SPRING 2015

biosupply trends

QUARTERLY

Special Focus: **SAFETY**

safe medicine

The Global Threat of Drug Integrity

The Continuing Threat of Foodborne Illness

Myths & Facts: Obesity

Biosimilars: The Pathway to Safe and Effective Regulation

'Right-to-Try': The Debate Rages On

Cutting-Edge Science for Severe PIs — Page 50

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*That's **TWICE** the amount of factor of the largest vial available for other FVIII/VWF products,[1-4] so patients may require:

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Alphanate®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

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

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

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Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

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

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

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.

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** CSL Behring. Humate P Package Insert. August 2013; **3.** Octapharma. Wilate Package Insert. January 2012; **4.** Kedrion. Koate-DVI Package Insert. August 2012.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

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ALPHANATE®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])

Sterile, lyophilized powder for injection.

Initial U.S. Approval: 1978

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

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

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

----------DOSAGE AND ADMINISTRATION ----------

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

Hemophilia A: Control and prevention of bleeding episodes

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

----------DOSAGE FORMS AND STRENGTHS ----------

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, 1500 and 2000 IU FVIII in single dose vials.

----------CONTRAINDICATIONS ----------

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

----------WARNINGS AND PRECAUTIONS ----------

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

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

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

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

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

- Pregnancy: No human or animal data. Use only if clearly needed.
- Pediatric Use: Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.

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Spring 2015

Features

Special Focus: Safety

Up Front

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BioFocus

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

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Safe Medicine: A Shared Responsibility

AS A SPECIALTY distributor of fragile biologics and transport-sensitive vaccines, FFF Enterprises has always taken a "safety first" approach when it comes to business best practices. Our commitment to channel integrity is at the core of everything we do, which is why the annual safety-themed issue of *BioSupply Trends Quarterly* is always one of my personal favorites.

In this issue, we take a look at some of the unique 21st-century challenges facing stakeholders in the healthcare arena. In our article "Safety in Medicine: Ensuring the Integrity of Drugs," we investigate current global efforts to stem the growth of counterfeit and adulterated drugs. Although improved safeguards are in place, in recent years, we've seen an uptick in supply chain safety risks and compromises, including the sale of contaminated products, a proliferation of fake online pharmacies promoting gray market pricing and hard-to-find drugs, and widespread distribution of counterfeits. Without a doubt, as the threats posed by a globalized marketplace and the complexity of the supply chain continue to grow, more needs to be done to protect the public.

Of course, our pharmaceutical supply chain is not the only widespread public health threat. Our food supply chain is also at risk, as outlined in our article "Foodborne Illness: A Continuing Threat to Public Health." The Centers for Disease Control and Prevention states that while serious foodborne illnesses are rarer than ever in the developed world, mild cases are still extremely common, and the potential for deadly consequences remains a very real concern. Statistics show one in six Americans (48 million) will contract a foodborne illness this year alone, with 128,000 of those cases requiring hospitalization and roughly 3,000 of them resulting in fatalities. Not surprisingly, outside the developed world, statistics are grimmer. Responsibility for preventing the spread of foodborne illness lies with many stakeholders, including ranchers, farmers, distributors, grocers, restaurateurs and the general public. The role of healthcare providers is also significant, since most foodborne illness outbreaks are now required to be reported to public health authorities.

Another hot topic making headlines is the debate surrounding biosimilar legislation. Should biosimilars be substituted for biopharmaceuticals? What are the best ways to legislate them? What guidelines should be used when naming these products? We explore the issues surrounding these and other questions in our article "Biosimilars: The Race for Approval." Of particular note is the fact that the U.S. Food and Drug Administration recently published its first edition of the *Purple Book*. As biosimilars are approved (the first of which was approved in March), they will be added to the *Purple Book* so healthcare professionals can view them.

