-cost options. There are four key updates for 2015: lower out-of-pocket prescription spending for Part D beneficiaries in the prescription drug "donut hole"; protection for Medicare Advantage beneficiaries from major cost increases or reduction in benefits through the Affordable Care Act; increased protection through established provider access and established best practices for beneficiaries affected by changes in Medicare Advantage plan networks; and payment adjustments to Medicare Advantage plans that include reducing excessive payments, basing part of Medicare payment on plan quality performance, and improving Part C payment scheduling and accuracy. Nearly 30 percent of Medicare beneficiaries are enrolled in a Medicare Advantage plan, and nearly half of enrollees are now in plans with a rating of four or more stars, a significant increase from 37 percent in 2013. ❖

Proposed Legislation to Curb Prescription Drug Abuse

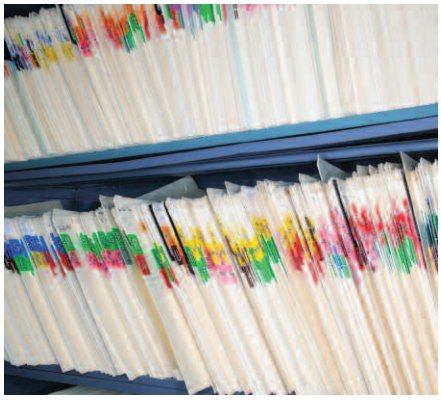
The Ensuring Patient Access and Effective Drug Enforcement Act (H.R. 4069) is a new piece of legislation that aims to curtail prescription drug abuse by mandating that drugmakers registered under the Controlled Substances Act conduct background checks and perform employee drug testing for those with access to controlled substances. Background checks must occur every two years for current employees and whenever a new employee is hired. The bill also intends to create a network of regulators, manufacturers and other partners to research possible solutions. If the bill passes, drugmakers could be fined up to $10,000 for not complying with the proposed requirements. ❖

New Security Risk Assessment Tool Helps with HIPAA Compliance

In March, the U.S. Department of Health and Human Services (HHS) released a new security risk assessment (SRA) tool to assist healthcare providers in small- to medium-sized offices oversee risk assessments of their facilities. The SRA tool, the result of a joint effort between the HHS Office of the National Coordinator for Health Information Technology and the Office for Civil Rights, provides a comprehensive and systematic approach for healthcare practices to conduct and record risk assessments to determine the information security risks in their organizations under the Health Insurance Portability and Accountability Act (HIPAA). The act mandates that organizations regularly review the administrative, physical and technical safeguards they have in place to protect patient information.

Risk assessments will enable providers to potentially avoid breaches in health data and other security violations by detecting gaps in their policies, systems and processes. Performing a security risk assessment is a fundamental prerequisite of the HIPAA Security Rule and a central requirement for providers pursuing payment through the Medicare and Medicaid EHR Incentive Program, also known as the meaningful use program.

The SRA tool is available as a downloadable application at www.HealthIT.gov/security-risk-assessment. The tool's website contains a user guide and tutorial video to help healthcare providers begin to use the application. The tool is available for both the Windows operating system and iOS iPads. ❖



Interactive Video Aims to Reduce Research Misconduct

Earlier this year, the U.S. Department of Health and Human Services Office of Research Integrity (ORI) and Office for Human Research Protections (OHRP) released a web-based training video known as "The Research Clinic" to help teach clinical and social researchers how to better protect research subjects and avoid research misconduct. The video allows viewers to take on the role of one of four characters and then determine the outcome of the storyline by selecting decision-making choices for each character. The characters include a principal investigator (PI) who must balance between doing what he thinks is best for his patients and his research; a clinical research coordinator who is pressured by the PI to falsify data and violate study protocols; a research assistant who has trouble following research protocols and obtaining informed consent; and an institutional review board (IRB) chair who must ensure that research subjects and the integrity of the research enterprise are protected while dealing with a culture resistant to change. Viewers are presented with various scenarios in which they are asked to select from among different courses of action, each of which results in a unique outcome.

The video was made as a result of findings from both ORI and OHRP. ORI reported that one-third of its research misconduct findings were related to falsification, fabrication and plagiarism of data by research team members. And, every year, OHRP receives more than

400 complaints alleging violations of regulations that were enacted to protect human subjects. Violations include the enrollment of ineligible subjects, failure to obtain or properly document informed consent, and the conduct of research without the review and approval by the IRB.

The video is available for free at ori.hhs.gov/TheResearchClinic. ❖

Clinical Studies Network to Help in Health Emergencies

In March, the U.S. Department of Health and Human Services established a network of five clinical research organizations aimed to design and conduct clinical studies required to develop medical countermeasures, including vaccines, drugs and diagnostic tests, that can help protect Americans against bioterrorism, pandemic influenza and other widespread health emergencies. The Biomedical Advanced Research and Development Authority (BARDA) clinical studies network includes EMMES Corp. of Rockville, Md.; PPD Development LLC of Wilmington, N.C.; Technical Resources International Inc. of Bethesda, Md.; Clinical Research Management Inc. of Hinckley, Ohio; and Rho Federal Systems Division Inc. of Chapel Hill, N.C. Contracts with each of these companies include a minimum guarantee of

$400,000 over the first two years for access to the clinical research organizations' resources. And, the contracts can be extended for up to a total of five years and a maximum of $100 million.

The BARDA clinical studies network will offer a complete gamut of services needed to plan, perform, monitor and interpret clinical studies. The services will also include performing clinical studies that are required by the U.S. Food and Drug Administration for the approval of a product for human use, comparing the properties of various products, or measuring the effectiveness of products kept in U.S. government reserves. In addition, the network will be able to enhance National Institutes of Health capabilities by conducting clinical studies in the event of a public health emergency. In the event of an emergency, the network will have the ability to use local institutional review boards or the national Public Health Emergency Research Review Board. ❖

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

Reimbursement FAQs

There's no doubt that complexity is the operational word for reimbursement, and this includes the rules and nuances that govern drugs and biologicals. Even though some healthcare practitioners' sites may contract with an outside provider of billing services, it's incumbent on the providers and their office staffs to know the background information on the requirements of what's reimbursable. One of the best sources of information remains MLN Matters *publications, a free service provided by the Centers for Medicare & Medicaid Services. See the details for accessing* MLN Matters *newsletters at the end of the column.*

Billing for Waste

Ensuring a healthy revenue stream should be a priority for healthcare practitioners in light of the April 2 announcement that the 2 percent sequestration cut for all Medicare reimbursement will continue at least until 2015. Therefore, this column will focus on an area that may be overlooked: billing for wasted drugs.

Several years ago, Medicare created the ability to bill for expensive waste in the outpatient setting shortly after moving to the reimbursement concept of "billing units representing actual dose given" rather than the "whole vial" method of billing under the outpatient prospective payment system (OPPS). While Medicare doesn't mandate billing for waste, it does make it possible to recoup some lost dollars under the OPPS rules. In fact, the Centers for Medicare and Medicaid (CMS) encourages scheduling patients so that drugs can be used efficiently. If the remainder of a single-dose vial must be discarded after being administered, the rules allow for reimbursement for the amount of the drug discarded, as well as the amount of the drug administered. (For the actual rule language, see CMS Publication 100-04, Chapter 17, Section 40 located at www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf.) Each Medicare Administrative Contractor (MAC) may have certain requirements as well. Some require the use of modifiers and others do not, but in all cases, following the rules and having clear documentation is essential.

Low implementation of waste billing is often a result of a combination of factors, including knowledge gaps, perceived low return, perceived resource constraints (too much complex work for the resulting yield), lack of IT systems support for the required level of automation and documentation in the outpatient area, and business risk assessment (a fear that a change in billing might lead to scrutiny).

Regardless of the reason for low implementation, the decision not to bill for outpatient waste is hurting everyone — especially now that bundled payment models are in vogue. Bundled payment calculations are based on "big data," including the history of payment for separately payable medications and biologicals, their drug administration costs and the payment for waste, as well as a myriad of nonseparately reimbursable products that are identified as being used. Not implementing waste billing (or to not bill for nonseparately reimbursable products) paints an inaccurately low picture of the true cost of medications that are included in the bundled payment.

Hints and How-to Guidelines for Waste Billing

Waste billing applies only to:

- outpatients
- Medicare (although some states also include this in Medicaid)
- drugs that Medicare actually pays for at a cost of more than $90 per day (in 2014)
- drugs that are listed on the quarterly average sales price (ASP) and not other classified CMS updates
- single-dose vials

In addition, healthcare practitioners can't bill for overfill in vials. The quarterly ASP National Drug Code matched tables show exactly how many billing units are in each vial so that waste can be correctly calculated.

Each Medicare administrative contractor and fiscal intermediary (MAC/FI) determines how they want waste billed for and what kind of documentation they require (such as the use of the JW modifier to identify the drug amount discarded or not administered to any patient). Therefore, healthcare practitioners shouldn't copy the way another bills for waste if they're not in the same MAC/FI.

Sample Methods for Waste Billing

1. Determine which drugs/biologicals are targets for waste billing when used for Medicare outpatients. Start with a manageable "top-10" list.

These could include:

- only those in single-dose vials
- only those that cost more than $90 per day according to ASP reimbursement tables
- expensive chemotherapeutics, biologicals and new uses of products (such

as the increased use of botulism antitoxin products in neurology and urology)

2. Create a new pharmacy drug master (PDM) description and corresponding charge description master (CDM) entry for each drug to indicate wasted product and to ensure that the billing units assigned to them match those assigned to the corresponding drug PDM and CDM listing. For instance:

• Drug A 100mg/ml — Billing Unit of 10mg

• Drug A 100mg/ml Waste — Billing Unit of 10mg

This isn't much work because healthcare practitioners will likely have only a very few expensive products to handle.

3. At order entry time, determine if waste billing will apply (for instance, is this the only or the last Medicare patient that day who will be receiving the drug that comes in a single-dose vial?). If so, enter both the order for the drug, as well as a separate order for the waste.

4. Document the amount ordered, administered and discarded in the medical record. This can be done through computer entry that generates a documentation space on the electronic medical administration record, or it can be done manually. ❖

HCPCS Codes Can Change

For several years, Healthcare Common Procedure Coding System (HCPCS) codes assigned to drugs and biologicals most often used a generic description. This changed somewhat abruptly with the advent of newer biologicals and biosimilars, which has resulted in the assignment of brand-specific HCPCS codes for some products. While many products have recently been assigned new HCPCS codes (see the previous Reimbursement FAQs column), two more drugs have recently been assigned new codes:

Granix (tbo-filgrastim) was approved as a new biologic product with its own labeled indications and not as a biosimilar. Effective Jan. 1, it has its own HCPCS code (J1446), and its own billing unit designation (5 mcg), as well as its own reimbursement rate and labeled indications. Using the HCPCS code, billing unit designation and applying the reimbursement rate for filgrastim is not appropriate if the prescribed drug is Granix. Continuing to use a miscellaneous code is not appropriate either and will result in zero reimbursement.

A new HCPCS code for Neupogen (filgrastim) was released Nov. 29, 2013, as part of the HCPCS code set updates that became effective Jan. 1. The new HCPCS code for Neupogen (injection, filgrastim, 1 mcg) is J1442. This new HCPCS code replaces both old Neupogen HCPCS codes of J1440 for 300 mcg and J1441 for 480 mcg. The new code has a billing unit designation of 1 mcg. It's critical for healthcare practitioners to ensure billing unit conversion is working in their systems so that the dose administered is converted into billing units to be billed:

• Neupogen 300 mcg = 300/1 = 300 billing units of 1 mcg (the single-use vial)

• Neupogen 480 mcg = 480/1 = 480 billing units of 1 mcg (the prefilled syringe)

Key points to remember: Granix and Neupogen have unique labeled indications, unique HCPCS codes and unique billing units assigned to them. Healthcare practitioners should check their systems carefully to ensure that they've captured these Jan. 1 changes and cleanse their system of any and all miscellaneous codes being used for products with assigned HCPCS codes.

Reference:
www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS.html

Creating an e-Library

Sign up for email notices of *MLN Matters* newsletters using the Centers for Medicare and Medicaid Services Medicare Learning Network at www.cms.hhs.gov/MLNProducts/downloads. For any of the *MLN Matters* articles as of June 2007, review the archive at list.nih.gov/cgi-in/wa.exe?A0=MLN-MATTERS-L. ❖

BONNIE KIRSCHENBAUM, *MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.*

Ask Our Experts

Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.

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.

Research

Adult Vaccination Coverage Below Healthy People 2020 Targets

Adult vaccination coverage remains well below Healthy People 2020 targets, according to the Centers for Disease Control and Prevention, which assessed vaccination coverage among adults ages 19 years and older for selected vaccines using data from the 2012 National Health Interview Survey. The survey summarizes analysis for pneumococcal, tetanus, hepatitis A, hepatitis B, herpes zoster and human papillomavirus (HPV) vaccines. Compared with 2011, there was only a modest increase in vaccination with the tetanus/diphtheria/acellular pertussis vaccine among adults ages 19 years to 64 years, herpes zoster vaccination among adults at least 60 years of age, and HPV vaccination among women ages 19 years to 26 years. Coverage with other vaccines among U.S. adults did not improve.

Pneumococcal vaccination coverage among high-risk adults ages 19 years to 64 years was 20 percent overall. Hepatitis A vaccination coverage with at least two doses among adults ages 19 years to 49 years was 12.2 percent, similar to the estimate for 2011. In 2012, 34.5 percent of women ages 19 years to 26 years reported receipt of at least one dose of HPV vaccine, up from 29.5 percent reported for 2011.

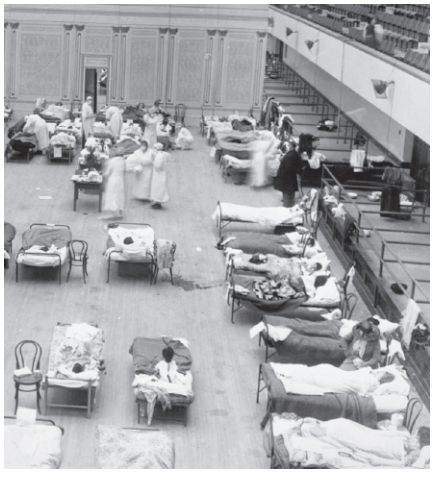
Authorities such as the Community Preventive Services Task Force recommend that healthcare providers incorporate vaccination needs assessment, recommendation and offer of vaccination into their usual clinical practice for adults. ❖

Research

Origin and Deadliness of 1918 Flu Virus Is Found

Researchers at the University of Arizona say they may have discovered both the origin of the influenza pandemic of 1918 that left 50 million dead worldwide, as well as what may have made the virus especially deadly for 20- to 40-year-olds. The findings could be used to predict how vulnerable certain age groups are to future flu strains, offering potential insight into vaccination strategies and pandemic prevention.

Michael Worobey, a professor of ecology and evolutionary biology at the University of Arizona, and his team used a "molecular clock approach" to reconstruct the molecules that gave rise to the 1918 pandemic virus (known as H1N1 influenza A virus, or IAV), the classical H1N1 swine flu virus and the flu that circulated in the wake of the pandemic from 1918 to 1957. They found no evidence that IAV leapt directly from birds to humans, or that its emergence involved any sort of swap in genes between human and swine flu strains — two of the prevailing theories



about the 1918 pandemic. Instead, they inferred that an H1 flu virus picked up genetic material from a bird flu strain. They believe, then, that the reason so many 20- to 40-year-olds were affected by the 1918 pandemic is because they had been exposed as children to another flu virus, H3N8, which circulated from 1880 to 1900. While their bodies developed an immunity to that earlier virus, H3N8 had a different antigenic protein than the 1918 H1N1 virus, which left that age group ill-equipped to fight off the new flu. Elderly people, by contrast, fared far better because they may have been exposed as children to an earlier H1N1-like virus, which means their immune systems would have been armed to repel the kind of virus that made up the 1918 flu.

"Imagine a soccer ball studded with lollipops," Worobey explained. "The candy part of the lollipop is the globular part of the HA protein, and that is by far the most potent part of the flu virus against which our immune system can make antibodies. If antibodies cover all of the lollipop heads, the virus can't even infect you." Therefore, said Worobey, "a person with an antibody arsenal directed against the H3 protein would not have fared well when faced with the viruses studded with H1 protein. We believe this mismatch may have resulted in the heightened mortality in the age group that happened to be in their late 20s during the 1918 pandemic." ❖

Research

Phase III Trial for Long-Acting Factor VIII Shows Positive Results

Positive results have been shown with the completion of pathfinder2, the first multinational Phase III trial evaluating the safety and efficacy of Novo Nordisk's long-acting recombinant factor VIII (FVIII), N8-GP (turoctocog alfa pegol), for hemophilia A patients 12 years and older.

In the trial, 175 patients were treated with a prophylactic regimen of 50 U/kg every fourth day, and 11 patients received on-demand treatment when bleedings occurred. Patients were treated for up to 21 months, resulting in median annualized bleeding rates of 1.3 and 30.9 episodes for patients treated prophylactically and on-demand, respectively. The pharmacokinetic data documented a single dose half-life of 18.4 hours and a mean trough level of 8 percent measured immediately before the next dose for patients on prophylaxis treatment. Among the 186 patients, one patient who responded well to prophylactic treatment throughout the trial developed an FVIII inhibitor, which is in line with expectations in a population of previously treated hemophilia A patients.

"We are very pleased with the results of pathfinder2," said Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk. "These results show that N8-GP has the potential to reduce the burden of treatment by decreasing the number of intravenous infusions while achieving strong results in terms of efficacy and safety for people with hemophilia A."

Novo Nordisk is expecting the three remaining trials in the pathfinder program to be finalized within the next 12 months. These trials are investigating N8-GP as a treatment for pediatric patients, surgical procedures and as once-weekly prophylactic treatment. ❖

Reimbursement

CMS to Increase Medicare Advantage Pay Rate by 0.4%

The Centers for Medicare and Medicaid Services (CMS) will increase the overall rate it pays Medicare Advantage plans by 0.4 percent in 2015, despite a proposed policy issued in February that signaled a 1.9 percent rate cut. The change is the result of "various policy changes" and "new estimates," according to Jonathan Blum, former CMS principal deputy administrator. These include the administration's approach to phasing in a new risk model and a decision to walk away from a proposal to require that home risk assessments be confirmed by in-office assessments. The Patient Protection and Affordable Care Act sought to bring the cost of Medicare Advantage more closely in line with traditional Medicare. Right now, Medicare Advantage plans are typically paid more than their traditional counterparts. "We are committed to the new model; however, for 2015, given the number of changes in other payment factors, we believe that providing a longer time frame for full implementation is appropriate," said a CMS fact sheet.

There are currently more than 15 million seniors enrolled in Medicare Advantage. Beneficiaries enrolled in the plans, administered by private companies that contract with Medicare, account for approximately 30 percent of the total enrolled in Medicare. ❖

Research

Blood Test Could Predict Death Risk

Researchers in Finland and Estonia have discovered novel biological markers that are strongly indicative of the risk of dying from any disease within the next five years. In their study, blood samples from more than 17,000 generally healthy people were screened for 100 biomarkers. Those people were then monitored for the next five years. During that time, 684 died from illnesses that included cancer and cardiovascular disease, all of whom had similar levels of four biomarkers: albumin, alpha-1-acid glycoprotein, citrate and a similar size of very-low-density lipoprotein particles. One in five people with the highest biomarker scores died within the first year of the study. "What is especially interesting is that these biomarkers reflect the risk for dying from very different types of diseases such as heart disease or cancer. They seem to be signs of a general frailty in the body," said Dr. Johannes Kettunen of the Institute for Molecular Medicine in Finland. "In the future, these measures can be used to identify people who appear healthy but in fact have serious underlying illnesses and guide them to proper treatment." The study was published in *PLOS Medicine*. ❖

Research

Facilitators Identified in Uptake of Flu Vaccine by Healthcare Personnel

Researchers recently conducted a quality improvement project to increase uptake of the influenza vaccine among healthcare personnel at a university student health center. A pre-intervention survey identified facilitators and hurdles to personnel's uptake of the vaccine. The survey results were used to implement four interventions, and a post-intervention survey was conducted to evaluate the effectiveness of the interventions. The most frequent facilitators of vaccination cited were protecting self/family, free vaccine, recommended by experts and convenient vaccination process, while the most common hurdle cited was concern about side effects. Post-intervention, the vaccination uptake increased from 71 percent in 2008-2009 to 77 percent in 2009-2010. Free vaccine and convenient vaccination process were rated as the most effective interventions, while education and the declination form used for the project were rated less favorably. The researchers noted the importance of identifying "facilitators and barriers that are unique to health centers to better plan and implement interventions to improve vaccination rates." ❖

Vaccine Update

Immune Response BioPharma Inc.'s flagship HIV/AIDS vaccine Remune has been granted orphan designation for **pediatric HIV/AIDS** by the U.S. Food and Drug Administration. Previous clinical studies of Remune have demonstrated distinct benefits in both immunologic and virologic parameters in HIV-1-infected individuals undergoing treatment. Data from clinical trials suggest that the vaccine may induce an HIV-specific T-cell response; induce cytokines and chemokines, substances that interfere with the virus attaching to and infecting normal cells; work with antiretroviral drugs as a complementary treatment for HIV infection; work in drug-naive patients to delay the need for initiation of highly active antiretroviral therapy; and be safe with no adverse side effects.

Novartis has received a breakthrough therapy designation from the U.S. Food and Drug Administration (FDA) for Bexsero (Meningococcal Group B Vaccine [rDNA, component, adsorbed]). Bexsero is already approved in Europe, Canada and Australia to help protect against invasive **meningococcal disease** caused by serogroup B (meningitis B). Novartis planned to file for U.S. licensure of Bexsero in the second quarter of 2014. In the last four months, Novartis has provided nearly 30,000 doses of Bexsero to students and staff at Princeton University and the University of California Santa Barbara following meningitis B outbreaks on their campuses under an Investigational New Drug (IND) designation from FDA. Further, the U.S. Centers for Disease Control and Prevention has recommended including the incoming freshman class at Princeton University in the at-risk group to receive Bexsero.

The U.S. Food and Drug Administration has expanded the approved age range for Sanofi Pasteur's Adacel active booster immunization for **tetanus, diphtheria and pertussis** to ages 10 years to 64 years. An open-label, multicenter Phase IV trial found that a single dose of the drug — which was approved for people ages 11 through 64 in 2005 — had similar antibody responses and rates of adverse reactions in 10-year-olds as it does in 11-year-olds.

The University of Pittsburgh and Sanofi-Pasteur are partnering to assess the efficacy of Sanofi-Pasteur's investigational **dengue** vaccine. Researchers from Pitt's Center for Vaccine Research are developing a test to determine whether a person's immunity to dengue virus is the result of vaccination or a previous infection. The recombinant, live-attenuated quadrivalent vaccine was tested in more than 4,000 healthy Thai schoolchildren in a 2009-2010 randomized trial. Results indicated that vaccine efficacy was 61.2 percent against dengue virus type 1, 81.9 percent against type 3 and 90 percent against type 4. However, the vaccine was unable to protect against serotype 2, according to researchers. The vaccine was safe and well-tolerated. Sanofi-Pasteur is expected to release data from its Phase III studies of the vaccine's efficacy later this year. ❖

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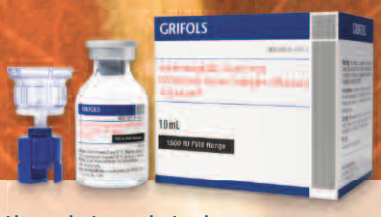

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Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

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

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- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
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The Anti-Vaccine Movement: Where Are We Now?

While the anti-vaccine bandwagon is collapsing amid studies discrediting the link between vaccines and autism, public distrust remains. With some vaccine-preventable diseases reaching epidemic status, is it too late to turn the tide?

By Trudie Mitschang

For many, actress Jenny McCarthy has become the poster mom of the anti-vaccine movement, thanks to her highly vocal stance against the measles, mumps, rubella vaccine (MMR) that she believes triggered her son Evan's autism. Her point of reference was a study published in the British medical journal *The Lancet* by Dr. Andrew Wakefield, a study that was later debunked and retracted after it was reported that Wakefield falsified data. According to Brian Deer, investigative journalist for London's *The Sunday Times*, Wakefield "was paid more than £400,000 ($665,000) by lawyers aiming to prove that the vaccine was unsafe."[1] In the fallout, Wakefield even had his medical license revoked.

Of course, the Wakefield study was not the only misguided weapon in the anti-vaccine movement's arsenal. Many who had earlier jumped on the anti-vaccine bandwagon held to the theory that the preservative in children's vaccines, thimerosal, was causing autism, despite the fact that the United States had removed thimerosal from most childhood vaccines in 2001. Statistics have shown that autism rates have steadily increased since 2001, disproving the thimerosal link. According to the Centers for Disease Control and Prevention (CDC) website, "Evidence from several studies examining trends in vaccine use and changes in autism frequency does not support an association between thimerosal and autism. Furthermore, a scientific review by the Institute of Medicine (IOM) concluded that 'the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.'"[2]

Recently, in a move that surprised critics and supporters alike, McCarthy herself publicly began backpedaling on her anti-vaccine stance, stating, "I've never told anyone to not vaccinate — I believe in the importance of a vaccine program, and I believe parents have the right to choose one poke per visit."[3]

The question is: Has any of this helped turn the tide of public cynicism and distrust regarding vaccine efficacy and safety? If the alarming increase of new cases of measles, pertussis (whooping cough) and chickenpox is any indication, the answer is a resounding "no." McCarthy's critics say her more balanced viewpoint is essentially "too little, too late," with measles outbreaks in states like California and New York more widespread than they've been in decades. According to Alan Hinman, a public health scientist who sits on the scientific advisory board of the pro-vaccine parent group Voices for Vaccines, many people continue to believe that vaccines cause autism, while others simply don't trust the federal government or the pharmaceutical companies responsible for these vaccines.[4]

Understanding the Parent Perspective

Although the supposed autism link is the most cited reason given for forgoing immunization, surveys show parents have other concerns as well. Some say they believe the current vaccination schedule recommended by CDC is too aggressive for an infant's immune system to handle, while others doubt the long-term safety of vaccines. A small percentage of parents cite religious reasons for opting out. A survey in Marin County, Calif., found several themes common to "anti-vax" parents, including a preference for natural immunity over vaccine immunity; a belief that children were at low risk for some vaccine-preventable diseases; and a lack of trust in the healthcare system or pharmaceutical industry.[4]

Although the supposed autism link is the most cited reason given for forgoing immunization, surveys show parents have other concerns as well.

Currently, 48 states allow parents to sign a vaccine-exemption form, although California now requires a doctor's signature on the form, leaving many providers wondering how to broach the sensitive topic with parents. To help parents better understand vaccines, some healthcare providers are starting to provide information or articles from scientific journals about vaccinations. Several states have also worked to make getting an exemption tougher. In Colorado, for example, where 4 percent of kindergartners in 2013 were not vaccinated for nonmedical reasons, a proposed bill sponsored by State Rep. Dan Pabon, a Democrat from Denver, would require parents to get a doctor's note or watch a video about risks before opting out of vaccines.[4]

Earlier this year, researchers confirmed that a 2010 whooping cough outbreak in California, the nation's worst in more than 50 years, was spread by children whose parents applied for nonmedical exemptions to school vaccination requirements. The study showed that more cases of whooping cough occurred in the clusters of unvaccinated children than not, resulting in 9,120 instances of the disease and 10 deaths. In San Diego County alone, there were 5,100 exemptions and 980 whooping cough cases.[5]

From the medical side of the equation, some physicians have resorted to their own defenses to protect their patients from those who won't vaccinate. Doctors at Olde Towne Pediatrics in Manassas, Va., have taken a hard-line defense and won't take new patients if the parents don't plan to vaccinate their children. It's not clear how many other physicians have followed suit, as experts say no comprehensive studies of the practice have been done.

"We don't want to put our patients at risk because people for their own personal reasons don't want to vaccinate," said Anastasia Williams, a managing partner of the practice who has been a pediatrician for 15 years. "We are doing our due diligence to protect our children who wait in our waiting room."[4]

From the medical side of the equation, some physicians have resorted to their own defenses to protect their patients from those who won't vaccinate.

From Personal Choice to Criminal Intent

Last year, a popular television show raised a compelling legal question regarding parents who don't vaccinate, creating a firestorm of controversy. What if a mother decided not to vaccinate her child for measles and her 4-year-old contracts the disease and then goes on to infect a 1-year-old who is too young to be immunized? And what if that baby dies?

That was the controversial topic during a season 10 episode of "Law & Order: Special Victims Unit." And, it's also the hypothetical case study in a provocative paper in the *Journal of Law, Medicine and Ethics* that explores whether there's a case for holding people legally accountable for the spread of disease when they choose not to vaccinate their children. "One can make a legitimate, state-sanctioned choice not to vaccinate, but that does not protect the person making that choice against the consequences of that choice for others," state bioethicist Arthur L. Caplan and his co-authors."[6]

The authors argue that since epidemiologists today can reliably determine the source of a viral infection, the parents of the unvaccinated child could be charged with criminally negligent homicide or sued for damages.

Not surprisingly, those in the anti-vaccine camp were outraged by the suggestion of legal action. After Caplan wrote a related post for the *Harvard Law School* blog, angry comments poured in. "This article is industry propaganda at its worst!" declared one angry parent.[6]

While the debate surrounding personal choice and public liability remains a hot-button topic, it's being triggered not only by television shows. Case in point: The San Diego 2008 measles outbreak that was triggered by an unvaccinated 7-year-old boy who infected 11 other unvaccinated kids, according to CDC.[7] It was reported that the majority of the cases occurred in kids whose parents had requested personal belief exemptions through the state of California, one of 17 states to allow them. But three of the infected were either too young or medically unable to be vaccinated. And overall, 48 children too young to be vaccinated were quarantined, at an average cost to the family of $775 per child. CDC noted that all 11 cases were "linked epidemiologically" to the 7-year-old boy, and that the outbreak response cost the public sector $10,376 per case.

Dorit Rubinstein Reiss, a professor of law at UC Hastings College of the Law in San Francisco, Calif., wrote a recent blog post titled "The Cost of Vaccine Misinformation." In addressing the question of liability claims against physicians and organizations who spread misinformation about vaccine efficacy, Reiss said, "The cost of the anti-vaccine misinformation is in harm and suffering. Those who make decisions based on misinformation — especially unvaccinated children and the victims who are subsequently infected by the unvaccinated — are the ones who bear the burden. It's time to put the monetary costs where they belong: on those providing the misinformation that causes harm, whether that harm is intentional or negligent."[8]

The Value of Vaccines

In many ways, vaccines are a relatively recent development in medical history. It was just a little more than 200 years ago when English scientist Edward Jenner observed that milkmaids who had been exposed to cowpox seemed immune to contracting the dreaded smallpox infection. In 1796, Jenner tested his hypothesis by inoculating a boy named James Phipps with material from cowpox blisters. He later repeated the experiment on the boy, but this time added a small amount of smallpox, hoping the procedure would immunize Phipps against infection. The experiment was a success, and Jenner's discovery ushered in the dawn of the immunization age.[9]

For many people today, it is difficult to imagine a time when diseases like diphtheria and polio ran rampant. For generations who have grown up with no memory of once-healthy children relegated to life in an iron lung due to an onset of

polio, complacency regarding immunization is yet another factor contributing to declining vaccination rates. In fact, in 1952, a record 57,628 cases of polio were reported in the U.S., leaving as many as 20,000 people a year paralyzed. The vaccine developed by Dr. Jonas Salk debuted on April 12, 1955, and while the last U.S. outbreak of polio was in 1979, health experts say growing pockets of unvaccinated children are cause for concern. "Scenarios for polio being reintroduced into the U.S. are easy to imagine, and the disease could get a foothold if we don't maintain vaccination rates," says Dr. Greg Wallace, a team leader for the CDC MMR and polio epidemiology branch.[10]

According to the World Health Organization, at least two million people in all age groups die every year from diseases preventable by recommended vaccines. In fact, statistics show that more Americans die each year from vaccine-preventable diseases than from car accidents, breast cancer or AIDS. Influenza, commonly referred to as the flu, is at the root of an estimated 400,000 deaths worldwide each year and surprisingly claims more lives than all other vaccine-preventable diseases combined.[11]

The American Academy of Pediatrics stated the following in their handout *Vaccine Safety: The Facts*: "Vaccines are necessary.... In many parts of the world, many vaccine-preventable diseases are still common. Since diseases may be brought into the United States by Americans who travel abroad or from people visiting areas with current disease outbreaks, it's important that your children are vaccinated."[12]

According to the World Health Organization, at least two million people in all age groups die every year from diseases preventable by recommended vaccines.

The good news is not all parents today have been swayed by the wealth of misinformation regarding vaccine safety. Voices for Vaccines, a parent-led organization that supports and advocates for on-time vaccination and the reduction of vaccine-preventable disease, states on its website: "At Voices for Vaccines, we believe it's time for parents who vaccinate to begin sharing their stories and telling the world why they choose to protect their children from vaccine-preventable diseases. The Voices for Vaccines blog, Parents Who Vax, provides parents who have chosen to vaccinate their children an opportunity to talk about their decisions to do so."[13]

"My little one is just over 7 months old, and we did our vaccines according to schedule," says Claire White, a young mother from Temecula, Calif. "What influenced my decision was seeing the devastating effects of many of these illnesses on very young children, from mild sickness to death. Modern medicine has its risks and complications, but the risk seemed very minimal, and for me, the benefit outweighed the risk."

When asked if the negative view of vaccines portrayed in the media had swayed her at all, White stated, "Media coverage has not influenced me at all. There is so much misinformation regarding vaccines that it is crucial that people are proactive and research information themselves and not just swallow whatever they are being fed." ❖

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An Update on Adult Immunizations

Compared with childhood vaccinations, adult vaccination rates are too low, resulting in thousands of deaths annually from vaccine-preventable diseases.

By Amy Scanlin, MS

While there is a great deal of focus on childhood immunizations, the recommendations for adult vaccines receive less attention by patients, physicians and even the media. There are 17 vaccine-preventable diseases targeted by immunization recommendations across a person's life span, with the majority of those vaccinations occurring in infancy and childhood; however, a fair number of vaccines require a new immunization or booster into and throughout adulthood. And, these adult recommendations are often overlooked or ignored.

One reason for this lack of emphasis is adults often (incorrectly) assume that the vaccines they received as children will carry over into adulthood. While in some instances this is true, in others, it is not. As we age, our immunity against some diseases for which we previously received vaccinations fades. Also as we age, we become more susceptible to and can become more seriously affected by some diseases. Add to this the fact that some of the newer vaccines, human papillomavirus, or HPV, for example, weren't available when today's adults were children (HPV only received the U.S Food and Drug Administration's [FDA's] approval in 2006), and the need for adults to continue receiving all recommended vaccines is well illustrated.

Still another barrier to adult immunization is the medical system itself — from healthcare providers not understanding that vaccines are needed by both healthy and unhealthy adults, to time constraints that prioritize treatment for acute and chronic illnesses over preventive care, and even insurance concerns. Medicare limits coverage for vaccines based on the type of plan, Medicaid vaccination coverage varies by state (with some states covering only a subset of recommended vaccines), some providers may not be eligible for reimbursement under some plans because they are not authorized as "in-network" providers for vaccination services, and until the Affordable Care Act (ACA) is fully implemented, many still don't have insurance coverage.[1]

Whatever the reasons, the vaccination rates for adults are too low. A recent Centers for Disease Control and Prevention (CDC) study that looked at six vaccines — pneumococcal, hepatitis A, hepatitis B, herpes zoster, HPV and tetanus antigen-containing vaccines — showed ranges of only an 18.5 percent vaccination rate for 18- to 64-year-olds for the pneumococcal vaccine to 64 percent for the tetanus antigen.[2]

"Generally when we think of vaccines, we tend to think of vaccines for children," says Dr. Kristine Sheedy, communications director for the Immunization Center at CDC. "Most adults … aren't aware that adults need vaccines too. Vaccines are needed throughout our lives based on age, health conditions, occupation, lifestyle and travel. Adult vaccines are safe and help prevent a number of common and serious diseases like pneumococcal disease, shingles and pertussis. Unfortunately, to some, adult vaccination isn't viewed as 'newsy.' Adult immunization rates have been low for a number of years, and there haven't been many changes in vaccines or new recommendations to the adult schedule. When it comes to adult vaccination, unfortunately, the story is one of lack of awareness."

ACIP Updates

In February, CDC Advisory Committee on Immunization Practices (ACIP) announced its 2014 recommended adult immunization schedule. There are some key changes for flu, tetanus, diphtheria acellular pertussis (Tdap), HPV, zoster virus, pneumococcal disease and meningococcal disease vaccines.

Influenza. Five new flu vaccines have been approved for adult use. A live attenuated flu vaccine (LAIV4; Flumist Quadrivalent [MedImmune]) indicated for healthy, nonpregnant persons age 2 years through 49 years, replaces the trivalent (LAIV3) formulation. An inactivated flu vaccine (IIV4; FluLaval Quadrivalent [GlaxoSmithKline]), indicated for persons age 3 years and older, will be available in addition to the previous trivalent formulation. A quadrivalent inactivated influenza vaccine (IIV4; Fluzone Quadrivalent [Sanofi Pasteur]), indicated for persons age 6 months and older, will be available in addition to the company's previous trivalent formulation. Also available are a trivalent cell culture-based inactivated influenza vaccine (ccIIV3; Flucelvax [Novartis]), indicated for persons age 18 years and older, and a recombinant hemagglutinin vaccine (RIV3; FluBlok [Protein Sciences]), indicated for persons age 18 years through 49 years.[3]

CDC recommends Flublok for those who have an allergy to eggs, as this vaccine contains no egg protein.

Healthy People 2020's target for flu vaccine administration to both noninstitutionalized adults age 18 years to 64 years and pregnant women is 80 percent, up from 24.9 percent for noninstitutionalized adults and 27.6 percent for pregnant women in 2008. The target for those 65 and older is 90 percent, up from 66.6 percent in 2008.[4]

Tetanus, diphtheria and acellular pertussis (Tdap). Adult immunization recommendations for the Tdap vaccine now match CDC's pediatric immunization schedule, with a booster given every 10 years after initial vaccine administration.

HPV. It is no longer recommended that adult healthcare workers get an HPV vaccine. However, as a reminder, vaccination is encouraged for immunocompromised persons through age 26 if they did not receive all of the three-dose series of the vaccine when they were younger.[5]

Whatever the reasons, the vaccination rates for adults are too low.

Zoster virus. It also is no longer recommended for adult healthcare workers to receive a zoster virus vaccine; however, a single dose of the vaccine is recommended by ACIP for all those who are 60 years of age and older (FDA has approved the vaccine for those 50 years of age and older, but ACIP recommends vaccinations no earlier than 60 years).[5]

Healthy People 2020 suggests a 30 percent zoster virus vaccination rate goal for those age 60 and older, up from 6.7 percent in 2008.[4]

Pneumococcal disease. Clarifications on the order of which pneumococcal vaccines should be administered have been made, depending on whether people require both the pneumococcal conjugate (PCV13) and/or pneumococcal polysaccharide (PPSV23) vaccines. Persons with immunocompromising conditions are recommended to receive both PCV13 and PPSV23 vaccines.

A one-time revaccination five years after the first dose of PPSV23 is recommended for persons age 19 years through 64 years with certain immunocompromising conditions. Persons who received one or two doses of PPSV23 before age 65 should receive another dose of the vaccine at age 65 or later, provided that it has been at least five years since their previous dose. After age 65, no further dose is needed.[5]

Healthy People 2020 lists a target of no more than 31 diagnosed cases of invasive pneumococcal disease per 100,000 adults age 65 and older, down from 40.4 in 2008, and nine cases of antibiotic resistant pneumococcal disease, down from 12.2 in 2008.[4]

Meningococcal disease. Distinctions have been clarified as to who should receive the conjugate and the polysaccharide

meningococcal vaccine. Also, the new recommendations clarify that the conjugate vaccine is not routinely recommended for those with HIV; however, should the patient receive this type of vaccine, two doses are recommended.

ACIP recommends to "administer two doses of quadrivalent meningococcal conjugate vaccine (MenACWY [Menactra, Menveo]) at least two months apart to adults of all ages with functional asplenia or persistent complement component deficiencies." Also, "revaccination with MenACWY every five years is recommended for adults previously vaccinated with MenACWY or MPSV4 who remain at increased risk for infection."[5]

Every year, it is estimated that 30,000 to 42,000 people in the U.S. die of vaccine-preventable diseases, almost all of whom are adults.

Healthy People 2020 has a goal of no more than 1,094 cases of meningococcal disease, down from 1,215, which was the average annual infection rate between 2004 and 2008.[4]

A CDC Vaccine Schedules app is available for healthcare professionals who recommend or administer vaccines. The free tool visually mimics the printed schedules, which are reviewed and published annually, provides the most current version of the child and adolescent schedules with immunization recommendations from birth through age 18; the catch-up schedule for children 4 months through 18 years; the adult schedule, including recommended vaccines for adults by age group and by medical condition; and a contraindications and precautions table, with all footnotes that apply to schedules. The app can be obtained at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html#download.

Improving Vaccination Administration

Improved availability and education about the recommended vaccines, as well as the frequency and severity of their associated diseases, is crucial to help reduce the incidence of disease. Every year, it is estimated that 30,000[6] to 42,000[4] people in the U.S. die of vaccine-preventable diseases, almost all of whom are adults. In addition, many thousands more become ill or die from complications related to those preventable diseases every year. For example:

- More than one million adults get shingles annually.
- 226,000 adults are hospitalized for the flu, and as many as 49,000 die from its complications.
- 175,000 adults are hospitalized for pneumonia, and nearly 4,000 die from invasive pneumococcal disease.
- As many as 1.4 million adults suffer from chronic hepatitis B and risk-associated liver cancer.
- 8,300 adults die annually of HPV-related cancers.[7]

What is interesting in comparison is that fewer than 1,000 American children die of vaccine-preventable diseases.[2] Clearly, there is a disconnect in the understanding and efforts between childhood and adult vaccinations. "It's a social norm that children are vaccinated, but there is less awareness that adults need vaccines as well," says Sheedy.

In September 2013, the National Vaccine Advisory Committee Standards for Adult Immunization Practice recommended expanding vaccine services by both pharmacists and community immunization providers, as well as increasing efforts of vaccine delivery in the workplace. However, before the reality of this expansion can happen, the financial barrier of these vaccines, particularly for smaller practices, must be overcome.

The ACA's first dollar coverage provision of ACIP-recommended vaccines for those with certain insurance carriers or who are under the expanded Medicaid plans is expected to increase the number of adults who will be insured to receive vaccines. Also, the ACA requires vaccines, when delivered by in-network providers of private insurance companies, be administered with no co-pays.

One of the most important predictors of whether adults receive their recommended vaccines is that the vaccine is offered during doctor visits, so physicians play a key role in raising awareness. "Our research shows hands down that raising awareness is at the top of the list," says Sheedy. "People are aware of the annual flu vaccine, and Merck has raised awareness of the shingles vaccine. We've got to talk to providers about best practices and push the tools that are available."

Other successful opportunities for increasing vaccine coverage include worksite and community interventions, automatic reminder calls and standing orders in electronic health records. Providers are also encouraged to enter immunization information into the Immunization Information System (IIS), or immunization registries, via meaningful use incentives for both Medicare and Medicaid.[1]

There is also hope for federal funding for adult immunization programs for those who are unable to afford them, much like Vaccines for Children. For instance, Oregon's Special Immunization Project 2012-2013 sought to strengthen the adult immunization infrastructure and increase access to vaccines, particularly influenza and Tdap vaccines, by a rate of

10 percent by offering a weekly free Tdap clinic for those without health insurance.