Also in this issue, we tackle some of the safety, medical, ethical and legal ramifications linked to the headline-making "right-to-try" initiatives. Lawmakers in at least 20 states either have introduced or have indicated they will introduce right-to-try legislation in 2015. The resulting debate is a heated one: Proponents argue that federal regulations that violate constitutional liberties can never trump state laws, while critics say right-to-try laws are far more likely to harm patients than help.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* and find it both relevant and helpful to your practice. We welcome your comments.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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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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Healthcare Providers' Medicare Appeals Further Delayed

Medicare appeals hearings from hospitals, doctors and other providers have been suspended by the Office of Medicare Hearings and Appeals (OMHA) because it has moved beneficiaries to the front of the line. As of this writing, approximately 900,000 appeals are awaiting decisions, with most filed by hospitals, nursing homes, medical device suppliers and other healthcare providers, according to Jason Green, OMHA's program and policy director. Hospitals file more appeals than all other providers due to an increasing number of Medicare payment denials for patients who have been admitted to the hospital but who auditors later say should have been kept instead for observation, a status that reduces payments. The wait times for health providers' cases have doubled since last year and are nearly four times longer than the processing time for beneficiary appeals.

In January, Chief Judge Nancy Griswold issued a "beneficiary-first" policy, a temporary measure that will remain in place as long as there is a backlog. Since then, beneficiaries have waited 113 days on average for a hearing compared with 235 days the year before. Reaching OMHA is the third of four stages in the appeals process and the first opportunity for Medicare beneficiaries or healthcare providers to present their case before a judge. The third stage offers higher odds for winning an appeal; previous levels involve only a review of the case files. ❖

Most Hospitals Will Fail to Collect on Medicare Quality Bonuses

This year, 55 percent of hospitals (1,700) that were graded on the federal government's most comprehensive review of quality received bonuses, but fewer than 800 of those will actually receive the money, according to a Kaiser Health News analysis. Those who won't receive the bonuses are being penalized through two other Medicare quality programs: one that punishes hospitals for having too many patients readmitted for follow-up care and another that lowers payments when too many patients develop infections or get injured during their hospital stays. In addition, payments are being lowered for hospitals that are not making enough progress in switching over to electronic medical records. Altogether, more than 6 percent of Medicare payments are contingent on performance.

The Hospital Value-Based Purchasing Initiative, now in its third year, is the only quality incentive that provides bonuses and penalties, as well as the only one that recognizes hospital improvement even if a hospital's quality metrics are still subpar. The value-based bonuses and penalties are based on 26 different measures, including how consistently hospitals followed a dozen recommended medical guidelines and how patients rated their experiences while in the hospital, as well as a new measure that encourages hospitals to deliver care in the most efficient manner possible. This year, Medicare judged hospitals based on how they performed in comparison with others in the second half of 2012 and all of 2013, as well as how much they had improved from two years before. Medicare adds a hospital's bonus or penalty to every Medicare reimbursement for a patient stay from October through the end of September. ❖