Best Practices in Action

"Children's vaccines are usually tied to a well-child exam, typically every few months during the child's first two years of life," says Alison Alexander, Immunize Oregon Coalition coordinator. "Since a child is closely monitored by a provider, the diligence is in part by the parent and reminder notices from the provider. Resources are limited for adults, generally speaking — nothing tied to well-visit exams."

However, improving those educational resources and access was at the heart of Oregon's Adult Immunization Project. Oregon is a great example of both state and counties working together to improve adult vaccination rates. With a $1.8 million grant awarded from CDC National Center for Immunizations and Respiratory Diseases through the Prevention and Public Health Fund (eight other states, as well as the city of Chicago, also received grants), participating counties (32 of Oregon's 36 counties) got to work in partnering with providers and businesses to educate and vaccinate. "The goal of our project was to strengthen adult immunizations in Oregon, particularly influenza and Tdap," says Kathy Scott, DrPH, assessment, readiness and epidemiology manager of the Oregon Immunization Program.

Some examples of Oregon's objectives, all of which were on target or even exceeded by mid-term 2012, were partnering with pharmacies to increase the number of flu vaccine doses given to adults (322,150 by mid-term 2012, up from 286,548 doses in 2011), in part by updating pharmacy protocols to use the IIS to look at patient vaccine history and forecast what they would need. The counties also partnered with large non-healthcare employers to encourage vaccinations either onsite or at a referring pharmacy, or to hold an educational campaign. "We had a goal of 116 employers, but everyone was engaged, and we had 170 participating at midpoint," says Scott. They encouraged healthcare institutions to increase their workers' vaccination rates (77 percent at midpoint), as well as those of long-term care facilities (57 percent) and ambulatory surgery centers (70 percent). Says Scott: "Our program was just one small part of this. Our project played a role, but there were lots of initiatives going on."

"As a health department, we partnered with local organizations providing flu vaccines to local businesses and asked that they also add Tdap. It was a huge success, and the whole goal now is sustainability," adds Heather Kaisner, MS, immunization coordinator and health communication specialist for Deschutes County Health Services, one of the participating counties.

Of course, all those involved in not just Oregon's Adult Immunization Project, but immunizations as a whole, must continually overcome obstacles to vaccinations such as time and budget constraints, as well as educating providers and patients. "The ideal time [to get vaccinated] is when adults go to their provider, but vaccines aren't always talked about," says Kaisner. However, those providers who do encourage vaccines tend to have patients who get vaccinated.

Deschutes County created a two-page pamphlet geared toward barriers based on feedback from focus groups. "There are a lot of myths and misconceptions out there, and you can't make assumptions," says Kaisner. "The more awareness we bring to healthcare, the better. I think a great resource, personally, are pharmacists. They have a great opportunity for education. With healthcare providers, we go when we are sick, and hopefully we go to well visits too, and hopefully providers also encourage vaccines."

Getting the word out plays an important part of all successful campaigns. Oregon utilized television, radio, newspapers and social media as part of its educational campaign. Sheedy says CDC is also using a mix of approaches to educate healthcare workers and patients about the new vaccine recommendations. "A core piece of that education is working with our partners," she says. "We don't have a lot of money to buy air time, so we count on our partners to get the message out to constituents. Pharmacists, private sector partners, healthcare professionals — all influential and trusted sources. If they make the recommendation, then patients are much more likely to get vaccinated. Part of what we want to do is raise awareness and create a new social norm." ❖

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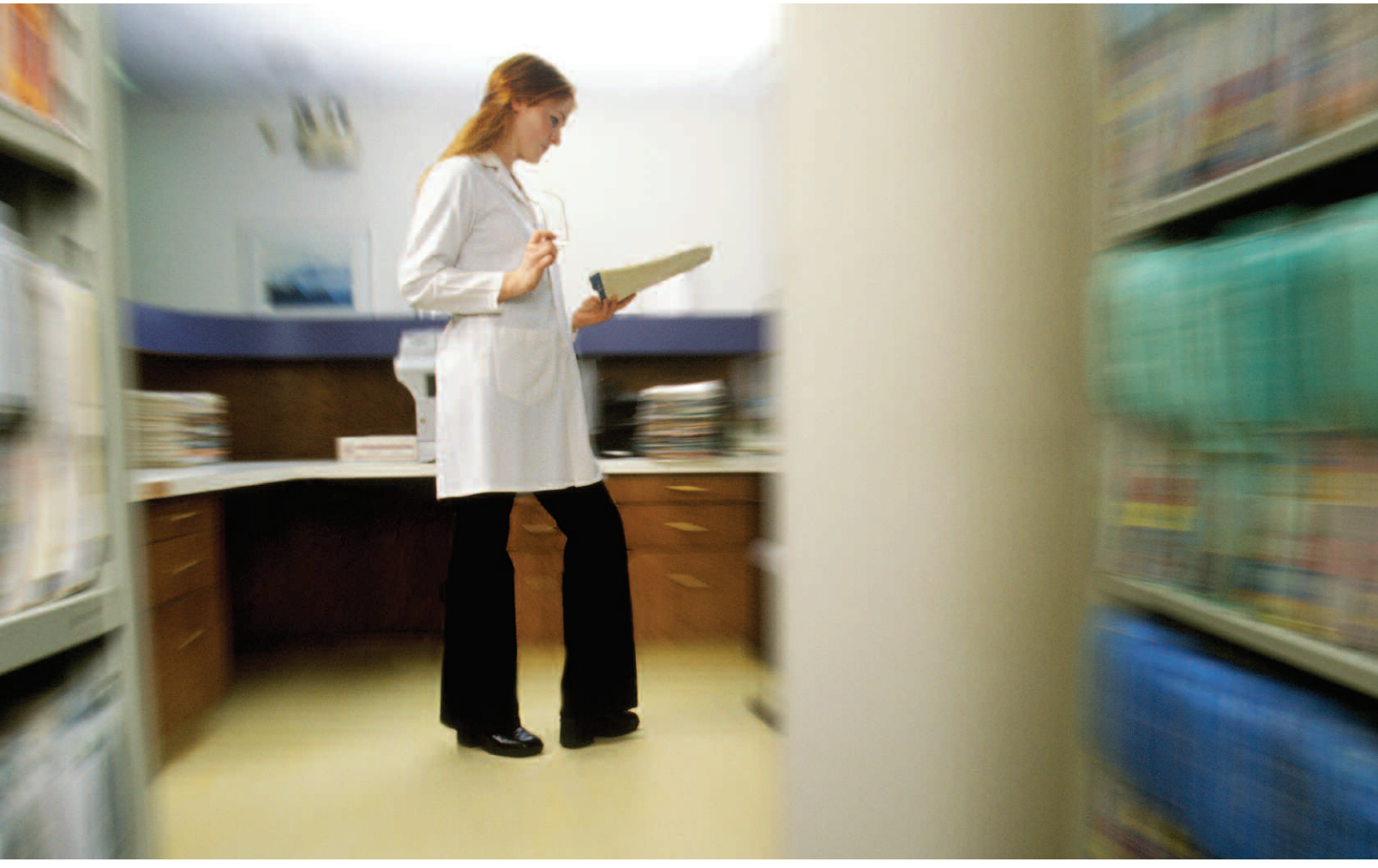
Containing an Outbreak: An Epidemiologist at Work



A look at how an epidemiologist conducts an investigation into a measles outbreak shows just how complicated containing an outbreak can be.

By Hillary Johnson, MHS

Yes, hello. We just admitted an infant with an upper respiratory infection, difficulty breathing, fever of 103, injected eyes and full body rash.

And so it begins.

In a typical day, my office can receive dozens of calls like the one above, and these become suspect cases. In the preliminary case status, a patient might be exhibiting clinical symptoms of a disease, but we do not yet have all the pieces of the puzzle (laboratory test results, travel history, vaccination history, exposure history, possible alternative diagnoses in the differential, etc.) to confirm or revoke it.

As an epidemiologist in a state health department, I am tasked with facilitating the testing, diagnosis and control of diseases deemed dangerous to public health. I am part of an experienced team that focuses exclusively on vaccine-preventable diseases — particularly any of the bugs normally prevented by the standard childhood vaccination schedule. If the disease is rare nowadays because it has a perfectly viable preventive measure (vaccination), then my team will probably participate in some part of the investigation.

In an ideal scenario, a medical provider calls us for direction while the patient is still present. The provider then collects the appropriate specimens, sends them to the state lab and correctly isolates the patient while results are pending. In the worst-case scenario, we are tracking down a patient after their doctor's visit to collect specimens and more information. In reality, it is usually somewhere in between.

The Case

A family races to their pediatric office, concerned over their little one's spiking fever and sudden rash spreading down her body. They pace in the waiting room until the pediatrician is available, then dash into the exam room, where the doctor determines the child is in respiratory distress and her fever too high for comfort. The child is then rushed to a hospital via ambulance, where she is eventually triaged in an emergency room and admitted to a pediatric ward. A day later, the child's serology results show she is IgM positive for the measles virus.

Measles Outbreaks Can Involve Some of the Most Comprehensive Follow-up

Once our team is notified of pending or confirmed test results, we spring into action, gathering as much information as possible. Measles is one of the most highly transmissible vaccine-preventable diseases, and the measles virus can stay in the air up to two hours after the original patient has vacated the room. A viral respiratory illness, it can lead to ear infections, pneumonia, encephalitis and even death, particularly in young children. Susceptible pregnant women exposed to measles risk premature birth or miscarriage.[1] While no longer endemic in the U.S., on an average day, 430 children (18 every hour) die of measles worldwide. In 2011, there were an estimated 158,000 measles deaths globally.[2] The U.S. saw 189 cases (11 outbreaks)[3] in 2013, and 2014 is already well on its way to surpassing that with 108 nationally reported cases as of April 5 this year.[4]

As an epidemiologist in a state health department, I am tasked with facilitating the testing, diagnosis and control of diseases deemed dangerous to public health.

To prevent further spread, we must act, and act quickly. MMR (measles, mumps, rubella), the measles vaccine, may serve as post-exposure prophylaxis or possibly modify the clinical course of disease if administered within the first 72 hours after exposure.[5] The MMR vaccine is highly effective at preventing disease, and certainly in states like Massachusetts, with high vaccination rates, most people are immune as a result. However, recent trends in alternative and delayed vaccine schedules, an increasingly mobile global population, and the occasional adult who missed routine vaccination efforts as a child mean that assumptions cannot be made. Identifying who was exposed and who is susceptible (requiring clinical intervention) becomes priority number one.

Immunity is determined by two documented doses of MMR on record, or a blood test showing immunity through the presence of IgG antibodies (either the result of vaccination or previous disease).

Some contacts are easy to identify; the child's immediate family is quickly cleared. The older siblings are on schedule and have their two documented doses, and serology testing shows the parents are immune. But who else has been exposed?

Tracing the Patient's Steps

In a small practice like the pediatrician's office where the child was first seen, everyone present when the child arrived, up to two hours after she left, would be considered exposed.

Working with the office administrators, we pull the day's appointment list, identifying any overlapping appointment times to ascertain potential contacts. Approximately 11 scheduled children make the list. Four children are infants, too young for

Indications and Important Safety Information

INDICATIONS: ALPROLIX, Coagulation Factor IX (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, coagulation factor IX concentrate indicated in adults and children with hemophilia B for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

ALPROLIX is not indicated for induction of immune tolerance in patients with hemophilia B.

CONTRAINDICATIONS: ALPROLIX is contraindicated in patients who have a known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients.

WARNINGS AND PRECAUTIONS: Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with factor IX replacement products, and are possible with ALPROLIX. Discontinue use of ALPROLIX if hypersensitivity symptoms occur, and initiate appropriate treatment. Patients using ALPROLIX should be

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monitored for the development of neutralizing antibodies (inhibitors). An association between the occurrence of a factor IX inhibitor and allergic reactions has been reported. Individuals with factor IX inhibitors may be at increased risk of anaphylaxis upon subsequent challenge. The use of factor IX products has been associated with the development of thromboembolic complications, especially in patients receiving continuous infusion through a central venous catheter. The safety and efficacy of ALPROLIX administration by continuous infusion has not been studied. One-stage clotting assays may be used to confirm that adequate factor IX levels have been achieved and maintained. Factor IX results can be affected by the type of aPTT reagent used. Measurement with a one-stage clotting assay using a kaolin-based aPTT reagent will likely result in an underestimation of activity level.

ADVERSE REACTIONS: Common adverse reactions observed in the Phase 3 clinical trial (incidence ≥1%) were headache and oral paresthesia.

Please see Brief Summary of full Prescribing Information on the following page.

ALPROLIX™ [Coagulation Factor IX (Recombinant), Fc Fusion Protein], Lyophilized Powder for Solution For Intravenous Injection.

Brief Summary of Full Prescribing Information

1 INDICATIONS AND USAGE

ALPROLIX™, Coagulation Factor IX (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, coagulation Factor IX concentrate indicated in adults and children with hemophilia B (congenital Factor IX deficiency) for:

- Control and prevention of bleeding episodes,
- Perioperative management,
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ALPROLIX™ is not indicated for induction of immune tolerance in patients with hemophilia B. [*see Warnings and Precautions* (5.3)].

4 CONTRAINDICATIONS

ALPROLIX™ is contraindicated in individuals who have a known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients. [*see Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with Factor IX replacement products, and are possible with ALPROLIX™. Early signs of allergic reactions, which can progress to anaphylaxis, may include angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea. Discontinue use of ALPROLIX™ if hypersensitivity symptoms occur, and initiate appropriate treatment.

5.2 Neutralizing Antibodies (Inhibitors)

Formation of neutralizing antibodies (inhibitors) to Factor IX has been reported during factor replacement therapy in the treatment of hemophilia B. Monitor all patients regularly for the development of inhibitors by appropriate clinical observations and laboratory tests [*see Warnings and Precautions*(5.4)].

An association between the occurrence of a Factor IX inhibitor and allergic reactions has been reported[1]. Evaluate patients experiencing allergic reactions for the presence of an inhibitor. Closely observe patients for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of exposure to the product.

Individuals with Factor IX inhibitors may be at an increased risk of anaphylaxis upon subsequent challenge with ALPROLIX™.

5.3 Thromboembolic Complications

The use of Factor IX products has been associated with the development of thromboembolic complications, especially in individuals receiving continuous infusion through a central venous catheter. ALPROLIX™ should be administered as bolus infusion over several minutes [*see Dosage and Administration* (2.3)]. The safety of ALPROLIX™ administration by continuous infusion has not been studied.

5.4 Monitoring Laboratory Tests

- To confirm adequate Factor IX levels have been achieved and maintained, monitor plasma Factor IX activity by performing the one-stage clotting assay [*see Dosage and Administration* (2.1)]. Factor IX results can be affected by the type of aPTT reagent used. Measurement with a one-stage clotting assay using a kaolin-based aPTT reagent will likely result in an underestimation of activity level.
- Monitor for the development of Factor IX inhibitors if the expected Factor IX activity levels in plasma are not attained, or if bleeding is not controlled with the recommended dose of ALPROLIX™. Perform a Bethesda assay to determine if Factor IX inhibitors are present.

6 ADVERSE REACTIONS

Common adverse reactions (incidence ≥1%) reported in clinical trials were headache and oral paresthesia.

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.

In the multi-center, prospective, open-label clinical trial with ALPROLIX™, 123 previously treated patients (PTPs, exposed to a Factor IX containing product for ≥100 exposure days) were evaluated, with 115 subjects treated for at least 26 weeks and 56 subjects treated for at least 52 weeks.

Adverse reactions (ARs) were reported in 10 of 119 (8.4%) subjects treated with routine prophylaxis or episodic (on-demand) therapy. They are summarized in Table 3.

No subject was withdrawn from study due to an adverse reaction. In the study, no inhibitors were detected and no events of anaphylaxis were reported.

Table 3: Summary of Adverse Reactions

System Organ Class	Adverse Reactions (AR)	Number of Subjects (%) N=119*
Nervous system disorders	Headache Dizziness Dysgeusia	2 (1.7) 1 (0.8) 1 (0.8)
Gastrointestinal disorders	Paresthesia oral Breath odor	2 (1.7) 1 (0.8)
General disorders and administration site conditions	Fatigue Infusion site pain	1 (0.8) 1 (0.8)
Cardiac disorders	Palpitations	1 (0.8)
Renal and urinary disorders	Obstructive uropathy	1 (0.8)
Vascular disorders	Hypotension	1 (0.8)

*119 previously treated patients (PTPs) on routine prophylaxis or episodic (on-demand) therapy

Obstructive uropathy was reported in one subject with hematuria who developed an obstructing clot in the urinary collecting system. The event resolved with hydration and the subject continued prophylactic treatment with ALPROLIX™. A causal relationship of clot formation to ALPROLIX™ was not established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproductive studies have not been conducted with ALPROLIX™. It is also not known whether ALPROLIX™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ALPROLIX™ should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

There is no information available on the effect of Factor IX replacement therapy on labor and delivery. Use only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

It is not known if ALPROLIX™ is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised if ALPROLIX™ is administered to nursing women.

8.4 Pediatric Use

Safety, efficacy, and pharmacokinetics of ALPROLIX™ have been evaluated in previously treated pediatric patients 12 years of age and older. No dose adjustment is required for adolescents.

Children under 12 years of age may have higher Factor IX body weight-adjusted clearance, shorter half-life, and lower recovery. Higher dose per kilogram body weight or more frequent dosing may be needed in these patients [*see Clinical Pharmacology* (12.3)].

The use of ALPROLIX™ in children younger than 12 years of age is supported by the clinical study of ALPROLIX™ in subjects 12 years of age and older and interim pharmacokinetic and safety data from a study of pediatric subjects including 8 subjects 2 to 5 years of age and 15 subjects 6 to 11 years of age who were exposed for a median of 21.3 weeks (1.1 to 45.7 weeks). The safety profile in subjects under 12 years of age is acceptable. Efficacy can be extrapolated from pharmacokinetic data to subjects < 2 years of age. [*see Clinical Pharmacology* (12.3)]

8.5 Geriatric Use

Clinical studies of ALPROLIX™ did not include a sufficient number of subjects age 65 and over to determine whether or not they respond differently than younger subjects.

17 PATIENT COUNSELING INFORMATION

- Advise patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise patients to report any adverse reactions or problems following ALPROLIX™ administration to their physician or healthcare provider.
- Advise patients to contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor IX therapy, as this may indicate the development of an inhibitor.
- Inform patients of the early signs of hypersensitivity reactions (including hives, chest tightness, wheezing, difficulty breathing and swelling of the face) and anaphylaxis. Instruct patients to discontinue use of the product and contact their healthcare provider if these symptoms occur.

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vaccination (including one a mere 14 days old). Because the MMR vaccine is not an option, these vulnerable children must immediately receive immune globulin (IG) to reduce their risk for infection and complications. The other seven children exposed have their vaccine records assessed. Those with two doses of vaccine on record are good. Those with only their first dose are scheduled to come in for their second right away.

But we are not done.

If you are following the details of this exposure, you will note that 11 children had pediatric appointments during our exposure hours. But how many children do you know attend their pediatric appointments on their own? We have only a list of those with appointments; we do not know who else accompanied them to the pediatrician's office and was also exposed.

Every child's caregiver is contacted to identify if additional parents, siblings or companions were also exposed during the child's visit. These interviews with caregivers reveal an additional 26 adults and children were exposed. Many of the siblings also have vaccine records at the pediatrician's office, so their status is quickly determined; however, many of the adult companions must contact their own primary care physicians, or quickly go in for vaccine and/or blood tests. All the while, time is ticking by.

Our original patient rode in an ambulance on her way to the hospital, and ambulatory staff plus any patients driven in the subsequent two hours also need their immunity status checked.

The hospital becomes the biggest and most arduous task. Working with hospital infection control staff, lists are drafted with overlapping patients in the emergency room and the pediatric ward. But this is a large hospital with departments and wards and hallways and people moving all about. Our index patient is highly infectious. Even if she stayed in one location, unless she had been in a negative air pressure room (she hadn't), anyone in shared airspace was at risk. Hospital engineers are called in to meet with us and discuss building airflow design. Going over HVAC schematic drawings, we determine the shared airspace was limited to the emergency department, pediatric ward and a neighboring radiology suite. Infection control staff are then able to produce a list of exposed patients from the hospital, which starts out at around 400 named individuals. Each of these patients must be contacted and their immunity assessed.

But, here again, this is just the starting point. How many people drive themselves to the emergency room? How many pediatric patients never have a guardian or visitor accompany them? As companions are identified, the list of exposed individuals grows and grows.

Whenever there is a medical facility exposure, we worry about patients, but we also worry about staff, the first line of defense for patients. The Centers for Disease Control and Prevention (CDC) recommends that all healthcare staff are up-to-date with their vaccines and have their immunity status documented and on record with their employer. When medical facilities have prepared this information ahead of time, they are not struggling in an emergency to determine not only exposed patients but also susceptible staff that will then need to be excluded from work. Sadly, in our experience, not every medical facility is prepared for such events. Infection control staff can end up spending hours and even days following up on potentially hundreds of exposed hospital staff. This high-risk occupational setting means that nonimmune staff must be excluded from work almost immediately to prevent putting the facility at further risk.

Epidemiologists Track the Flu

From September through May of each year, influenza plays a particular role in many state epidemiology programs. The flu can easily wipe out a wing of a long-term care facility, or strike suddenly in an institution housing medically fragile populations (those with underlying health conditions or developmental delays). On a daily basis, epidemiologists consult with facilities experiencing influenza clusters, providing guidance on antivirals and other control measures to reduce spread. Aggregately, epidemiology staff collect flu laboratory samples and surveillance data in real time to predict seasonal trends, identify circulating strains and detect antiviral resistance immediately. Because the flu vaccine makeup is different every year, these surveillance activities at the state level are critical to informing future vaccines. The B strain included in the 2013-2014 seasonal flu vaccine was identified through the Massachusetts State Laboratory surveillance and strain typing efforts and appropriately named: B/Massachusetts/2/2012 (B/Yamagata lineage).[7]

The Extent of Exposure

Patients with measles are infectious beginning four days before through four days after their rash begins. A patient's medical visits are often the easiest thing to track. However, their other activities before their diagnosis also need to be examined. In the case of our young child, further inquiry determines she was unvaccinated (due to age), and her family had traveled abroad around the time she would have acquired the infection. On her return to the U.S., her illness began. Based upon her

infectious period, international and domestic flights had been exposed. This requires coordination with CDC and U.S. quarantine stations to obtain flight manifests and notify the other states and countries involved. We must drill down to the exact seat our patient sat in, as airflow patterns on a plane may vary, and quarantine stations need to determine who exactly had been exposed and should be notified.

What Happens When a Contact Is Not Immune?

Exposed individuals who do not have evidence of immunity (either through vaccination records or a blood test) and who do not receive the vaccine immediately (either because we could not contact them early enough or they refused vaccination) must be excluded from public activities through a full incubation period (the period of time when they may potentially develop disease). For measles exposure, quarantine would begin on the fifth day after exposure and continue through the 21st day. During this time, children must stay home from group daycare facilities or schools, and adults must stay home from work. It can undoubtedly be a burden, not to mention the obvious stress associated with watchful waiting and the chance one might get sick. But such exclusions help to stop the spread of disease by reducing the possibility of further exposure, and they have been the cornerstone of public health disease intervention for generations.

Emerging Technology Can Aid an Investigation

If epidemiology was the subject of a primetime investigative television drama, our office would have touch screen computer systems and a tech-savvy Goth girl in pigtails hacking into every surveillance system or video camera in the city, tracing an index case's every step and easily identifying every location of exposure.

Reality is much more sobering. My computer monitor rests on a stack of medical textbooks, and my operating system is still an antiquated Windows XP. I do not have caller ID on my office phone, and I do not get free coffee. This is true government work. But, while we do not have cutting-edge office resources, the field is still benefiting from technology in several ways.

Fun Times at the Jersey Shore

In 2013, county health officials investigating a string of mumps cases were able to link at least 21 people with mumps to having visited a particular Jersey Shore bar known for a fun party atmosphere.[8] Because mumps is spread through tiny droplets of saliva or mucus, sharing cups, utensils or locking lips (classic Jersey Shore activities) were the perfect transmission vector.

The hospital becomes the biggest and most arduous task.

One of our measles cases this year traveled from several locations via taxicabs. Previously, without the case being able to identify the taxi drivers (would you remember the name and contact information for your last cab driver?), these would be considered lost to follow-up. However, because our case had utilized a new mobile app to order three of her cab rides, she was able to produce email receipts with cab driver names, contact information and exact pick-up and drop-off times. With that information, we were able to contact the mobile app company and identify the exposed drivers, as well as any clients picked up within the next two hours. Drivers and subsequent clients were all able to receive follow-up and vaccination as needed. Such mobile and GPS technologies are assisting in disease intervention more and more.

It's All in the Timing

Every vaccine-preventable disease differs in transmissibility, infectiousness and follow-up. With measles, the timing for intervention is very specific. For a disease like pertussis, the window for preventive prophylaxis is much larger. But, they all require the same thorough diligence and partnerships with medical providers, schools and local health officials. Every hour that passes is one hour closer to an exclusion period or may mean a child might not get a preventive dose of vaccine or medication. Sometimes, a patient appears with a clinically classic set of symptoms. Confirmation with test results is immediate, and disease control can begin right away. Other times, the case before us presents more of a challenge. A rash might not have progressed classically, or a normally key symptom may be missing in the clinical picture. Sometimes, you may be convinced the patient in front of you has measles, but then it comes to light that three other children who attend the same daycare were just diagnosed with hand, foot and mouth disease (and there's your real answer). Or, a patient eventually reveals that he recently started a new medication, and the rash started shortly thereafter (suddenly an allergic reaction is much higher on the differential).

Measles Outbreak in Brooklyn, N.Y.

In the spring of 2013, the New York City Department of Health and Mental Hygiene identified a measles outbreak in an unvaccinated religious community in Brooklyn.[6] From the outbreak, six generations of measles infections were identified across two neighborhoods. Fifty-eight cases of measles were confirmed, and more than 3,500 contacts were identified and followed up. Significant isolation and control measures were implemented in order to stop the spread. The largest outbreak of measles in the U.S. at the time since 1996, the outbreak was traced back to an intentionally unvaccinated 17-year-old adolescent traveling to London who returned to New York City while infectious. Complications in spread included pneumonia in one child and hospitalization of two pregnant women, one of whom miscarried.

These additional details are critical as we wait for laboratory confirmation of a case: Has a patient engaged in recent travel? If not, have they had any foreign visitors recently? Is anyone else at work sick? Is the patient vaccinated? Any of these answers can help sway an investigation, and they are particularly important when laboratory test results are questionable. Our lab once received a nasopharyngeal swab from a provider office that tested negative, even though the clinical picture and background information on the patient was highly indicative of disease. This didn't sit right. Further investigation revealed the swab had sat "lost" on a shelf at the medical office for several days before someone found it and sent it in to the state lab. With unclear specimen handling and cold chain history, the specimen had been unsatisfactory for testing, and a negative result was not a surprise. Timing of specimens is also critical. If collected too early, a serology might be falsely positive because IgM antibodies have not yet mounted in sufficient quantities. If collected too late, a nasopharyngeal swab might not pick up enough virus to show up on a PCR test or culture.

In a fictional primetime TV drama, test results would be immediate and black or white. In reality, testing and retesting may be required. The decision to initiate a public health response is a judgment call based upon balancing the information at hand vs. the dangers of delaying follow-up. When lives are on the line, there is little room for error.

All told, our team spent the next month following up on more than 600 exposed individuals. Thanks to the combined efforts of medical facility staff, local health officials and several vaccination clinics, this exposure did not lead to any secondary cases. Countless individuals had to be vaccinated, and many were excluded from public activities through a full incubation period to help stop the spread.

The full follow-up from an outbreak can take weeks, particularly if there are second and third generations of disease (or six, as in the 2013 measles outbreak in Brooklyn, N.Y.[6]). Larger vaccination campaigns and follow-up may be required, and additional control measures may be implemented as needed. While not every suspect case under investigation pans out into confirmed disease and requires such intensive contact tracing and follow-up, epidemiologists must be ready and able to respond if they do.

Hello, we have a hospitalized patient with a high fever who seems to be developing a rash on his trunk. He's febrile and showing signs of fatigue, rhinorrhea and myalgia. He just came back from a hiking trip in a highly Lyme-endemic area where he was exposed to many ticks. We are pretty sure this is Lyme disease, but his wife is pregnant so we'd like to send in a serology for measles and rubella testing to the state lab just to be cautious.

Here we go again. ❖

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The Changing Face of HIV

There is no cure for this disease, but with effective treatments, it is no longer a death sentence.

By Jim Trageser

Formerly a death sentence and a disease that at one time attracted as much political attention as scientific, HIV/AIDS confounded the medical establishment when it was first diagnosed in the early 1980s — and fanned fears of a new plague that modern medicine would be unable to halt. However, advances in treatment over the past decade and a half have changed a diagnosis of human immunodeficiency virus/acquired immune

deficiency syndrome (HIV/AIDS) from a death sentence to a manageable condition — much like other chronic diseases such as hepatitis A or diabetes. And, public education campaigns, as well as changing public attitudes toward sexual behavior, have softened most of the opprobrium once directed at those who contract the virus.

What Is HIV?

HIV is the name of both the disease (sometimes referred to as HIV/AIDS) and the virus that causes it.[1]

It was 33 years ago that public health agencies first began to notice a class of symptoms that indicated a spreading type of immunological disease. In 1981, the Centers for Disease Control and Prevention (CDC) in its weekly newsletter reported on a high incidence of a rare form of pneumonia among gay men in Los Angeles. Within 12 months, public health agencies had tracked similar outbreaks of unusual diseases associated with compromised immune systems in other parts of the United States, and for the first time, researchers began tying these together and searching for a cause.[2]

By late summer of 1982, the term AIDS was in use by CDC. But, it wasn't until 1983 that the cause of this new disease was first isolated. Originally called the lymphadenopathy-associated virus (after its location in an infected patient's lymph nodes), by 1985 independent research had confirmed a virus as the cause of AIDS and, thus, coined it HIV.[2]

HIV weakens the body's immune system by attacking and killing a type of white blood cell critical to the body's defenses — a cell called CD4. Too few CD4 cells, and the body is unable to fight off infections or defend itself against otherwise rare forms of cancer that normally would be disposed of before they formed tumors.[3]

But, while health officials didn't recognize the pattern of infections caused by the HIV virus until 1981, and didn't discover the cause until 1983, researchers since have determined that the virus likely was present in the United States since the mid-1970s (at the latest). After studying the genetic makeup of HIV and other viruses that target our closest animal relations, researchers now believe that modern HIV is descended from a virus that infected African chimpanzees in the 19th century. Human beings who hunted and ate the chimps likely contracted this simian immunodeficiency virus, or SIV, which mutated in the following decades into the form that today causes HIV.[4]

As with SIV, the HIV virus is not very robust and cannot survive outside the host. It can be contracted only from bodily fluids — blood, semen or vaginal fluid — from someone who is infected. The main methods of transmission are unprotected sexual contact, blood transfusions and sharing of unsterilized hypodermic needles among illicit drug users.[5]

Symptoms of HIV

The symptoms of HIV vary, depending on the individual and the stage of the disease. Many, but not all, people infected experience flu-like symptoms that are often described as the "worst flu ever" within two to four weeks after HIV infection. This is the first stage, known as "acute retroviral syndrome" (ARS), or "primary HIV infection," which is the body's natural response to the HIV infection and causes symptoms such as fever (the most common symptom), swollen glands, sore throat, rash, fatigue, muscle and joint aches and pains, and headache that can last anywhere from a few days to several weeks. On the other hand, not everyone who is infected with HIV develops ARS. Many people who are infected with HIV do not have any symptoms at all for 10 years or more.[6]

Then, the disease moves into the clinical stage, the second stage, sometimes called "asymptomatic HIV infection." Depending on treatment, people can live with clinical latency between 10 years and several decades.

AIDS is the third stage of infection when the body's immune system is weakened. AIDS symptoms can include rapid weight loss; recurring fever or profuse night sweats; extreme and unexplained tiredness; prolonged swelling of the lymph glands in the armpits, groin, or neck; diarrhea that lasts for more than a week; sores of the mouth, anus or genitals; pneumonia; red, brown, pink or purplish blotches on or under the skin or inside the mouth, nose or eyelids; and memory loss, depression and other neurologic disorders. Many of the severe symptoms and illnesses of AIDS come from the opportunistic infections that occur because the body's immune system has been damaged.[6]

Diagnosing HIV

HIV is diagnosed through blood or oral fluid tests that look for antibodies the immune system makes in response to the presence of the HIV virus.[7] If this test is positive, a second test to confirm the results is ordered before a diagnosis is made. The second test may use a different method to look for the antibodies, or it may be designed to detect HIV antigens or genetic material (RNA).[8]

However, as the HIV virus is slow to replicate, the infection is also slow to develop. It generally takes weeks to months before newly infected patients will have enough HIV virus in their bloodstream to generate a positive test. Yet, they are already contagious during this period.[7]

Treating HIV

CDC estimates that 1.1 million Americans currently have HIV.[9] Unfortunately, there is presently no cure for HIV. Once it is contracted, patients will have it for the rest of their

lives. There is also no vaccine to protect against HIV at this time.

The maintenance use of antiretroviral drugs has proven effective at suppressing the virus — slowing its development to allow patients' immune systems to continue to fight the secondary infections that can make HIV/AIDS deadly if left untreated.[10] However, these drugs are merely treatments, and patients on maintenance regimens remain contagious and capable of spreading the virus.

CDC estimates that 1.1 million Americans currently have HIV.

Most physicians prescribe a mixture of up to three antiretroviral drugs in a combination known as a "cocktail." There are five different types of these drugs, classified by the method they use to fight the HIV virus:[11]

• Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) that mimic DNA building blocks the virus needs to replicate itself, but don't work properly for that process

• Non-nucleoside reverse transcriptase inhibitors (NNRTIs) that interfere with an enzyme needed by the virus to replicate itself

• Protease inhibitors (PIs) that interfere with another enzyme that allows the virus to cut up its genes into smaller pieces during replication

• Entry/fusion inhibitors that make it more difficult for the HIV virus to penetrate the membrane of the CD4 white blood cells, preventing individual cells from being infected

• Integrase inhibitors that interfere with an enzyme necessary to the virus's ability to reproduce itself

By crafting a strict schedule of multiple combinations of these drugs, physicians are able to help their patients continue to live full, active lives. While there are side effects to these drugs, with more than 30 individual drugs spanning these five classes, doctors are often able to minimize the side effects suffered by their patients by changing the combinations.

Ongoing Research

The top priority of medical researchers is to develop a fully effective vaccine to prevent HIV. However, because the body never fully rids itself of the HIV virus the way it does with other dangerous viruses, the traditional approach of introducing weakened or dead viruses to stimulate the body's production of antibodies tailored to that specific virus has not been successful.[12]

Still, research continues for a potential HIV vaccine that will prevent HIV's spread and lead to its ultimate demise. There is also ongoing research into vaccines that might alter the disease's development in ways that lower the rate of its transmission.[13]

Short of eradicating HIV via inoculation, researchers are also exploring new leads on various forms of prevention — from creams and gels that would create an HIV-proof barrier during sexual activity, to drugs to reduce the risk of contracting HIV. CDC is now promoting use of PrEP, or pre-exposure prophylaxis, to reduce the risk of contracting HIV by those engaged in ongoing high-risk behavior.[14]

Additional research continues, of course, into finding yet more drugs to join the 30 or so antiretroviral drugs already being used to further slow the development of HIV in infected patients. It is hoped a future antiretroviral drug, or a combination of them, will be successful in ridding the body of the virus completely — providing a true cure for HIV.[15] ❖

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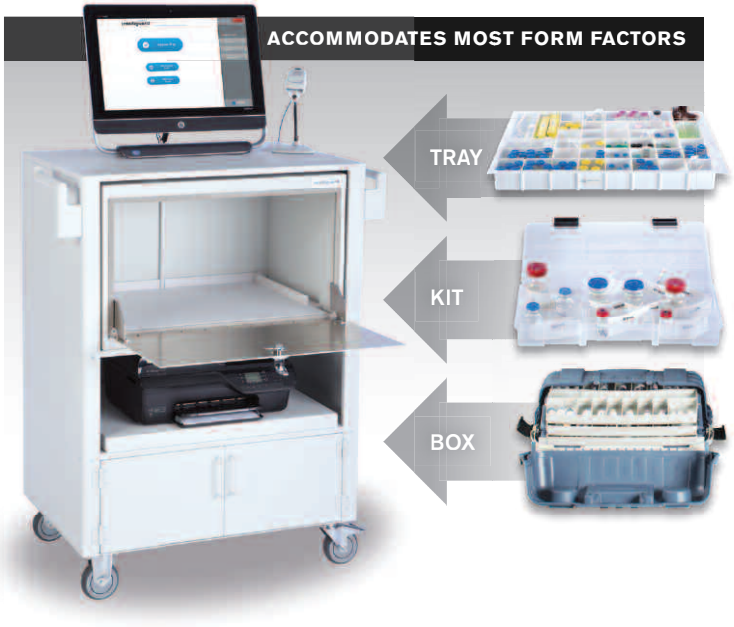

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HOW THE ACA AFFECTS HEALTHCARE PROVIDERS

By Ronale Tucker Rhodes, MS

Physicians can expect to experience many changes in the way they practice as provisions of the Affordable Care Act continue to be implemented.

When the deadline arrived for uninsured Americans to sign up for healthcare insurance under the Affordable Care Act (ACA), the tally was a sharp turnaround from the troubled beginnings of enrollment last fall. According to President Obama, eight million Americans purchased insurance during the six-month sign-up period, achieving the results that congressional budget analysts had first anticipated. That tally is based on the number of people who enrolled for coverage by the deadline (extended by two weeks to mid-April) through the new federal insurance marketplace operating in three dozen states, as well as people who enrolled in 14 state-run marketplaces.[1,2]

As of this writing, eight million people have now signed up for health insurance through the exchanges. How will these numbers and, more important, the ACA as a whole affect the healthcare community? The answers range from very bad to very good depending on who replies. It is clear that ACA is a very complex piece of legislation that will continue to bring about sweeping changes for physicians as provisions go into effect. Here, we take a look at some of the prominent changes that will affect healthcare providers in 2014 and beyond.

Universal Coverage

One of the main goals of the ACA is to provide quality, affordable healthcare for all Americans with a requirement for all Americans to purchase healthcare insurance. In addition to the eight million individuals who purchased healthcare insurance through the marketplaces, there are two very large populations that add to the numbers of insured patients as a result of specific provisions of the ACA. One provision allows youth under age 26 to remain on their parents' insurance plans whether they live in their parents' home or not. Other provisions include the ban on the insurance industry practice of refusing to cover pre-existing conditions and the elimination of lifetime caps on healthcare coverage.

Data from the Commonwealth Fund Health Insurance Tracking Surveys of Young Adults, conducted in November 2011 and March 2013, showed that increasing numbers of young adults during that period became aware of, and took advantage of, the ACA's requirement that health plans offering dependent coverage insure children through age 25. In March 2013, an estimated 15 million 19-to-25-year-olds — half this age group — had been on a parent's health insurance policy in the prior 12 months, up from 13.7 million prior to November 2011. Of the 15 million young adults on a parent's plan, an estimated 7.8 million likely would not have been eligible to enroll in that plan prior to the ACA.[3]

The tracking survey also suggested that as young adults ages 19 to 29 gained awareness of the new coverage options available in January 2014, they would eventually enroll in large numbers. However, the survey found that only 27 percent of 19-to-29-year-olds were aware of the marketplaces. Lack of awareness was lowest among those who were uninsured during the year and those with low to moderate incomes.[3] As of March 1, 27 percent of the 7.1 million enrollees in the marketplaces were in the 18 to 35 age group.[4]

While there are no data on the number of individuals with pre-existing conditions that are now able to purchase insurance, the numbers are estimated to be in the millions. In fact, it is projected that as many as 30 million Americans are expected to gain health insurance through the ACA. The question is: Are more patients a good thing for doctors? Because the American healthcare infrastructure has had workforce shortages for decades, the influx of so many new patients could flood a delivery system that is already strained. According to a 2012 compilation of state workforce studies and reports, every state needs more physicians. And, there are shortages not just of primary care physicians (PCPs), but also of specialists.[5]

It is projected that as many as 30 million Americans are expected to gain health insurance through the ACA. The question is: Are more patients a good thing for doctors?

The ACA relies heavily on the concept of the patient-centered medical home model and free preventive care, both of which require enough PCPs to deliver services.[5] Unfortunately, the nation's physician population is approximately one-third PCPs and two-thirds specialists, which is widely agreed to be suboptimal.[6] The projected PCP shortage is currently estimated at 8,000, and over the next decade it is projected to range from 20,400 to 45,000, even with the use of nurse practitioners and physician assistants.[5]

Compounding this problem is that many of the new health insurance plans, which are low-cost or free plans, have limited networks, so the in-network doctors could be burdened with more patients than they can handle.[7] The good news is that the ACA has provisions to combat this problem. It provides grants and contracts to support primary care training, and encourages physician training in community-based settings to offset the greater orientation toward specialty care in hospital-based residency training.[6]

There are also a great number of provisions to increase the number of physicians in medically underserved areas. The ACA authorizes grants to increase training in geriatrics and behavioral health, and provides incentives for general surgeons who practice in medically underserved areas. It includes changes to the National Health Service Corps (a program of the Health Resources and Services Administration) that may expand the number of providers able to serve in shortage areas in exchange for loan repayment or scholarships. It authorizes programs that aim to increase the diversity of the physician workforce by encouraging underrepresented minorities to enter health profession education and supporting them in their studies. It provides training in rural areas to encourage physicians to practice there at the conclusion of their training. And, last, it includes provisions that are intended to reduce isolation and increase contact with colleagues such as continuing education programs for health providers in rural areas.[6]

The ACA seeks to make healthcare more accessible and safer for Medicare and Medicaid patients, and it provides many changes and incentive programs for healthcare providers to do so.

One more way the law is designed to increase physicians is by improving existing care facilities and increasing the number of available jobs. The ACA has funded 190 construction and renovation projects at health centers, and will support more than 485 new construction and renovation projects at health centers with 245 completely new centers in the next year. These projects are estimated to serve almost four million people, creating nearly 19,000 new jobs, including positions staffing the new facilities.[8]

Medicare and Medicaid

According to a budget document from the Centers for Medicare and Medicaid Services (CMS), Medicare, Medicaid and Children's Health Insurance Program (CHIP) will cover almost 116 million Americans in 2014. That equals approximately 37 percent of the nation's total population and approximately 43 percent of the population that will have some kind of health insurance.[9] The ACA seeks to make healthcare more accessible and safer for Medicare and Medicaid patients, and it provides many changes and incentive programs for healthcare providers to do so.