AVERAGE BONUS FOR LARGE HOSPITALS THAT HAVE MORE THAN 400 BEDS: **NEARLY $213,000**

AVERAGE PENALTY FOR LARGE HOSPITALS THAT HAVE MORE THAN 400 BEDS: **ABOUT $1.2 million**

AVERAGE BONUS FOR HOSPITALS WITH 200 BEDS OR FEWER: **ABOUT $32,000**

AVERAGE PENALTY FOR HOSPITALS WITH 200 BEDS OR FEWER: **ABOUT $131,000**

28 PERCENT OF HOSPITALS WILL BREAK EVEN OR GET EXTRA MONEY.

AVERAGE BONUS FOR HOSPITALS UNDER THE VALUE-BASED PURCHASING INITIATIVE: **0.44** PERCENT INCREASE

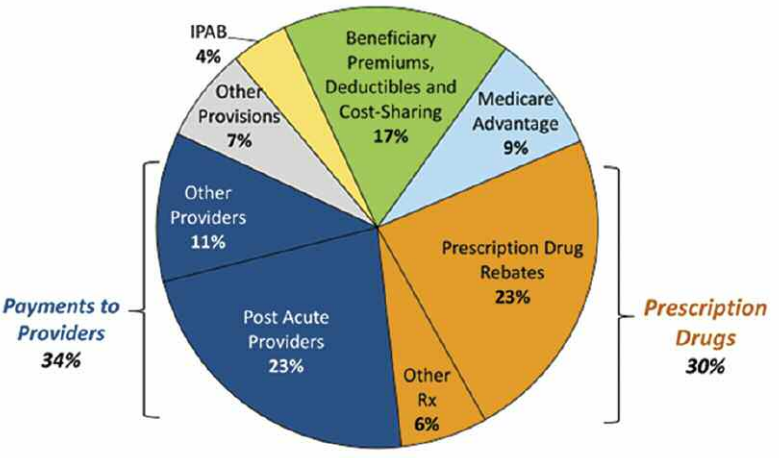
AVERAGE PENALTY FOR HOSPITALS UNDER THE VALUE-BASED PURCHASING INITIATIVE (NOT INCLUDING OTHER PENALTY PROGRAMS): **0.30** PERCENT REDUCTION

President's FY2016 Budget Set to Reduce Net Medicare Spending

The president's FY2016 budget proposal released in February by the Office of Management and Budget would reduce net Medicare spending by $423 billion between 2016 and 2025 and is estimated to extend the solvency of the Medical Hospital Insurance Trust Fund by approximately five years. Highlights of the budget proposal include:

- reductions in Medicare payments to providers, most of which affect providers of post-acute care (34 percent of proposed cuts)
- a requirement by drug manufacturers to provide Medicaid rebates on prescriptions for Part D Low Income Subsidy enrollees, a proposal that was also included in the president's FY2014 and FY2015 budgets (30 percent of proposed cuts)
- increases in income-related premiums and prescription drug copayments for low-income enrollees to encourage the use of generic drugs, an increase in the Part B deductible for new enrollees and a new home health copayment for new enrollees (17 percent of proposed cuts)
- a repeal of the Sustainable Growth Rate formula and $54 billion in new Medicare spending ❖

Figure 1.
Distribution of Medicare Savings in President Obama's FY2016 Budget



Total Medicare Savings, 2016-2025 = $498 billion

Note: Excludes provisions that would increase Medicare spending and excludes interactions between provisions. IPAB is the Independent Payment Advisory Board. Numbers may not sum due to rounding.

Source: Kaiser Family Foundation Analysis of the Budget of the United States Government, Fiscal Year 2016.

HHS Announces $840 Million Initiative to Improve Patient Care and Lower Costs

The U.S. Department of Health and Human Services (HHS) has launched the Transforming Clinical Practice Initiative, an $840 million investment over the next four years to support 150,000 clinicians. The initiative will fund successful applicants who work directly with medical providers to rethink and redesign their practices, moving from systems driven by quantity of care to ones focused on patients' health outcomes and coordinated healthcare systems. The applicants can include group practices, healthcare systems, medical provider associations and others. The effort will help clinicians develop strategies to share, adapt and further improve the quality of care they provide while keeping costs down. Strategies could include giving doctors better access to patient information (such as prescription drug use to help them take their medicines properly); expanding the number of ways patients are able to communicate with clinicians caring for them; improving the coordination of patient care by primary care providers, specialists and the broader medical community; and using electronic health records on a daily basis to examine data on quality and efficiency.

"The administration is partnering with clinicians to find better ways to deliver care, pay providers and distribute information to improve the quality of care we receive and spend our nation's dollars more wisely," said HHS Secretary Sylvia M. Burwell. "We all have a stake in achieving these goals and delivering for patients, providers and taxpayers alike." The initiative is one part of a strategy advanced by the Affordable Care Act. ❖

Payments for Healthcare: A New Day Is Dawning

In late January, the Department of Health and Human Services (HHS) announced that it would fundamentally reform how it pays providers for treating Medicare patients in the coming years. For the most part, the announcement was seen as a positive step that focuses on the quality of care delivered rather than the quantity. Speeding up the transition from fee-for-service to pay-for-performance and forcing Medicare to commit to this payment method were applauded.