Shortage areas. To encourage physicians to treat Medicare patients in shortage areas such as rural communities, the ACA provides a 10 percent Medicare bonus payment for primary care physicians and general surgeons.[10] It also requires increased Medicare and Medicaid payments in primary care, where there is a large and growing salary gap with specialists, and provides incentives to coordinate care and compensate for administrative duties that specialty physicians do not have.[6]

Medicaid expansion. For states that have agreed to expand their Medicaid program, the ACA increases Medicaid reimbursements to match Medicare rates for primary care services — an increase that is fully funded by the federal government.[10] States that have expanded Medicaid include Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Hawaii, Illinois, Iowa, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oregon, Rhode Island, Vermont, Washington and West Virginia. As of this writing, states still considering expanding Medicaid include Indiana, Missouri, Pennsylvania, Utah and Virginia.[11]

Medicare Advantage. Until recently, CMS had announced that Medicare Advantage plans would see a rate cut of 1.9 percent. Medicare Advantage plans are typically paid more than their traditional counterparts, and the ACA sought to bring the cost of Medicare Advantage more closely in line with traditional Medicare. However, on April 7, CMS announced that it would instead increase the rate it pays Medicare Advantage plans by 0.4 percent in 2015 — a result of "various policy changes" and "new estimates," according to Jonathan Blum, former CMS principal deputy administrator.[12]

Quality vs. Quantity. But, Medicare reimbursement under the ACA for hospitals now hinges upon "quality" rather than "quantity," which many programs address.

READMISSION REDUCTION PROGRAM

Effective Oct. 1, 2012, a readmission reduction program was established to provide incentives for hospitals to implement strategies to reduce the number of costly and unnecessary hospital readmissions. CMS defines a readmission as "an admission to a subsection(d) hospital within 30 days of a discharge from the same or another subsection(d) hospital." Subsection(d) hospitals, per the Social Security Act, include short-term inpatient acute care hospitals excluding critical access, psychiatric, rehabilitation, long-term care, children's and cancer hospitals.

About 20 percent of Medicare patients are readmitted to a hospital within one month after discharge, which CMS considers

excessive and an indicator of quality of care, or lack thereof. The incentives for reducing readmissions are escalating penalties that decrease a hospital's payments from all of its Medicare cases. In 2012, if rates of readmission to a discharging or another inpatient prospective payment system (IPPS) hospital were deemed excessive, the hospital's IPPS payments were decreased up to 1 percent for all Medicare payments. In October 2013, the penalty went up to 2 percent, and in October 2014, it will increase to 3 percent.

A hospital's readmission ratio was determined based on the frequency of Medicare readmissions within 30 days for acute myocardial infarction, congestive heart failure and pneumonia for patients who were discharged from July 2008 through June 2011. CMS determined the excess readmission ratios for those three diagnoses based on a National Quality Forum endorsed methodology, which looked at three years of discharge data and at least 25 records for each condition. The ratio includes adjustments for clinical factors such as patient demographic attributes, comorbidities and patient frailty. In 2015, additional conditions/measures for the initial inpatient admission will be added to the current list of three and will likely include the MedPAC recommendations of chronic obstructive pulmonary disease, coronary artery bypass grafting and percutaneous transluminal coronary angioplasty procedures, and other vascular procedures.[13]

Since the implementation of the readmission reduction program, rates of readmission have fallen. From 2007 to 2011, the all-cause 30-day hospital readmission rate among Medicare fee-for-service beneficiaries was 19 percent. In 2012, that rate declined to 18.5 percent, and in the first eight months of 2013, it declined to 18 percent. This translates into an estimated 130,000 fewer hospital readmissions between January 2012 and August 2013.[14]

Bundled Payments for Care Improvement

The Bundled Payments for Care Improvement (BPCI) initiative is another method for increasing higher quality healthcare at a lower cost to Medicare. Under BPCI, organizations enter into payment arrangements that include financial and performance accountability for episodes of care. It comprises four broadly defined models of care that link payments for multiple services that beneficiaries receive during an episode of care. Model one includes an episode of care focused on the acute care inpatient hospitalization under which awardees agree to provide a standard discount to Medicare from the usual Part A hospital inpatient payments. Models two and three involve a retrospective bundled payment arrangement in which actual expenditures are reconciled against a target price for an episode of care. Model four involves a prospective bundled payment arrangement in which a lump sum payment is made to a provider for the entire episode of care. BPCI is a three-year initiative that began Jan. 31, 2013, to assess whether the models being tested actually achieve improved patient care and lower costs to Medicare.[15]

Hospital Value-Based Purchasing Program

The ACA has also established the Hospital Value-Based Purchasing (VBP) program, which builds on earlier legislation — the 2003 Medicare Prescription Drug, Improvement and Modernization Act and the 2005 Deficit Reduction Act — that established a way for Medicare to pay hospitals for reporting on quality measures. The Hospital VBP rewards acute-care hospitals with incentive payments for the quality of care for Medicare patients based on how closely they follow best clinical practices and how well they enhance patients' experiences of care.[16]

In 2013, 45 percent of a hospital's score was based on how frequently it followed basic clinical standards of care such as removing urinary catheters from surgery patients within two days to decrease the chance of infections. Thirty percent of the score was based on how patients rated the way they felt they were treated[14] in the hospital using the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, the first national standardized, publicly reported survey of patients' perspectives of hospital care. The HCAHPS survey asks discharged patients 27 questions about their recent hospital stay, 18 of which are core questions about critical aspects of patients' hospital experiences (communication with nurses and doctors, responsiveness of hospital staff, cleanliness and quietness of the environment, pain management, communication about medicines, discharge information, overall rating, and whether they would recommend the hospital). The survey also includes four items to direct patients to relevant questions, three items to adjust for the mix of patients across hospitals, and two items that support congressionally-mandated reports. It is administered to a random sample of adult patients across medical conditions between 48 hours and six weeks after discharge, and it is not restricted to Medicare patients.[17]

Medicare reimbursement under the ACA for hospitals now hinges upon "quality" rather than "quantity," which many programs address.

To assess quality, Medicare looks not only at how hospitals

score in comparison with each other, but also how much each improves from two years previously compared with other hospitals. A hospital is judged on whichever score is higher, so some hospitals with subpar quality rankings still get more money because they show vast improvement. The amount of a hospital's bonuses and penalties will remain unclear until the start of the following fiscal year, because it depends on how much a hospital ultimately bills Medicare.

Beginning in 2015, the ACA requires all physicians to participate in the Physician Quality Reporting System.

More hospitals received penalties than bonuses in 2013, the second year of the Hospital VBP, and the average penalty was steeper than it was in the first year. In 2013, Medicare raised payment rates to 1,231 hospitals. Another 1,451 hospitals were paid less for each Medicare patient they treated.[16]

Physician Quality Reporting System

Beginning in 2015, the ACA requires all physicians to participate in the Physician Quality Reporting System (PQRS) that was a result of the Tax Relief and Health Care Act of 2006. The PQRS authorizes a financial incentive for eligible professionals. For 2013 and 2014, eligible professionals who satisfactorily report quality data in the 2013 PQRS program can qualify for an incentive equal to 0.5 percent of the total estimated Medicare Part B allowed charges for all covered professional services furnished during the applicable reporting period. In the case of a group practice participating in the group practice report option, that incentive is based on the total estimated Part B charges for all covered professional services furnished by the group practice. Eligible professionals who did not satisfactorily report quality data under PQRS 2013 are subject to a 1.5 percent payment reduction in 2015. For PQRS 2014, penalties will increase to 2 percent in 2016 and subsequent years.[18] The 2014 PQRS program consists of 110 individual quality measures eligible for claims-based reporting.[19] Reporting for the PQRS involves adding codes to the electronic or paper claim form that is submitted to Medicare.

Accountable Care Organizations

Finally, accountable care organizations (ACOs) are yet another way to encourage healthcare providers to provide high-quality care to Medicare patients. An ACO is a network of doctors and hospitals that share responsibility for providing coordinated care to patients. The goal of coordinated care is to ensure that patients, especially the chronically ill, get the right care at the right time while avoiding unnecessary duplication of services and preventing medical errors. When an ACO succeeds in both delivering high-quality care and spending healthcare dollars more wisely, it shares in the savings it achieves for the Medicare program. About four million Medicare beneficiaries (an estimated 14 percent of the U.S. population) are now in an ACO, and combined with the private sector, more than 428 hospitals have already signed up.

Providers in an ACO are jointly accountable for the health of patients, and they must seamlessly share information. Those who save money while also meeting quality targets keep a portion of the savings. Providers can choose to be at risk of losing money if they aim for a bigger reward, or they can enter the program with no risk. In addition, CMS created a second strategy known as the Pioneer Program for high-performing health systems to pocket more of the expected savings in exchange for taking on greater financial risk. If an ACO is unable to save money, it might have to shoulder the costs of investments made to improve care such as adding new nurse care managers, and it may also have to pay a penalty if it doesn't meet performance and savings benchmarks. ACOs sponsored by physicians or rural providers, however, can apply to receive payments in advance to help them build the infrastructure necessary for coordinated care.[20]

Electronic health records. A significant investment will be required of all healthcare providers to comply with the ACA's requirement for the adoption of electronic health records (EHRs). The Health Information Technology for Economic and Clinical Health Act, part of the ACA, set the groundwork for healthcare reform. It provided $27 billion in Medicare and Medicaid incentive payments to go to doctors and hospitals that adopt electronic medical records under federally established guidelines. The legislation was passed to ensure that patients' privacy is protected and to transform toward a more efficient and less expensive healthcare model.[21] As of Jan. 1, all public and private healthcare providers and other eligible professionals must have adopted and demonstrated "meaningful use" (MU) of EHRs in order to maintain their existing Medicaid and Medicare reimbursement levels.

The Medicare EHR Incentive Program started in 2011 and will continue through 2016. The program was designed in three stages with increasing requirements and participation. Originally, all EPs needed to begin participating by meeting the stage-one requirements for a continuous 90-day period in their first year of MU and a full year in their second year of MU. After meeting the stage-one requirements, providers will then have to meet stage-two requirements for two full calendar

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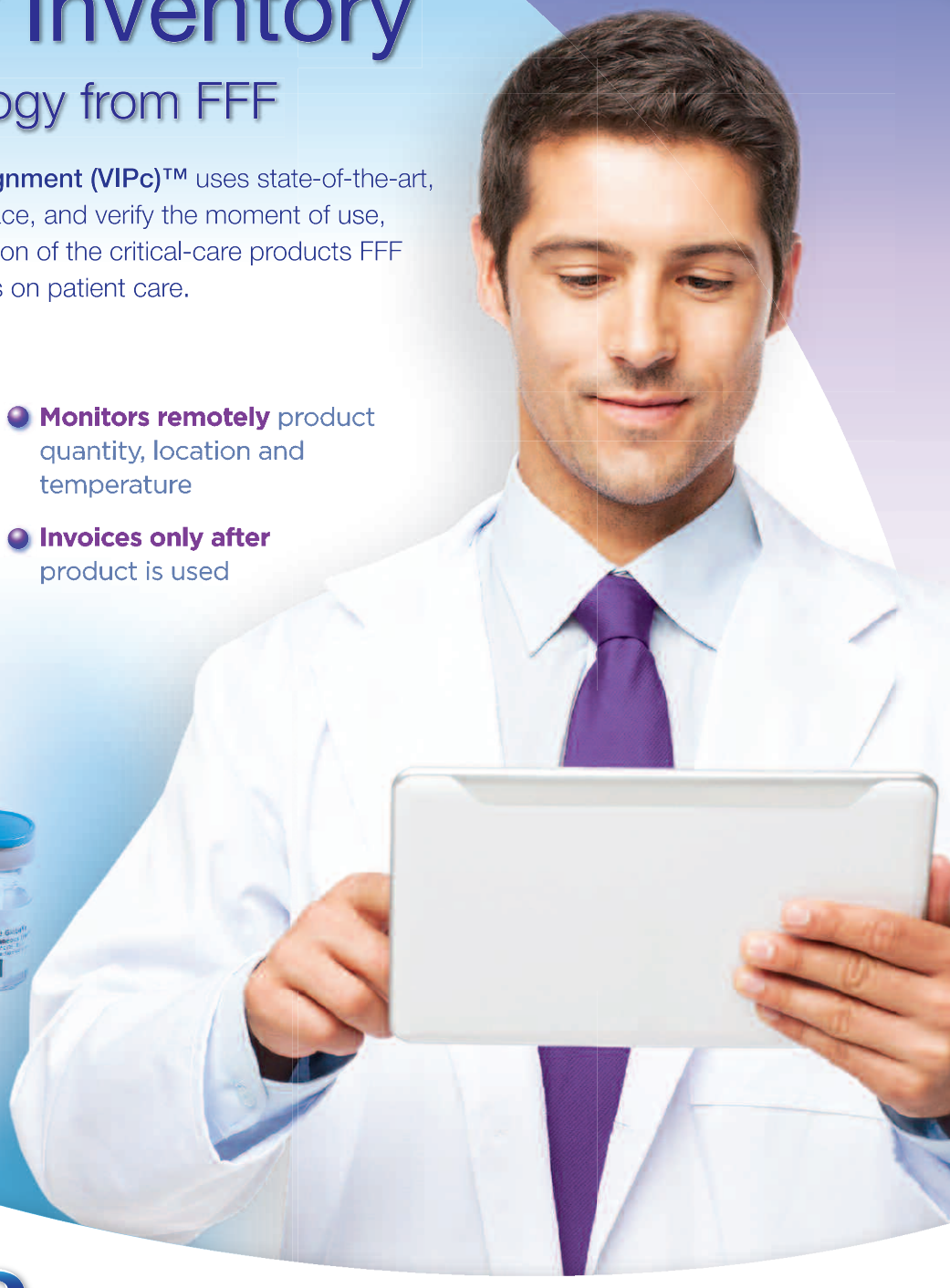

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years. However, for 2014 only, the reporting periods have been revised. Because of delays in the publication of regulations that require EHR vendors to upgrade their systems to meet certified technology criteria, all providers are required to demonstrate MU for only a 90-day EHR reporting period, regardless of what stage they're in. But, the 90-day reporting period is different for those who are a first-time participant in the program or for those who began MU prior to 2014, as well as their EHR vendor's readiness to meet the Office of the National Coordinator's 2014 certification criteria. Those in their first year of reporting in 2014 can report on any 90-day period but need to report by July 3 and no later than Oct. 1. On the other hand, those who began reporting in earlier years must report on either the Jan. 1 through March 31 quarter, April 1 through June 30 quarter, July 1 through Sept. 30 period or Oct. 1 through Dec. 1 period.

First-year program participants are eligible to receive an incentive payment of $24,000. Those who report after July 3 are still eligible to receive the incentive payment, but they also will receive a 2015 program adjustment, which amounts to a 1 percent decrease in Medicare reimbursement for all claims submitted in 2015. However, if they do not report by Oct. 3, they will not receive an incentive payment and will still be penalized the 1 percent in 2015. EPs who do not successfully demonstrate MU will have a negative payment adjustment made to their Medicare reimbursement, which starts at 1 percent in 2015 and increases each year that an EP does not demonstrate MU for a maximum of 5 percent.[22]

A significant investment will be required of all healthcare providers to comply with the ACA's requirement for the adoption of electronic health records.

To obtain the incentive bonus, providers must use a certified EHR product and demonstrate they have met all of CMS' MU requirements.[21] Meaningful use, as defined by HealthIT.gov, consists of using digital medical and health records to improve quality, safety, efficiency and reduce health disparities; engage patients and family; improve care coordination and population and public health; and maintain privacy and security of patient health information.[23] For calendar years 2011 through 2016, EPs who demonstrate MU of certified EHR technology can receive up to $44,000 over five years under the program. These bonuses are equal to 75 percent of the provider's allowable Medicare charges during the reporting year, and are made based on the calendar year. The first calendar year's payments are for only the 90-day reporting period, and subsequent years are for the entire calendar year.[22]

Health Information Exchanges

Some of the incentives offered under the ACA encourage the implementation of other changes, including health information exchanges (HIEs). For example, BPCI provides incentives for hospitals and doctors to coordinate information exchanges to improve quality of care, reduce unnecessary services and decrease preventable errors. HIEs connect physicians and facilities, enabling collaboration on patient treatment through the exchange of EHRs.[24] While HIEs don't replace provider-patient communication, they can greatly improve the completeness of patients' records because past history, current medications and other information is jointly reviewed during visits.[25]

There are currently three forms of HIEs. The first, the directed exchange, is used by providers to securely send patient information such as laboratory orders and results, patient referrals or discharge summaries directly to another healthcare provider. The information is sent over the Internet in an encrypted, secure and reliable way among healthcare professionals who already know each other, and is commonly compared to sending a secure email. The second, the query-based exchange, is used by providers to search and discover accessible clinical sources on a patient. This type of plan is typically used when delivering unplanned care such as by emergency room physicians to adjust treatment plans or avoid adverse medication reactions or duplicate testing. And the third, the consumer-mediated exchange, provides patients with access to their health information similar to how they might manage their finances through online banking.[25]

However, the value of electronically exchanging data relies upon the standardization of data. Once standardized, the data transferred can seamlessly integrate into the recipients' EHRs. HIE organizations (HIOs) provide the capability to electronically move clinical information between disparate healthcare information systems while maintaining the meaning of the information being exchanged. They also provide the infrastructure for secondary use of clinical data for purposes such as public health, clinical, biomedical and consumer health information research, as well as institution and provider quality assessment and improvement. Most HIOs currently are regional health information organizations (RHIOs), which facilitate accessibility and exchange of health-related information on individuals for a specified, contiguous geographic area. They typically include a range of participating healthcare provider entities, as well as other health stakeholders such as

payers, laboratories and public health departments, and they are often managed by a board of directors comprised of representatives from each participating organization.[26]

There also is another HIE infrastructure being rolled out to comply with elements of the ACA that is powered by the open cloud by IBM and others. Using these open systems, healthcare organizations achieve compliance with the sharing provisions of the ACA while also complying with the security requirements of HIPAA and other regulations. It is forecasted that as much as 40 percent of storage in the cloud may be medical records-related in the near future.[27]

Administrative Simplification

How physicians bill and are reimbursed is also addressed by the ACA. Section 1104 of the ACA, titled Administrative Simplification, has four goals: 1) it provides for standardization of electronic billing that may allow for the use of machine-readable cards to record payment and insurance information, similar to a credit card; 2) it determines patient financial responsibility at the point of care; 3) it minimizes paper billing or communications; and 4) it speeds up reimbursement for health services and monitors how quickly insurers are making payments.[28] Eligibility verification and claims status operating rules were required to be adopted by July 1, 2011, and effective by Jan. 1, 2013. Claims remittance/payment and electronic funds transfer operating rules were required to be adopted July 1, 2012, and effective Jan. 1, 2014. Other operating rules were required to be adopted by July 1, 2014, and must be effective by Jan. 1, 2016.[29]

However, even with these systems in place, the onus is still on the patient. If an insurance company won't pay for a service or procedure, the patient still must pay the bill. And, with an influx of patients, healthcare providers may need to rethink how they charge patients and make sure patients understand they are responsible for whatever costs their insurance company will not cover. The ACA provides for "navigators" to help with these issues, but the insurance company can still deny claims.[28]

Medical Networks

With the influx of more patients and new regulations that increase paperwork and the cost of treating patients due to the shift in value-based healthcare models, many physicians in private practice will need to shift to medical networks to pool their resources.[19] Only about 40 percent of family doctors and pediatricians remain independent, according to the American Medical Association, and many feel that the increased costs of treating patients have been accelerated by the ACA.[30]

The trend being seen these days is for groups of three to five doctors to work together and pool their resources to be more efficient. More doctors are able to see more patients, group according to several specialties and work together to improve their administration.[20]

Also under the ACA, doctors with small private practices will be able to join together with other small businesses to purchase health insurance in the marketplaces, which provides them with greater bargaining power when shopping for health insurance for their employees.[10]

Malpractice Reform

Several provisions of the ACA will help to reduce healthcare spending. But, the cost of healthcare will continue to remain high. Indeed, healthcare in the U.S. costs two-and-a-half times more than most developed nations in the world, including European countries like France, Sweden and the United Kingdom. On a more global scale, U.S. healthcare costs now represent 17.6 percent of GDP.[31] A contributing factor to these costs is malpractice litigation. In 2012, there were a total of 12,142 paid medical malpractice claims in the United States for a total of $3.6 billion in payouts, which averages to nearly $297,000 per paid claim.[32]

Many physicians in private practice will need to shift to medical networks to pool their resources.

Malpractice reform, often known as medical tort reform, has been tackled in a number of states, including California and Texas. But attempts at passing similar regulations on the federal level have failed since the 1970s. The ACA doesn't include tort reform, per se, that would change the rules when patients sue their doctors for medical errors or malpractice.[33] However, the ACA does authorize $50 million in funding for state projects that develop, implement and evaluate alternatives to current tort litigation such as certificate of merit programs, which require a finding that a suit has merit before it can proceed to trial, and health courts, which would have cases heard by a panel of medical experts rather than a jury. Each state applying for funds can develop an alternative system, but that system must allow for the resolution of disputes and promote a reduction of healthcare errors by encouraging the collection and analysis of patient safety data related to disputes by organizations that engage in efforts to improve patient safety and the quality of healthcare.[34]

Applications for grants were due Jan. 20, 2010. On July 11, 2010, HHS awarded $23 million in grant funding, including

seven three-year demonstration projects and 13 one-year planning grants. The impact on physicians will be different in each state, depending on how the demonstration project is constructed. The American College of Physicians believes that each project selected for funding will be assessed according to its capacity for lowering liability insurance premiums and reducing the frequency and severity of malpractice claims without denying injured patients appropriate redress for physician negligence.[34]

Good and Bad

While any new system will have both proponents and opponents, the implementation of the ACA has sparked debate about controversial issues. Its concepts are noble: providing health insurance to more individuals, making healthcare more affordable, removing some of the barriers and limits and providing better quality care. But, as the ACA continues mandating specific provisions through 2014, the healthcare profession will struggle to adapt to meet the demands of more patients with a shortage of physicians, increased paperwork to account for improved care quality, and potential cuts in reimbursement for Medicare and Medicaid if benchmarks aren't met. ❖

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Myths and Facts: Skin Cancer

By Ronale Tucker Rhodes, MS

Because one in five Americans will develop skin cancer in the course of a lifetime, it's important that individuals understand the risks of sun exposure and how to protect against the sun's harmful rays.

Every year, Americans have 4,380 hours of suntanning opportunity, which is the number of daylight hours.[1] In addition to the sun's rays, there are almost 20,000 tanning salons in the U.S. in which more than one million people tan each year.[2] The result is the diagnosis of more than 3.5 million skin cancers in over two million people annually. This translates to more than one in five Americans who develop skin cancer in the course of their lifetime. In fact, over the past three decades, more people have had skin cancer than all other cancers combined.[3] Yet, despite these statistics, people still flock to warm climates and tanning salons in pursuit of a suntan. And, many people continue to ignore the warnings to minimize the damage the sun can cause, mainly because of a misunderstanding about how harmful the effects of the sun's rays are and how to protect against them.

Separating Myth from Fact

Myth: Skin cancer is a less serious form of cancer.

Fact: Skin cancer is the most common of all cancers. It is a very serious form of cancer causing one death every 57 minutes. Approximately 9,480 people died of melanoma, the most deadly form of skin cancer, in 2013. An estimated 3,900 to 8,800 people died from squamous cell carcinoma, another type of skin cancer, in 2012.[3]

Myth: There's only one type of skin cancer.

Fact: There are many types of skin cancer. The three most common are melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Melanoma begins in melanocytes (pigment cells).[4] It is estimated that melanoma will account for more than 76,000 cases of skin cancer in 2014.[5] It accounts for less than 5 percent of skin cancer cases but the vast majority of skin cancer deaths. One in 50 men and women will be diagnosed with melanoma of the skin during their lifetime. The majority of people diagnosed with melanoma are white men over age 50. And, women age 39 and under have a higher probability of developing melanoma than any other cancer except breast cancer. It is the most common form of cancer for young adults ages 25 to 29 years old and the second most common form of cancer for young people ages 15 to 29. Fortunately, survival with melanoma increased from 49 percent (1950 through 1954) to 92 percent (1996 through 2003).[3]

BCC begins in the basal cell layer of the skin.[4] An estimated 2.8 million people in the U.S. are diagnosed annually with BCC. The number of women under age 40 diagnosed with BCC has more than doubled in the last 30 years. And, while it is rarely fatal, it can be highly disfiguring if allowed to grow.[3]

SCC begins in the squamous cells.[4] It is the second most common form of skin cancer, with an estimated 700,000 cases of SCC diagnosed each year in the U.S. And, the incidence of squamous cell carcinoma has been rising, with increases up to 200 percent over the past three decades in the U.S.[3]

Between 40 percent and 50 percent of Americans who live to age 65 will have either BCC or SCC at least once.[3]

Myth: Only fair-skinned people are at risk of skin cancer.

Fact: People of all skin types can develop all types of skin cancer. BCC is the most common type of skin cancer for people with fair skin, whereas in people with dark skin, SCC is the most common type of skin cancer. While melanoma is rare in people with dark skin, when it does develop, it is usually found under the fingernails or toenails, on the palms of the hands or on the soles of the feet.[3]

Myth: Skin cancer develops only on parts of the body that have gotten too much sun.

Fact: Skin cancer can develop on all parts of the body, even those not exposed to the sun. BCC usually occurs in places that have been in the sun, most commonly the face. In people with fair skin, SCC usually occurs on parts of the skin that have been in the sun such as the head, face, ears and neck. However, in people with dark skin, SCC is usually found in places that are not in the sun such as the legs or feet.[4] Melanoma can occur on any skin surface. In men, it's often found on the skin of the head, on the neck or between the shoulders and hips. In women, it's often found on the skin of the lower legs or between the shoulders and hips. And, melanoma is more likely than other skin cancers to spread throughout the body. SCC can sometimes spread to other parts of the body, but BCC rarely does. When skin cancer cells do spread or metastasize, they break away from the original growth and enter blood vessels or lymph vessels, as well as other tissues, and attach to form new tumors.[3]

Over the past three decades, more people have had skin cancer than all other cancers combined.

Myth: Sun exposure is needed for the body to get vitamin D.

Fact: The safest way to get vitamin D is through diet and supplements. The body does produce some vitamin D following exposure to the sun's ultraviolet B (UVB) radiation. However, after a limited amount of sun exposure (approximately five minutes daily for a Caucasian in New York at 12 p.m. in summer), vitamin D production reaches its maximum.[6] In fact, most people get enough UV exposure to maintain vitamin D levels through their usual outdoor activities.[7]

Myth: Only people who don't use sunscreen and spend too much time in the sun get skin cancer.

Fact: Limiting sun exposure can reduce the risk of getting skin cancer, but the risk is not reduced to zero. Genes also influence the risk of developing skin cancer even for some people who wear sunscreen conscientiously but have a family history of skin cancer.[8] In fact, a new study provides some understanding of why some people are at greater risk of skin cancer because of their family history. A team led by the Wellcome Trust Sanger Institute in Hinxton, United Kingdom, found that people with mutations in a certain gene were at extremely high risk of melanoma. The mutations switch off a gene known as POT1, which protects against damage to packets of DNA known as chromosomes. According to Dr. David Adams, co-author of the study's report that appeared in *Nature Genetics*, "The mutations in this gene result in damage to the end of the chromosomes, and chromosomal damage in general is linked to cancer formation; that's the pathway for it."[9]

There also is a high risk of skin cancer for people who improperly use sunscreen. A sunscreen wth a sun protection factor (SPF) of 30 or higher should be applied a half hour before sun exposure so it has time to penetrate the skin. And, sunscreen should be reapplied regularly.[8] A quick way to calculate how long a sunscreen will protect the skin is to multiply SPF by 10 to determine how many minutes after an application it needs to be reapplied.[10] It should be reapplied sooner if swimming or sweating a lot.[11]

Using a sunscreen that only protects against sunburn can also increase risk of skin cancer. The U.S. Food and Drug Administration (FDA) recently revised its rules for labeling on sunscreen bottles. For a sunscreen label to claim it can prevent sunburn, the product must pass the SPF test, which shows how long a sunscreen protects against UVB rays that cause sunburn. SPF levels range from 2 to more than 70. The higher the number, the longer the protection lasts. For a product to claim it can prevent skin cancer, it must pass the broad-spectrum test to show it can protect skin from both UVB rays and UVA radiation, which contribute to skin cancer and early skin aging.[11]

Even people who avoid outdoor activities are at risk for skin cancer because they, too, are exposed to UV radiation through routine activities like walking a dog or trying to find a parked car.[8] And, while glass does block most UVB rays, UVA radiation can get through unless a special window film that blocks most UVA radiation is installed.[6]

Research shows that some supplements may help to protect against skin cancer.

Myth: Using sunscreen and avoiding the sun are the only ways to protect against skin cancer.

Fact: While sunscreen and avoiding the sun are effective ways of protecting against skin cancer, research shows that nutrition and supplements can also play a role. According to Dr. Ronald Moy, a cosmetic dermatologist and a fellow of the American Academy of Cosmetic Surgery, antioxidants are the secret weapon against skin cancer. "Blackberries, blueberries, strawberries, artichokes, beans, prunes, plums and green tea are all high in antioxidants, which can help protect the skin cells from DNA damage caused by the sun," Moy says.[12]

A recent study published in the journal *Cancer Research* claims that coffee drinkers may be at a reduced risk of developing BCC. The researchers evaluated data on 113,000 men and women, all of whom drank three or more cups of coffee a day. They discovered that rates of BCC were 20 percent less among this control group compared with those who drank no coffee at all, and the active substance in question appears to be caffeine. "Caffeine may help the body kill off damaged skin cells," says Dr. Josh Zeichner, an assistant professor of dermatology at Mount Sinai Medical Center in New York. "If you get rid of these cells that are damaged, then they don't have the opportunity to grow and form cancers." The findings correlate with a 2011 study at Rutgers University that identified a link between caffeine and skin cancer prevention. That study found that caffeine appears to be an effective topical treatment for protecting skin against damage caused by excessive exposure to the sun's UV rays.[13]

Other research shows that some supplements may help to protect against skin cancer. Researchers at the University of Manchester in the United Kingdom demonstrated how omega-3 fish oils could help protect against skin cancer. It was the first clinical trial to examine the impact of fish oils on the skin immunity of human volunteers. In the study, 79 volunteers took a daily 4-gram dose of omega-3, equivalent to about one-and-a-half portions of oily fish, and were then exposed to either eight, 15 or 30 minutes of summer midday sun using a special light machine. That group was then compared with a second group taking a placebo. The researchers found that immunosuppression was 50 percent lower in people who took the omega-3 supplement and were exposed to eight and 15 minutes of sun compared with people who did not take the supplement.[14]

In another study conducted at the University of Texas Health Science Center in San Antonio, scientists observed that resveratrol (an antioxidant found in grape skins), grape seed extract, D-glucarate (a cellular detoxifier), calcium and ellagic acid work in harmony to protect against skin cancer when administered both orally and topically in mice with skin cancer. Even in low doses, the plant agents exerted maximum therapeutic effects when combined with each other because each compound plays a specific and unique role in the process. When administered individually, however, these compounds were not particularly effective.[15]

Myth: Sun protection is needed only on hot, sunny days.

Fact: Even on cloudy days, the sun's rays can damage the skin. In fact, 80 percent of the sun's UV rays can penetrate through clouds and fog.[6]

Myth: Dark skin protects against skin cancer.

Fact: Naturally darker skin doesn't prevent skin cancer. While skin cancer is less common among African-American and Hispanic populations than among Caucasian populations, African-Americans and Hispanics who develop melanoma are more likely to die from the disease than are Caucasians.[8] The overall melanoma survival rate for African-Americans is only 77 percent versus 91 percent for Caucasians.[3] It is believed that this difference in patient outcomes is that dark-skinned people are less likely to seek treatment for skin lesions before the disease has reached an advanced stage. For example, acral lentiginous melanoma, the most common melanoma in African-

Americans and Asians, often goes unrecognized because it affects parts of the skin where cancer is not expected such as the palms, soles of the feet and nail beds.[8] The most common form of skin cancer among African-Americans and Asian Indians is SCC. SCC in African-Americans also tends to be more aggressive and is associated with a 20 percent to 40 percent risk of metastasis.[3]

Myth: Tans shield the skin from damage.

Fact: A base tan may delay sunburn, but it will not prevent damage from UV radiation. Tanning is the body's attempt to defend itself against previous exposure to UV radiation by increasing the amount of pigment in the skin, which means the DNA in suntanned skin has already been damaged by UV radiation. And, DNA damage can lead to mutations that cause cancer. In addition, a substantial amount of UV radiation will still penetrate any tan.[8]

Myth: Tanning beds are safer than tanning in the sun.

Fact: The U.S. Department of Health and Human Services and the World Health Organization's International Agency of Research on Cancer panel has declared UV radiation from the sun and artificial sources such as tanning beds and sun lamps as known carcinogens. Indoor tanning equipment, which includes all artificial light sources, including beds, lamps, bulbs, booths, etc., emits both UVA and UVB radiation, the amount of which is similar to the sun and, in some cases, might be stronger.[16] One minute in the average indoor tanning machine in England is twice as carcinogenic as one minute in the midday Mediterranean sun. And, frequent tanners using new high-pressure sun lamps may receive as much as 12 times the annual UVA dose compared with the dose they receive from sun exposure.[3]

Many studies have shown that indoor tanning causes skin cancer. Some studies have found a 59 percent increase in the risk of melanoma in those who have been exposed to UV radiation from indoor tanning, and the risk increases with each use. Other studies have shown that exposure to radiation from indoor tanning devices is associated with a risk of SCC and BCC. In fact, a recent study estimates that this exposure causes more than 450,000 cases of SCC and BCC, and 10,000 melanoma cases each year in the U.S., Europe and Australia.[16]

On May 6, 2013, FDA issued a proposed order for stricter regulations on indoor tanning devices. And, several states have laws that prohibit minors under the age of 17 or 18 from using indoor tanning devices.[16]

Dispelling the Myths Now

The American Cancer Institute estimates that 9,710 people will die from melanoma in 2014, a death rate that has remained consistent since 2001. During this same time frame, the incidence of melanoma has continued to climb,[17] which means treatment for this skin cancer has greatly improved. But the cost of treating skin cancer is high. In 2010, the estimated cost of treating melanoma was $2.36 billion. The latest figure available for the cost of treating nonmelanoma skin cancers was $1.4 billion in 2004.[3] Yet, despite its risks and the escalating costs of treatment, people still flock to warm climates and to tanning booths in pursuit of a tan. With no end in sight to the allure of a tan and time in the sun, it's important for individuals to understand the facts about the harmful effects of the sun's rays and to take the necessary precautions to protect themselves as best they can ❖

Many studies have shown that indoor tanning causes skin cancer.

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In the Pipeline: Novel Plasma Proteins for Major Cardiovascular Disorders

BY KEITH BERMAN, MPH, MBA

OVER THE 70 years since biochemist Edwin Cohn and his Harvard Medical School laboratory first purified human albumin for use in severe burns and hemorrhagic trauma, nearly 30 therapeutic proteins from human plasma have been purified, proven safe and effective and approved for use. Most of these products (Table 1) are indicated as replacement therapies for rare congenital plasma protein deficiencies or to treat other narrowly defined conditions. But, recently, several leading plasma fractionators have embraced an important new product development focus: identifying and developing new plasma-based protein therapeutics to treat common serious clinical disorders.

Three of the most ambitious of these initiatives hope to exploit the functionality of two proteins purified from human plasma — plasmin and the apolipoprotein A-1 component of high-density lipoprotein (HDL) — both purified from human plasma — to improve health outcomes in patients stricken with acute ischemic stroke, acute peripheral arterial occlusion and acute coronary syndrome.

Table 1. Approved Types of Biologics Purified from Human Plasma

Albumin Products
Albumin 5%
Albumin 25%
Plasma Protein Fraction 5%

Coagulation Products
Antihemophilic Factor
Antihemophilic Factor/von Willebrand Factor Complex
Anti-Inhibitor Coagulant Complex
Coagulation Factor IX
Factor IX Complex
Fibrin Sealant
Absorbable Fibrin Sealant Patch
Fibrinogen Concentrate
Factor XIII Concentrate
Protein C Concentrate
Prothrombin Complex Concentrate
Thrombin, Topical

Immune Globulin Products
Immune Globulin (Intramuscular)
Immune Globulin Intravenous
Immune Globulin Subcutaneous
Botulism Immune Globulin Intravenous
Cytomegalovirus Immune Globulin Intravenous
Hepatitis B Immune Globulin Intravenous
Hepatitis B Immune Globulin Intramuscular
Rabies Immune Globulin
Rho(D) Immune Globulin Intravenous
Tetanus Immune Globulin
Vaccinia Immune Globulin Intravenous
Varicella Zoster Immune Globulin

Other Products
Alpha-1-Proteinase Inhibitor
C1 Esterase Inhibitor

Human Plasmin: The More Direct Path to Thrombolysis

Composed of cross-linked fibrin and aggregated platelets, a blood clot or thrombus may form following an injury to a blood vessel or as a result of improper activation of hemostasis. When a thrombus blocks more than about 90 percent of the cross-sectional area of an artery, the tissue perfused by that artery will develop anoxia, resulting in infarction. A thrombus that detaches from the artery can cause arterial embolism and potentially lead to infarction in almost any organ in the body.

But it has also long been known that fibrin-containing blood clots can spontaneously degrade on their own. In the late 19th century, the French physiologist Jules Dastre hypothesized that this phenomenon is mediated by a protein enzyme, and coined the term "fibrinolysis" for this process. Finally, in the mid-1940s, the active enzyme that breaks down fibrin (plasmin) and its inert circulating zymogen (plasminogen) were both identified and named by Christensen and MacLeod at New York University.[1]

The final steps leading to fibrinolysis are straightforward: Plasminogen binds to a blood clot or cell surface and is converted to plasmin through interactions with a number of enzymes. The most important of these is tissue plasminogen activator (tPA). A recombinant version of tPA (Activase, Genentech) is indicated for fibrinolysis — or thrombolysis — in three acute conditions: myocardial infarction, ischemic stroke and pulmonary embolism.

While tPA or urokinase, another plasminogen activator (PA), often are used to treat acute peripheral arterial occlusion (aPAO), they have disadvantages that limit their clinical utility. Because tPA acts one step upstream by converting plasminogen to the active fibrinolytic plasmin, even partial dissolution of the thrombus occluding the peripheral artery can take hours; frequently, tPA doesn't work at all. The clinical utility of tPA is further limited by the need for physicians to use low doses to minimize the risk of intracranial hemorrhage and other systemic bleeding risks — again slowing and reducing the likelihood of effective clot lysis.

Acute peripheral arterial occlusion (aPAO). The direct action of plasmin to degrade fibrin in arterial thrombi makes it logically appealing for the treatment of aPAO. Preclinical models have documented a striking safety advantage of plasmin over plasminogen activators. In part, this may be attributable to reserves of circulating alpha-2 antiplasmin, which rapidly neutralizes plasmin, allowing higher doses and mitigating the risk of bleeding complications elsewhere in the body.

A recently completed Phase I dose-escalation study sponsored by Grifols evaluated a human plasmin concentrate in 83 patients, in seven dose cohorts ranging from 25 mg to 175 mg, with acute lower extremity arterial or bypass graft occlusion.[2] A specially designed balloon catheter was used to more precisely deliver the plasmin to the clot area and thereby minimize the risk of hyperfibrinolysis and bleeding elsewhere in the circulation. Fifty percent or greater thrombolysis occurred in nearly 80 percent of subjects receiving 125 mg to 175 mg of plasmin, as compared with 50 percent who received 25 mg to 100 mg. Major bleeding was infrequent (under 5 percent of subjects) with no trend toward more bleeding at higher dosages of plasmin.

Based on findings from that Phase I trial, investigators are now evaluating a 150 mg plasmin dose in an ambitious Phase II study (Table 2) examining the effect of initial proximal pulse infusion and differing infusion periods and infusion rates on aPAO thrombolysis. In addition to six active treatment arms, patients in this 160-subject trial are also being randomized to receive a plasminogen activator (tPA or urokinase) or saline placebo. Outcomes assessed for up to 30 days post-procedure include:

- Avoidance of open surgical procedures
- Avoidance of amputation
- Avoidance of additional catheter-directed thrombolysis with a PA or mechanical device atherectomy
- Physiological reperfusion (improvement in ankle brachial index)
- Arterial patency (duplex ultrasound imaging)

Roughly 100,000 persons are afflicted annually with aPAO,[3] with most cases involving the legs. Despite its slow action and inherent bleeding risk, most patients receive low-dose tPA in an attempt to dissolve the clot, with moderate success. The commercial prospects for plasmin will hinge on whether a pivotal trial can show improved outcomes relative to tPA with a similar or lesser incidence of bleeding complications.

Acute ischemic stroke. Accounting for more than 85 percent of the nearly 800,000 strokes that occur each year in the U.S., ischemic stroke kills more than 130,000 victims and exacts a very large toll in permanent disability. The estimated national cost in healthcare, medications and lost productivity is a staggering $39 billion.[4]

Brain tissue is particularly sensitive to anoxia: In a typical middle cerebral artery ischemic stroke, an estimated two million nerve cells are lost for each minute that reperfusion is not achieved;[5] thus, the well-known principle "time lost is brain lost." The objective, then, is to at least partly dissolve the arterial clot as rapidly as possible and restore blood flow.

Currently, only tPA is indicated and used for thrombolysis in ischemic stroke. Again, by converting plasminogen into active fibrin-degrading plasmin, tPA can make a critical difference for some patients if administered within three hours — or for selected patients

within 4.5 hours[6] — after initial stroke symptoms. A pooled analysis of eight trials documented that initiation of tPA thrombolysis within 90 minutes increased the odds of an excellent outcome by 2.6-fold, in the 91- to 180-minute window by 1.6-fold, and in the 181- to 270-minute window by 1.3-fold.[7] After that, tPA offers no meaningful benefit, even as the risk of iatrogenic intracerebral or other hemorrhage remains. Only an estimated 100,000 of the nearly 700,000 ischemic stroke victims this year will reach a stroke treatment facility and have imaging studies completed to exclude intracranial hemorrhage within three hours. There is currently no approved drug therapy for treatment of ischemic stroke after three hours.

Assuming it is shown to have acceptably low risk of bleeding complications, there are two ways that plasmin could cut the toll in stroke-related death and long-term disability:

An obvious unmet need exists for a safe and effective fibrinolytic for ischemic stroke patients.

- Effectiveness beyond the three-hour window during which tPA can be utilized following onset of stroke symptoms
- Superior effectiveness in relation to tPA during the three-hour post-onset window period

Grifols and its collaborators in Europe, Australia and the U.S. are currently conducting a Phase I/IIa safety and dose-ranging study in about 60 subjects with acute ischemic stroke localized in the middle cerebral artery. The investigators are evaluating plasmin doses between 20 mg and 60 mg, delivered through a catheter into the thrombus within nine hours of stroke onset.

An estimated 315,000 ischemic stroke patients are diagnosed by qualified stroke specialists between three and nine hours of stroke onset — three times the number who present within the initial three-hour time window.[3] An obvious unmet need exists for a safe and effective fibrinolytic for these patients in particular, but whether plasmin is up to the task will, of course, hinge on results of a large, well-designed, controlled clinical trial.