New payment models such as accountable care organizations (ACOs) and bundled payments that reward value, improve patient outcomes and cut down on the volume of unnecessary procedures are being pushed with a new fast-paced implementation time frame. The goal? A move from the 20 percent of Medicare payments that currently come from alternative payment programs to 30 percent by the end of 2016 and 50 percent by the end of 2018.

Health Care Payment Learning and Action Network

A variety of partners will work with a new group, the Health Care Payment Learning and Action Network, to expand alternative payment models into their programs. The network held its first meeting in March. In addition, HHS is expected to ramp up efforts to work with states and private payers to facilitate the adoption of alternative payment models.

According to a Centers for Medicare and Medicaid Services (CMS) fact sheet, HHS has broken down the framework into categories based on how providers will receive payment:

Category 1: fee-for-service with no link of payment to quality

Category 2: fee-for-service with a link of payment to quality

Category 3: alternative payment models built on fee-for-service architecture

Category 4: population-based payment

Value-based purchasing includes payments made in categories 2 through 4. Moving from category 1 to category 4 involves two shifts: increasing accountability for both quality and total cost of care, and a greater focus on population health management as opposed to payment for specific services.

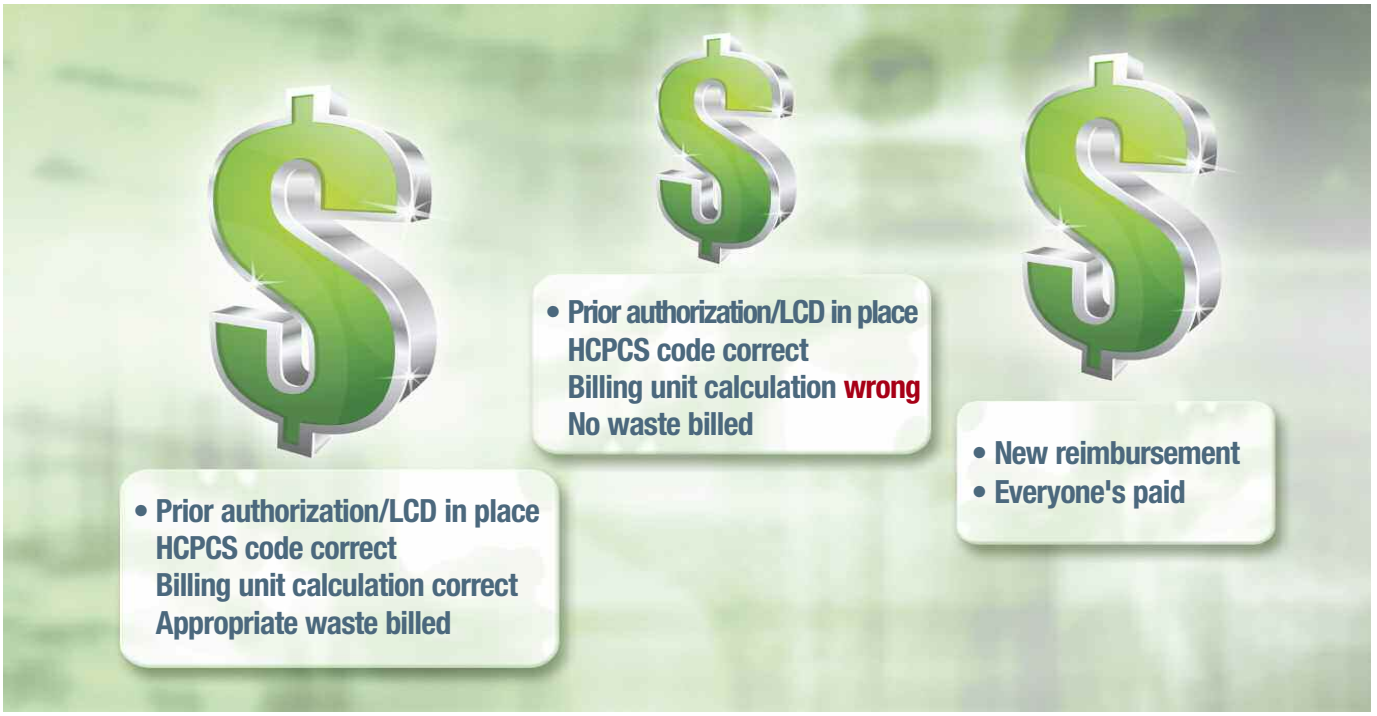
HHS believes that with alternative payment models like ACOs that have been up and running since 2011, an estimated 20 percent of Medicare reimbursements had already shifted to categories 3 and 4 by 2014.[1]