Reconstituted HDL Promising for Acute Coronary Syndrome

High-density lipoprotein (HDL) is actually a combination particle that contains hydrophilic apolipoproteins — mainly apolipoprotein A-1 (apoA-I) — enwrapping hydrophobic cholesterol. A key function of HDL is to facilitate transport of these lipids out of cells in arterial walls to the liver for clearance. Not surprisingly, higher circulating HDL levels are associated with lower

Table 2. Clinical Studies Currently Evaluating Human Plasmin as a Thrombolytic Therapy

Condition	Target Enrollment	Study Design	Product Administration	Objectives
Acute ischemic stroke (due to clot in middle cerebral artery)	61	Phase I/IIa open-label, sequential dose escalation safety study	Plasmin administered locally through a catheter to the clot within 9 hours of stroke onset. 20, 40 and 80 mg doses tested in 3 different groups	Safety of escalating plasmin doses. Proportion of subjects with treatment success, defined as partial or complete arterial recanalization
Acute peripheral arterial occlusion	160	Phase II open-label, 8-arm study (with blinded plasminogen activator and placebo groups)	150 mg intra-thrombus plasmin administered at varying infusion rates and infusion periods. Plasminogen activator comparators may include tPA or urokinase	Proportion of subject with >50% thrombolysis. Incidence of bleeding events, deaths and adverse events

Table 3. Clinical Study Currently Evaluating Plasma-Based Apolipoprotein A-1 in Acute Myocardial Infarction

Condition	Target Enrollment	Study Design	Product Administration	Objectives
Type I (spontaneous) acute myocardial infarction with evidence of myocardial necrosis	1,200	Phase IIb randomized, placebo-controlled safety and efficacy study	Low dose and high dose apolipoprotein A-1 (CSL112) administered intravenously once weekly for four consecutive weeks	Safety as defined by drug-induced liver injury and change in renal status. Time to first occurrence of major adverse cardiovascular event (MACE)

risk of atherosclerosis, in particular coronary atherosclerosis that can eventually lead to thrombosis and acute myocardial infarction (AMI).

CSL Behring and its collaborators have shown that four once-weekly infusions of an apoA-I purified from donor human plasma dramatically elevate measures indicative of reverse cholesterol transport, while rapidly raising blood levels of apoA-I. This "reconstituted high-density lipoprotein" (rHDL) appears also to powerfully impede inflammation, primarily by inhibiting pro-inflammatory cytokine production.[8]

Encouraged by these findings, in May, the company initiated a Phase IIb study to evaluate rHDL in patients with AMI and evidence of myocardial necrosis (Table 3). A total of 1,200 subjects will be randomized to receive four infusions of a low dose or high dose of rHDL or placebo. In addition to safety, the time to first occurrence of a major adverse cardiovascular event (MACE) will be captured for the three study arms.

The target population for a pivotal clinical trial may be a subset of patients with acute coronary syndrome (ACS) associated with AMI or unstable angina. Ten percent to 15 percent of patients experience a MACE over the 12 months following an episode of ACS. If short-term administration of rHDL can significantly reduce that rate and it is well tolerated, particularly with respect to liver function, it could become part of the standard treatment armamentarium for many of the estimated 600,000 patients hospitalized with ACS each year.

The Plasma Industry Steps Up Its Game

Evaluating a human plasma protein or any potential new product for complex conditions like ischemic stroke, aPAO and ACS presents special challenges. Outcomes in these major vascular disorders may be influenced by a number of patient demographic variables and underlying comorbidities. There are established treatment regimens against which the candidate plasma protein must be directly compared. To demonstrate safety and efficacy, clinical testing requirements are necessarily more extensive, and subject enrollments significantly larger than, say, clotting factor replacement therapy for a specific hereditary coagulation disorder.

In pursuing these and other bold new product development initiatives, leading manufacturers in the plasma products industry have signaled their willingness to address these challenges, accept the risks and make the necessary investments. Clearly, the potential rewards offer ample justification: the prospect that treatment with purified plasma proteins now discarded as waste can cut the risk of serious morbidity in patients with major debilitating and life-threatening disorders. ❖

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Acquired Hemophilia: A Physician's Perspective

BY TRUDIE MITSCHANG

Dr. Craig Kessler has been a specialist in acquired hemophilia since the late 1980s.

DR. CRAIG KESSLER is professor of medicine and pathology, section chief of hematology and director of the Coagulation Laboratory at Georgetown University Medical Center. A graduate of Tulane School of Medicine, Dr. Kessler received his specialty training in hematology and oncology at The Johns Hopkins Hospital. An international expert in the area of disorders of coagulation, Dr. Kessler has a particular interest in hemophilia. He also has expertise in the treatment of hematologic malignancies.

BSTQ: What are the underlying causes of acquired hemophilia (AH)?

Dr. Kessler: AH is an autoimmune disorder. It occurs when the immune system produces antibodies that mistakenly attack healthy tissue, specifically specialized proteins known as clotting factors, most often clotting factor VIII. The immune system normally responds to a foreign substance by producing specialized proteins called antibodies. Antibodies work by destroying foreign substances directly or by coating them with a substance that marks them for destruction by white blood cells. When antibodies target healthy tissue, they may be referred to as autoantibodies. Researchers believe that a triggering event (such as an infection or underlying disorder) may induce the immune system to produce autoantibodies. Autoantibodies in AH are also termed inhibitors because they inhibit the function of the affected clotting factor.

BSTQ: AH is difficult to diagnose. What are some obvious symptoms?

Dr. Kessler: The clinical signs and symptoms of AH differ from those of hereditary hemophilia. Affected individuals may display bruising anywhere on the body due to bleeding into the skin, and bruising can occur spontaneously. Sometimes you see large, purple discoloration that has spread over a significant area of the body such as an entire limb or the chest or abdomen. Discoloration of the skin due to bleeding underneath the surface is definitely a telltale sign; I recently walked into an examination room and made a diagnosis from the doorway. Despite these visible symptoms, the reason most physicians don't recognize AH is primarily due to its rarity. The second reason is you need a good laboratory that will run the right tests.

BSTQ: What inspired you to become on expert on this rare disease?

Dr. Kessler: At the time, back in the late '80s there wasn't anybody else focused on it. There was one other person in the U.S. publishing widely on AH, and from a research perspective, I thought it was a very interesting disease. It combines all of the elements of coagulation with immunology and all diseases associated with development of inhibitors. It is a specialty that requires an interest in internal medicine and allows you to play detective and do a lot of sleuthing. Once diagnosed, AH has a large number of treatment options, none of which work for everybody. From a clinician's perspective, it is a challenging, low-incidence disease with patients who are desperate for answers. I felt I was up to the challenge.

From a clinician's perspective, AH is a challenging, low-incidence disease with patients who are desperate for answers.

BSTQ: How has treatment for AH evolved?

Dr. Kessler: Bypassing agents are the

recommended first-line therapy due to their rapid action and high level of effectiveness. When I first began studying this disease, the treatment modality centered on a pig plasma purified factor VIII. The pig plasma was developed for AH specifically because the antibodies that formed in AH did not cross-react with the factor VIII from the pig. This was extremely interesting to me, so I decided to do some clinical trials in that area and later became involved with some people who were trying to develop a genetically engineered version of the porcine factor VIII as a treatment form. They stopped manufacturing the original porcine factor VIII material about nine years ago, when it became apparent that the pigs being used to manufacture the product were infected by parvovirus, and there was a theoretical possibility that the virus could be transmitted to humans, though it was never proven. Since then, the development of recombinant factor VIIa (NovoSeven) has been the most significant contribution to the treatment of AH in my lifetime.

BSTQ: Why was the development of recombinant factor VIIa so significant?

Dr. Kessler: Novo Nordisk's NovoSeven was approved by the U.S. Food and Drug Administration in 2006. It's a bypassing agent that has a proven efficacy in life-threatening bleeding episodes in AH patients. Because it is artificially created in a lab, it does not contain human blood or plasma and, consequently, there is no risk of blood-borne viruses or other such pathogens. NovoSeven has been well-tolerated and associated with few side effects. It is administered via infusion any time there is a bleed, but there are currently some clinical trials checking to see if this product can be administered in a prophylactic manner to actually prevent bleeding episodes.

BSTQ: What should clinicians be aware of when AH is diagnosed?

Dr. Kessler: They should recognize the role of the hemophilia treatment center (HTC) as a center of excellence. The community physician will probably not be able to handle this type of patient on his or her own — not from the laboratory, blood bank or diagnostic perspectives. The HTC is a resource in the community staffed with hematologists who have seen these types of patients before and can provide guidance to make the treatment of the disease more cost-effective and reduce morbidity. Every state in the country has one, and there's a whole network of these HTCs usually based in tertiary care or university hospitals. There is a list of locations on the National Hemophilia Foundation's website at www.hemophilia.org. ❖

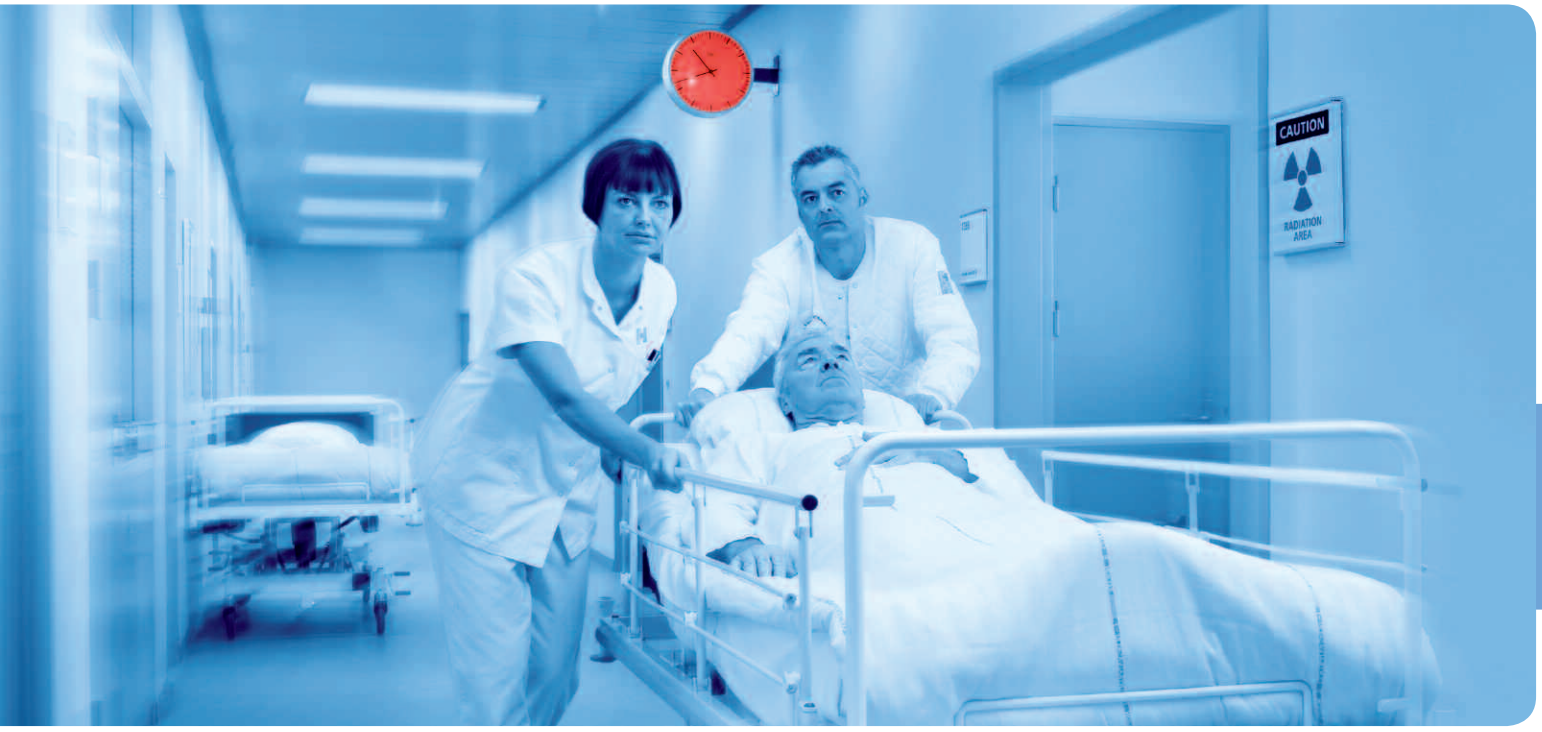
TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

Understanding AH

Acquired Hemophilia (AH) is a rare blood disorder marked by sudden bleeding in patients without a previous personal or family history of hemophilia. In patients with AH, the body starts producing antibodies that fight its own blood-clotting proteins. Incidences of AH are rare, occurring in one case per million persons annually, but it is believed that current statistics underestimate the true figure given that AH is so difficult to diagnose.

Treating patients diagnosed with AH has a two-fold objective, the first being to control the affected bleeding areas, and the second to remove the inhibitor causing the disorder. Because there is a high risk of bleeding complications during treatment, patients diagnosed with AH are encouraged to seek care from specialized hemostasis units with experience treating AH. Statistically, AH patients tend to be elderly with other underlying health complications such as heart disease, hypertension or diabetes. Of those patients, 20 percent tend to suffer a relapse of AH between one week to 14 months following immunosuppressive therapy, but of those who relapse, 70 percent achieve another remission following a second round of therapy.

When treating a life-threatening bleed from acquired hemophilia, every second counts.



Indications and Usage

NovoSeven® RT (Coagulation Factor VIIa [Recombinant]) is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to FVIII or FIX and in patients with acquired hemophilia; prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to FVIII or FIX and in patients with acquired hemophilia; treatment of bleeding episodes in patients with congenital FVII deficiency and prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency.

Important Safety Information

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® RT have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

Thrombotic events following the administration of NovoSeven® RT occurred in 0.3% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.2% in clinical trials within the approved indications. Fatal and non-fatal thrombotic events have been identified through postmarketing surveillance following NovoSeven® RT use for each of the approved indications.

novo nordisk®

NovoSeven® RT is the only bypassing agent approved for acquired hemophilia[1]

Count on NovoSeven® RT

For acquired hemophilia, NovoSeven® RT was 95% effective or partially effective as first-line therapy[2]

Data were extracted from a review of experiences with rFVIIa for the treatment of acquired hemophilia in compassionate-use programs, the Hemophilia and Thrombosis Research Society (HTRS) registry, and independent published reports. Efficacy was defined as "effective" and "partially effective" treatment outcomes. "Ineffective" treatment was determined by the inability to stop the bleeding episode or by the physician describing treatment as not effective.[2]

For Unique Billing Support Services

- Downloadable guide to coding and provider billing for NovoSeven® RT available at novosevenrt.com
- Healthcare Common Procedural Coding System (HCPCS) for NovoSeven® RT (1 mcg equivalent): **J7189**[3]

Talk to your authorized distributor to learn more about NovoSeven® RT or visit NovoSevenRT.com.

FFF Enterprises 800.843.7477 x1903

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Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with activated or nonactivated prothrombin complex concentrates (aPCCs/PCCs) have an increased risk of developing thrombotic events in association with NovoSeven® RT treatment. Caution should be exercised when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, post-operative immobilization, elderly patients, and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications.

Development of antibodies against FVII has been reported in FVII-deficient patients after treatment with NovoSeven® RT. FVII-deficient patients should be monitored for prothrombin time (PT) and FVII coagulant activity before and after administration of NovoSeven® RT.

Use with caution in patients with known hypersensitivity to NovoSeven® RT, its components, or mouse, hamster, or bovine proteins.

Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis.

The most frequently reported adverse reactions in patients treated with NovoSeven® RT are rash, pruritus, urticaria, pyrexia, therapeutic response decreased, and venous thromboembolic events occurring in >.1% to <1% of patients.

Please see brief summary of Full Prescribing Information on following pages.

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.

NovoSeven® RT is a prescription medicine. Novo Nordisk provides patient assistance for those who qualify.
Please call 1-866-310-7549 to learn more about Novo Nordisk assistance programs.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Rx only

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

WARNING: SERIOUS THROMBOTIC ADVERSE EVENTS ASSOCIATED WITH THE USE OF NovoSeven® RT OUTSIDE LABELED INDICATIONS

Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven® have been reported during postmarketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven® RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven® RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. *[See Warnings and Precautions]*

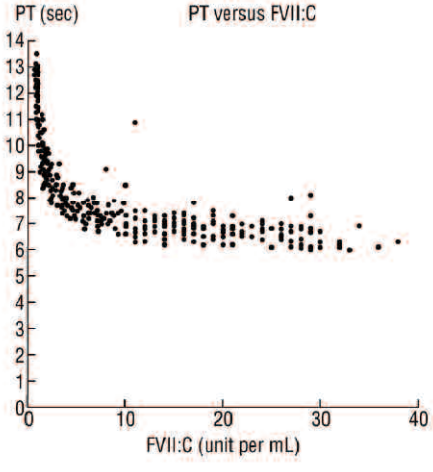
Safety and efficacy of NovoSeven® RT has not been established outside the approved indications.

INDICATIONS AND USAGE: NovoSeven® RT, Coagulation Factor VIIa (Recombinant), is indicated for: Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia; Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia; Treatment of bleeding episodes in patients with congenital Factor VII (FVII) deficiency; Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Thrombotic Events within the Licensed Indications: Clinical trials within the approved indications revealed that thrombotic events of possible or probable relationship to NovoSeven® occurred in 0.28% of bleeding episodes treated, with the incidence within hemophilia patients with inhibitors to be 0.20%, and in acquired hemophilia an incidence of 4%. Thrombotic events have been identified through postmarketing surveillance following NovoSeven® RT use for each of the approved indications. The incidence of thrombotic events can not be determined from postmarketing data. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) have an increased risk of developing thrombotic events due to circulating tissue factor (TF) or predisposing coagulopathy *[See Adverse Reactions]*. Caution should be exercised when administering NovoSeven® RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven® RT should be weighed against the risk of these complications. Patients who receive NovoSeven® RT should be monitored for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the NovoSeven® RT dosage should be reduced or the treatment stopped, depending on the patient's symptoms. **Thrombotic Events outside the Licensed Indications:** NovoSeven® has been studied in placebo controlled trials outside the approved indications to control bleeding in intracerebral hemorrhage, advanced liver disease, trauma, cardiac surgery, spinal surgery, and other therapeutic areas. Safety and effectiveness has not been established in these settings and the use is not approved by FDA. Two meta analyses of these pooled data indicate an increased risk of thrombotic events (10.0% in patients treated with NovoSeven® versus 7.5% in placebo-treated patients). Arterial thromboembolic adverse events including myocardial infarction, myocardial ischemia, cerebral infarction and cerebral ischemia were statistically significantly increased with the use of NovoSeven® compared to placebo (5.3 to 5.6% in subjects treated with NovoSeven® versus 2.8 to 3.0% in placebo-treated patients). Other arterial thromboembolic events (such as retinal artery embolism, renal artery thrombosis, arterial thrombosis of limb, intracardiac thrombus, bowel infarction and intestinal infarction) have also been reported. While venous thromboembolic events such as deep venous thrombosis, portal vein thrombosis and pulmonary embolism have been reported in clinical trials, the meta analysis of these pooled data from placebo-controlled trials performed outside the currently approved indications did not suggest an increased risk of venous thromboembolic events in patients treated with NovoSeven® versus placebo (4.8% in patients treated with NovoSeven® versus 4.7% in placebo-treated patients). In spontaneous reports of women without a prior diagnosis of bleeding disorders receiving NovoSeven® for uncontrolled post-partum hemorrhage, thrombotic events were observed. During this period, patients are at increased risk for thrombotic complications. **Post-Hemostatic Dosing:** Precautions should be exercised when NovoSeven® RT is used for prolonged dosing. **Antibody Formation in Factor VII Deficient Patients:** Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven® RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. **Hypersensitivity Reactions:** NovoSeven® RT should be administered with caution in patients with known hypersensitivity to NovoSeven® RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. **Laboratory Tests:** Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven® has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven® RT administration is unknown.



INR: NovoSeven® has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven® on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized. aPTT: While administration of NovoSeven® shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds. FVIIa:C: FVIIa:C levels were measured two hours after NovoSeven® administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

ADVERSE REACTIONS: The most frequently reported adverse reactions in patients treated with NovoSeven® are rash, pruritus, urticaria, pyrexia and venous thromboembolic events occurring in > 0.1% to < 1% of patients. Therapeutic response decreased has also been reported at a similar rate. It is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage in the package insert. **Clinical Trials Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice. Thrombotic events following the administration of NovoSeven® occurred in 0.3% of bleeding episodes treated, with the incidence in acquired hemophilia of 4% and in hemophilia patients of 0.2% in clinical trials within the approved indications *[See Warnings and Precautions]*. Adverse reactions observed in clinical trials for all labeled indications of NovoSeven® included pyrexia, injection site reaction, headache, hypertension, nausea, vomiting, pain, edema, rash (including allergic dermatitis and rash erythematous), pruritus, urticaria, hypersensitivity, cerebral artery occlusion, cerebrovascular accident, pulmonary embolism, deep vein thrombosis, angina pectoris, increased levels of fibrin degradation products, disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and AT-III, thrombosis at i.v. site, non-specified thrombosis, thrombophlebitis, superficial thrombophlebitis. The following sections describe the adverse event profile observed during clinical studies for each of the labeled indications. Hemophilia A or B Patients with Inhibitors: Two studies (Studies 1 and 2) are described for hemophilia A or B patients with inhibitors treated for bleeding episodes. The table below lists adverse reactions that were reported in ≥2% of the 298 patients with hemophilia A or B with inhibitors that were treated with NovoSeven® for 1,939 bleeding episodes.

Body System Reactions	# of episodes reported (n=1,939 treatments)	# of unique patients (n=298 patients)
Body as a whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Fibrinogen plasma decreased	10	5
Cardiovascular		
Hypertension	9	6

Other reactions reported in 1% of patients were: allergic reaction, coagulation disorder, DIC, edema, fibrinolysis increased, headache, injection site reaction, pain, pruritus, purpura, rash, thrombosis and therapeutic response decreased. Serious adverse reactions occurred in approxi-

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Coagulation Factor VIIa (Recombinant)

mately 3% of the patients and included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, therapeutic response decreased, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and hepatic function abnormal. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome. Surgery Studies: Two clinical trials (Studies 3 and 4) were conducted to evaluate the safety and efficacy of NovoSeven® administration during and after surgery in hemophilia A or B patients with inhibitors. In one study (Study 3), two patients had adverse reactions (acute post-operative hemarthrosis and internal jugular thrombosis). No deaths occurred during the study. In another study (Study 4), four of 24 patients had serious adverse reactions, all being decreased therapeutic response. Two reactions were observed in each treatment arm (bolus injection and continuous infusion). No deaths occurred during the study period. **Postmarketing Experience:** The following adverse reactions have been identified during post approval use of NovoSeven®. 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. These adverse reactions were reported following the use of NovoSeven® in labeled and unlabeled indications that included individuals with and without coagulopathy: high D-dimer levels and coagulopathy, thrombosis, thrombophlebitis, arterial thrombosis, and thromboembolic events including myocardial ischemia, myocardial infarction, cerebral ischemia, cerebral infarction, renal artery thrombosis, intracardiac thrombus, portal vein thrombosis, thrombophlebitis, peripheral ischemia, deep vein thrombosis and related pulmonary embolism, injection site pain, headache, nausea and isolated cases of hypersensitivity/allergic reactions including anaphylactic shock, flushing, urticaria, rash, and angioedema *[See Warnings and Precautions]*. Fatal and non-fatal thromboembolic events have been reported with use of NovoSeven® when used for off-label or labeled indications. There have been no confirmed reports on inhibitory antibodies against NovoSeven® or FVII in patients with congenital hemophilia A or B with alloantibodies. The Hemophilia and Thrombosis Research Society (HTRS) Registry surveillance program is designed to collect data on the treatment of congenital and acquired bleeding disorders. All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355 or at www.novosevensurveillance.com. Congenital Factor VII Deficiency: Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society (HTRS) registry showed that at least 75 patients with Factor VII deficiency had received NovoSeven® - 70 patients for 124 bleeding episodes, surgeries, or prophylaxis regimens; 5 patients in the pharmacokinetics trial. In the compassionate/emergency use programs, 1 non-serious adverse reaction (intracranial hypertension) and 1 serious adverse reaction (IgG antibody against rFVIIa and FVII) were reported. One adverse reaction (localized phlebitis) was reported in the literature. No adverse reactions were reported in the pharmacokinetics reports or for the HTRS registry. No thromboembolic complications were reported for the 75 patients included here. As with all therapeutic proteins, there is a potential for immunogenicity. In compassionate/emergency use programs patients with factor VII deficiency formation of antibodies against NovoSeven® and FVII (frequency: common (≥ 1/100 to < 1/10)) have been reported. In some cases, the antibodies showed inhibitory effect in vitro. Risk factors that may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived factor VII, severe mutation of FVII gene, and overdose of NovoSeven®, were present. Patients with factor VII deficiency treated with NovoSeven® should be monitored for factor VII antibodies. Acquired Hemophilia: Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven® for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 experienced 8 serious adverse reactions. Thrombotic serious adverse events included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Additional serious adverse reactions included shock and cerebrovascular accident. Three of the serious adverse reactions had a fatal outcome (shock, cerebral artery occlusion and myocardial infarction).

OVERDOSAGE: There are no adequate and well controlled studies to support the safety or efficacy of using higher than labeled doses in the indicated populations. Dose limiting toxicities of NovoSeven® RT have not been investigated in clinical trials. The following are examples of accidental overdose. **Congenital Factor VII Deficiency:** A newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven® (single dose: 800 micrograms per kg body weight). Following additional administration of NovoSeven® and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported. A Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke). **Hemophilia A or B with Inhibitors:** One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

More detailed information is available upon request.

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100 College Road West
Princeton, NJ 08540, USA
1-877-NOVO-777
www.NovoSevenRT.com

Version: 20121203-V7

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

0113-00012931-1 1/13

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NovoSeven® RT
Coagulation Factor VIIa (Recombinant)

Helping Healthcare Care for More Than 25 Years

"Business continuity is essential for any company, but when you are dealing with critical care products, there are lives hanging in the balance."

— Patrick M. Schmidt, Chief Executive Officer, FFF Enterprises, Inc.

BY TRUDIE MITSCHANG

FFF ENTERPRISES IS widely touted as the largest and most trusted distributor of plasma products, vaccines and other specialty pharmaceuticals and biopharmaceuticals in the U.S. But, like many great American success stories, the company and its founder, Patrick M. Schmidt, had humble beginnings. In 1988, Schmidt opened his company with a $100 investment in patient examination gloves. Today, FFF boasts more than a billion dollars in annual sales and a company culture that emphasizes putting patient safety first. Thanks to the implementation of several technologies and distribution best practices, FFF has helped secure a once-unstable biopharmaceutical supply chain and, ultimately, minimize the risk of potentially dangerous counterfeits in the pipeline. The company's website features real-time updates of its impressive counterfeit-free distribution track record — at press time, it was 9,484 days and counting.

"I hope the marketplace is a safer place than when we started 26 years ago, but at the same time, there is a lot of evil in the world, and there are still ways around the system," says Schmidt. "We launched our Verified Electronic Pedigree [VEP] in 2004 because we noticed all of our competitors had adopted the same language we use as far as promising a secure supply chain experience. We wanted to take it a step further by offering verification through technology — VEP electronically displays the chain of custody for every product we ship."

As CEO of FFF Enterprises, Inc., Patrick Schmidt takes pride in his company's success in helping to secure the specialty biopharmaceuticals marketplace over the past 26 years.

A committed Christian, Schmidt uses frequent analogies to biblical principles when explaining the business decisions that have led to the company's exponential growth and "outpouring of blessings" in recent years: "I believe there is a covenant between the leadership of the company and the rest of the team — we are going to do everything we can to honor you and your service to the company, and we expect the same in return. That is the essence of leading by example."

Improving Access to Specialty Medications

In April, it was announced that the University HealthSystem Consortium (UHC) selected FFF as its centralized distributor for the UHC Specialty

Pharmacy Program. The program, which is designed to improve access to specialty medications for participating hospitals and patients, is by all accounts a game changer for FFF, expanding its reach as a distributor of plasma-based biologics like intravenous immune globulin (IVIG) and clotting factor, and propelling it into the specialty pharmaceutical business, which is projected to grow to approximately $400 billion by 2020. "We cut our teeth in specialty pharmaceuticals with two of the toughest territories," says Schmidt. "If we can handle the supply challenges that are inherent with plasma products, I think we are in a position to handle other drugs that historically experience less supply volatility. I don't know how much this changes the game, but I know for sure we're in the game."

Another example of FFF's quality commitment is epitomized by its specialty pharmacy subsidiary, NuFACTOR, which was established to provide immune globulin, clotting factor and vaccines directly to patients. Launched in 1995 to primarily serve the hemophilia community, NuFACTOR has experienced exceptional growth, leaping from $16.6 million in revenue in 2011 to an unprecedented $70 million in 2014. "We had the opportunity to sell NuFACTOR on several occasions, but we never did because we believed then, as we do now, that there are tremendous synergies between wholesale distribution and specialty pharmacy," explains Schmidt. "It took a while to get all cylinders firing together, but I think the growth we've seen to date is just preparation for what's to come."

Expanding and Investing in the Future

With headquarters in Temecula, Calif., FFF serves customers across the nation, many on the East Coast. To expand its capacity to serve more customers, FFF is preparing to open a second distribution facility in Kernersville, N.C. Slated to house 164 new team members, the North Carolina location will also feature a NuFACTOR pharmacy, allowing FFF to ship products for same business day delivery anywhere in the country. "It became mandatory for us to expand our center of operation," says Schmidt. "As we looked to the future, it became apparent that we needed multiple sites that are prepared to handle 100 percent of our business for an extended period of time in the event of a natural disaster. Business continuity is essential for any company, but when you are dealing with critical care products, there are lives hanging in the balance."

FFF has helped secure a once-unstable biopharmaceutical supply chain and, ultimately, minimize the risk of potentially dangerous counterfeits in the pipeline.

FFF has also been investing in technology as part of the company's strategic growth plan. In late 2013, the company launched its Verified Inventory Program-Consignment (VIPc). VIPc provides inventory management utilizing advanced RFID technology that eliminates carrying costs, and invoices only when products are used. The system also continuously monitors product inventory and automatically replenishes stock as it is used. Additionally, VIPc preemptively pulls and replaces product well before its beyond-use date, eliminating liability for expired product. Schmidt explains that the key program benefit is that it streamlines inventory management to give providers more time to focus on patient care. "Also, we wanted to be able to give manufacturers real-time visibility into where their drug is, how it is being stored, and the velocity at which it's being used," he adds. "With this program widely in use, we can envision the capability of our emergency pager team being able to locate a requested drug within the closest VIPc inventory cabinet and shipping it out in record time, reducing costs and response time, and improving patient care."

FFF has celebrated a number of milestones in recent years; July 2013 marked its 25th year in business, an achievement that coincided with revenue growth exceeding $150 million. Schmidt says the company's success can be attributed to prayer, hard work and a willingness to remain flexible while navigating the ever-changing healthcare landscape. "I think the phrase 'helping healthcare care' has become even more significant in recent years," he explains. "Roles have changed, risk has shifted and, in response, we've had to come up with better ways of doing business. That's why we are strategically investing in technology, because in this industry, you can easily get left behind. Technology is like our blood system — we will need it in order to survive." ❖

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

BioResearch

Summaries of up-to-date clinical research published internationally.

Albumin Versus Crystalloids in ARDS

Experimental and clinical data show that, compared with crystalloids, colloid fluid therapy mediates multiple beneficial effects in the lungs of patients suffering from acute respiratory distress syndrome (ARDS), including reduced alveolar-capillary permeability, reduced histological damage, reduced inflammatory cell infiltration and faster hemodynamic stabilization. With recent evidence associating use of hydroxyethyl starch products with increased risk of kidney injury and death in septic patients, there is growing interest in the use of albumin to increase intravascular volume expansion in ARDS.

A systematic review of four databases by this study's authors yielded 4,130 publications addressing the use of colloids and crystalloids with respect to oxygenation and/or mortality in adults with ARDS. Three of these studies (totaling 206 patients) met predefined inclusion criteria: the ARDS patient subgroup from the large Saline Versus Albumin Fluid Evaluation (SAFE) trial comparing 4% albumin to saline, and two U.S. trials comparing 25% furosemide plus albumin or saline for the treatment of acute lung injury.

The weighted mean difference (WMD) in change in PaO2/FiO2 significantly increased for patients receiving albumin therapy in the first 48 hours (WMD = 62 mm Hg, 95% confidence interval [CI] 47 to 77, $P < 0.0002$) and after seven days (WMD = 20 mm Hg, 95% CI 4 to 36, $P < 0.017$). The calculated pooled risk of death was 34 percent (34 of 100) for patients receiving albumin versus 38.5 percent (40 of 104) for patients receiving saline; this relative risk of 0.89 was not statistically significant (95% CI 0.62 to 1.28, $P = 0.539$). Given these findings indicating improved oxygenation using albumin and the small size and limited outcomes data from this meta-analysis, the investigators proposed a double-blinded trial comparing colloid and crystalloid fluid resuscitation in ARDS patients.

Uhlig C, Silva PL, Deckert S, et al. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care *2014 Jan 9;18(1):R10 [Epub ahead of print].*

Prophylaxis with Anti-Inhibitor Coagulant Complex Reduces Bleeding Episodes

Prophylactic treatment with an anti-inhibitor coagulant complex (FEIBA NF [Factor Eight Inhibitor Bypassing Activity], Baxter Healthcare) reduced the median annualized bleeding rate (ABR) more than three-fold as compared with on-demand treatment with the product to control acute hemorrhages, according to a Phase III study of 36 subjects with hemophilia A or B and inhibitory alloantibodies to factor VIII or factor IX.

Over a one-year period, 17 subjects with high-titer or low-titer inhibitors refractory to factor VIII or factor IX replacement therapy were treated prophylactically with 85 ± 15 U/kg bolus intravenous doses of FEIBA NF every other day, while 19 subjects received FEIBA NF on demand at the discretion of the individual investigator. The median ABR during prophylaxis was 7.9 events, compared with 28.7 events during on-demand treatment — a statistically significant 72.5 percent reduction in relation to the on-demand treatment arm ($P = 0.0003$).

Three subjects (17.6 percent) on prophylaxis experienced no bleeding episodes, whereas none receiving on-demand treatment were free of bleeding episodes. The prophylaxis group reported greater reductions in pain scores and fewer days absent from work or school because of bleeding episodes. A post hoc analysis comparing bleeding events during the 12 months prior to study initiation against the 12-month study period found 12 of 16 prophylaxis group subjects experienced a reduction in bleeding episodes, compared with just two of 19 on-demand group subjects. Total usage of FEIBA NF was three times higher in the prophylaxis group than in the on-demand group ($P = 0.0067$). The safety of prophylaxis was found to be comparable to that of on-demand treatment; no thromboembolic events were identified in either treatment arm.

[Editorial note: In December 2013, the U.S. Food and Drug Administration expanded the approved indications for FEIBA NF to include routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B who have developed inhibitors.]

Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. Haemophilia *2014 Jan;20 (1):65-72.*

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.*

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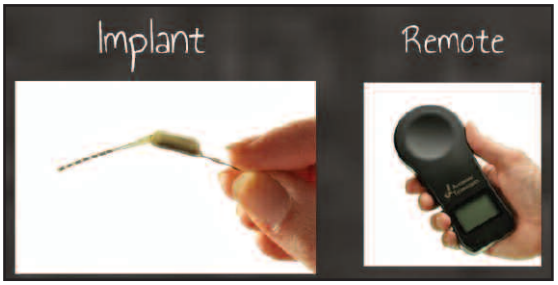


Electronic Aspirin

A technology under clinical investigation is a patient-powered tool for blocking sphenopalatine ganglion (SPG) signals at the first sign of a headache. The system involves the permanent implant of a small nerve-stimulating device in the upper gum on the side of the head normally affected by headache. The lead tip of the implant connects with the SPG bundle, and when a patient senses the onset of a headache, he or she places a handheld remote controller on the cheek nearest the implant. The resulting signals stimulate the SPG nerves and block the pain-causing neurotransmitters. The therapy has successfully completed a trial of its technology on European patients with cluster headaches, also known as "suicide" headaches. The same device is being trialed for use on migraine headache patients in Europe, and the company plans to offer it for patients suffering from cluster and migraine headaches in the United States, too.

Autonomic Technologies Inc., (650) 216-6106, www.ati-spg.com/us/en

Medical Robot

The RP-VITA robot was designed to transform the delivery of acute care by expanding the use of remote consults and increasing workflow efficiency. Developed by InTouch Health and iRobot, RP-VITA eliminates the need for telemedicine-specific staffing and support with intuitive, easy-to-use features that encourage physician adoption and clinical use. Features include AutoDRIVE capabilities that allow RP-VITA to safely navigate and travel to selected destinations without requiring user guidance; a ControlStation App for the iPad to enable fast and easy access and control from anywhere; and a Cloud-based, SureCONNECT infrastructure to maintain reliable connections under highly variable network conditions. The device has U.S. Food and Drug Administration clearance and is HIPAA-compliant to ensure safe and effective consults in high-acuity clinical environments.

InTouch Health, (805) 562 8686,
www.intouchhealth.com/products-and-services/products/rp-vita-robot

Needle-Free Diabetes Monitor

Echo is developing a blood glucose monitor that utilizes the company's Symphony CGM System, a noninvasive (needle-free), wireless, continuous glucose monitoring (CGM) system designed to provide accurate, real-time blood glucose data conveniently and continuously. Symphony incorporates Prelude, the company's proprietary skin permeation device, a transdermal sensor, wireless transceiver and data display technologies. Symphony is designed to improve patient monitoring of blood glucose for patients in hospital critical care units and, subsequently, for people with diabetes. All existing FDA-approved continuous glucose monitoring systems are needle-based, requiring insertion of a glucose sensor into the patient's skin. Symphony is a noninvasive CGM system that does not require insertion of its glucose sensor and thus does not give rise to the risks or discomfort associated with needle-based CGM systems. Following skin permeation with Prelude, a biosensor is placed on the permeated site. After a brief warm-up period, Symphony wirelessly provides the patient's glucose level every minute to a remote monitor. The monitor then tracks the glucose levels and rate of glucose changes and provides visual and audible alarms if the patient's glucose levels move outside the target range, which can be personalized for each patient.

Echo Therapeutics, (215) 717-4100, www.echotx.com/prelude-skinprep-system.shtml

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Guide to International Pharma Regulation, 2014 Edition

Author: U.S. Food and Drug Administration

This guide is a one-stop authority for quick, accurate answers to questions regarding regulatory developments affecting drug production in more than 45 nations. Included are more than 150 reports highlighting changes from the past year. Topics include changes in inspection practices, quality manufacturing standards, new patent regulations, sunshine and transparency regulations, tough new bribery laws, labeling and marketing regulations, changing pharmacovigilance requirements, anti-counterfeiting measures, orphan drug regs, and dozens more key topics.

www.fdanews.com/products/45746&hittrk=14225?utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=31876632

Guide to FDA Pharma GMP Regulations — 2014

Author: U.S. Food and Drug Administration

This compilation of pharmaceutical good manufacturing practices (GMP) regulations is an all-electronic reference delivered on CD. It contains the current text of FDA's GMP regulations for drugs, biologics and combination products with federal register announcements and hard-to-find background information, as well as guidance to help maintain compliance. In addition, the guide contains full explanations of why FDA has written the rules the way it has, touching on all aspects of pharma GMPs and adding perspective to FDA's thinking on a host of issues, including labeling and expiration dating, quality control unit responsibilities, responsibilities for oversight of contract manufacturers, employee qualifications, individual liability for adulterated products, storage of quarantined product, cleaning validation, acceptance testing, stability testing, combination products and many other issues drugmakers must deal with daily.

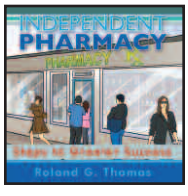
www.fdanews.com/products/37354&hittrk=14109?utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=29334443

Health IT Safety Plan

Author: Department of Health and Human Services

A new set of guides and interactive tools to help healthcare providers more safely use electronic health information technology products such as electronic health records (EHRs) are now available. Titled the Safety Assurance Factors for EHR Resilience (SAFER), the guides are a suite of tools that include checklists and recommended practices designed to help healthcare providers and the organizations that support them assess and optimize the safety and safe use of EHRs. The SAFER guidelines complement existing health IT safety tools and research developed by the Agency for Health Research and Quality and the Office of the National Coordinator for Health Information Technology. Each SAFER guide addresses a critical area associated with the safe use of EHRs through a series of self-assessment checklists, practice worksheets and recommended practices. Areas addressed include high-priority practices, organizational responsibilities, patient identification, computerized physician order entry and decision support, test results review and follow-up, clinical communication, contingency planning, system interfaces and system configuration. Each SAFER guide also has extensive references and is available as a downloadable PDF and as an interactive web-based tool.

www.healthit.gov/saferguide



Independent Pharmacy Steps to Greater Success

Author: Roland G. Thomas

This book contains a myriad of information and tips on how to succeed in the independent pharmacy business, and provides readers with an innovative new business model. The author wrote this book after seeing so many, perhaps unintentional, errors in judgment regarding primarily the physical aspects and the lack of utilization of the tools available to independent pharmacies. The information comes from what the author has learned through trial and error, and shows how he has pushed the envelope and invested his time and money to learn as much as possible.

www.amazon.com/Independent-Pharmacy-Steps-Greater-Success/dp/149072155X

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Medicare Reimbursement Rates* Rates are effective July 1, 2014 through September 30, 2014. ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$75.83	$74.62
CARIMUNE NF	CSL Behring	J1566	$57.42	$56.50
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$77.61	$76.36
GAMMAGARD LIQUID	Baxter	J1569	$79.36	$78.09
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$57.42	$56.50
GAMMAKED	Kedrion	J1561	$80.64	$79.35
GAMMAPLEX	Bio Products Laboratory	J1557	$80.73	$79.44
GAMUNEX-C	Grifols	J1561	$80.64	$79.35
OCTAGAM	Octapharma	J1568	$63.92	$62.89
PRIVIGEN	CSL Behring	J1459	$74.14	$72.95

** Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PIDD	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PIDD, ITP	3 g, 6 g, 12 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			0.5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxter	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxter	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Laboratory	IVIG: PIDD, ITP	2.5 g, 5 g, 10 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PIDD	1 g, 2 g, 4 g, 10 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g

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

2014-2015 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
bioCSL	AFLURIA (IIV3)	5.0 mL multi-dose vial	9 years and older*	90658/Q2035
		0.5 mL single-dose syringe		90656
GlaxoSmithKline	FLULAVAL (IIV3)	5.0 mL multi-dose vial	3 years and older	90658/Q2036
	FLULAVAL QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	3 years and older	90688
	FLULAVAL QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
	FLUARIX QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 mL single-use nasal spray	2–49 years	90672
Novartis	FLUVIRIN (IIV3)	5.0 mL multi-dose vial	4 years and older	90658/Q2037
		0.5 mL single-dose syringe		90656
	FLUCELVAX (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661
Protein Sciences	FLUBLOK (RIV3)	0.5 mL single-dose vial	18–49 years	90673
Sanofi Pasteur	FLUZONE (IIV3)	5.0 mL multi-dose vial	6 months and older	90658/Q2038
		0.5 mL single-dose syringe	3 years and older	90656
	FLUZONE QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	6 months and older	90688
		0.25 mL single-dose syringe	6–35 months	90685
		0.5 mL single-dose syringe	3 years and older	90686
		0.5 mL single-dose vial	3 years and older	90686
	FLUZONE HIGH-DOSE (IIV3)	0.5 mL single-dose syringe	65 years and older	90662
	FLUZONE INTRADERMAL (IIV3)	0.1 mL single-dose microinjection system	18–64 years	90654

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 Cell culture-based trivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years.

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