Is this just another government program? No. Insurers are surging ahead as well with newly defined plans. Most notable are Anthem and United Healthcare. According to *Forbes*, Anthem wants to transition away from the traditional fee-for-service model toward value-based payments by focusing on enhancing payments for performance and shared-risk arrangements that change the interactions between insurers and providers.[2] Similarly, UnitedHealth is involved in implementing value-based payments such as the one announced in late 2014: a new bundled payment program that will pay MD Anderson Cancer Center in Houston a flat fee to provide head and neck cancer care.[3]

Quality is Vital

The quality and accuracy of providers' use of ICD-9 and ICD-10 codes, how they handle reimbursement through the

Figure 1. Impact of Billing Errors on Pooled Average Reimbursement Across All Facilities



revenue cycle, their adherence to prior authorizations, local coverage determinations (LCDs) or national ones (NCDs), as well as documentation and medical records, are vital. Use of these codes is the only way of telling the patient's story completely and accurately.

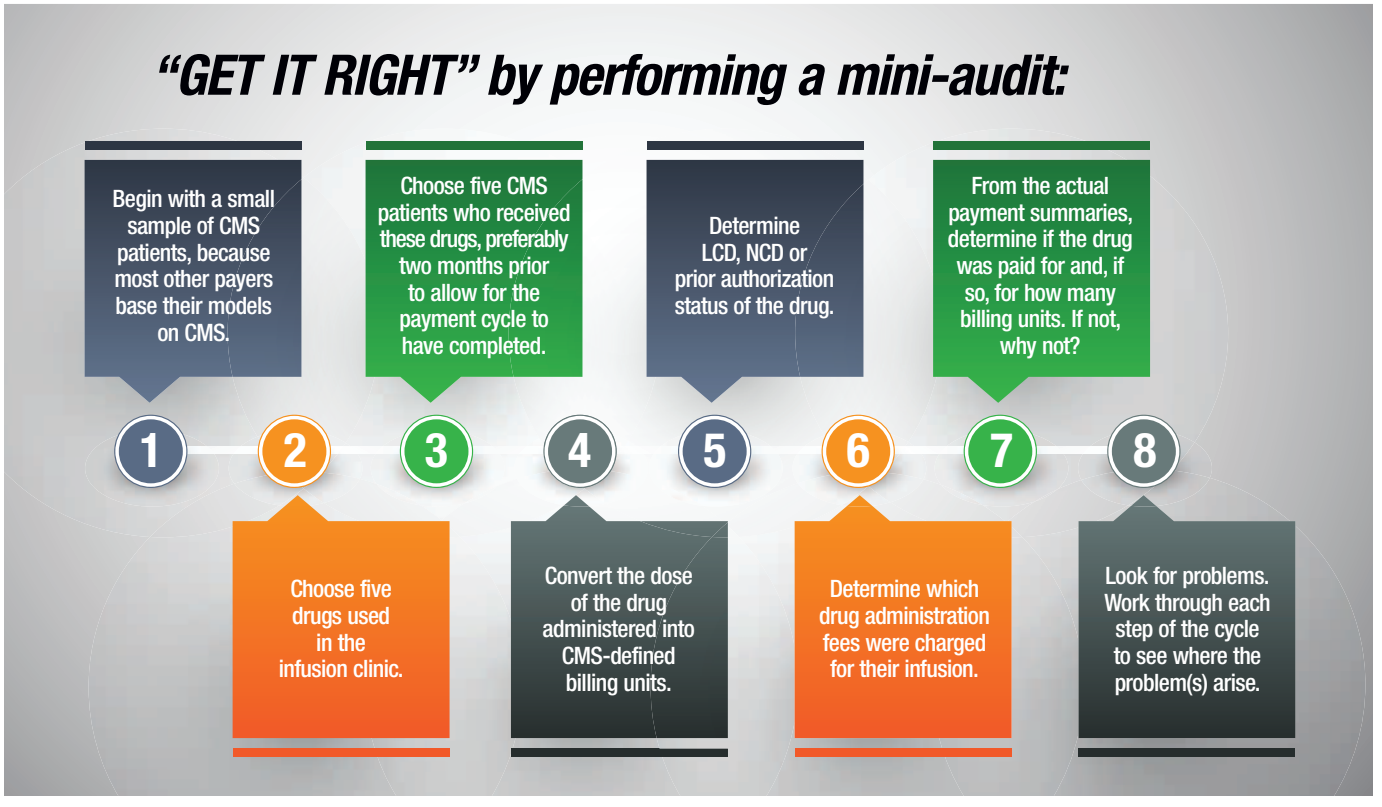
These new payment mechanisms are based on cumulated big data pools. While these payment mechanisms apply to all aspects of care, the remainder of this column will focus on medications. From a pharmacy perspective, cumulated data pools mean that all drugs and drug administration fees billed in the recent past form the basis of the drug components of the new offerings. Providers need to be confident that theirs are accurate, or they may be complicit in billing errors and misrepresentation of cost.

Complicity refers to the act of helping someone else behave inappropriately or illegally either deliberately or accidentally because of lack of attention or failure to look for and correct problems. It's not uncommon for providers to find themselves complicit concerning the rates of reimbursement for products and services. Many times, they are unaware there are problems in their infrastructure, which often include failing to pay strict attention to billing systems for drug products and drug administration fees; failing to use appropriate codes, descriptions and billing unit conversions; neglecting to bill for some drugs at all because it's "too complicated for too little return" (these patients and products get averaged into calculations, but at $0); failing to ensure appropriate and complete documentation; and assuming computer systems work without careful checks and confirmation.

Focus on "Getting it Right"

Hospital and healthcare facilities have revenue cycle teams, groups of financial executives and an IT infrastructure, all of which are tasked with ensuring appropriate and correct reimbursement. While these services may be outsourced, the responsibility still lies with the practice site. Therefore, getting it right starts with using the correct ICD-9/ICD-10 codes to identify the conditions the patient is being treated for. Since payment for drugs is often restricted to labelled indications, specific use in specific disease states or as part of a defined treatment pathway, it's essential that this data is transmitted to the payer. Next come prior authorizations, LCDs and NCDs. If the payer has requirements for use, providers need to meet these and document them in a manner that is codable to be transmitted to the payer.

Billing for the drug itself depends on using the correct healthcare common procedure coding system code (some of which are brand-specific, including those for immune globulin products) and correctly converting the actual dose administered into the number of CMS-defined and -assigned billing units. These are specific to each drug, and Medicare and most other payers require



converting the dose of the drug given into billing units that are then submitted for billing. Providers are not paid for the entire vial — only for the amount used for that patient. But, they can bill for waste if the product purchased in a single dose vial has been used for a Medicare patient. Medicare makes a provision for billing for waste; most other payers don't. If a temporary miscellaneous code for a new drug is used, an NDC code is needed. That code is the only thing that will actually identify which drug was used.

It is essential to ensure that this conversion is working correctly through all steps — from the drug being entered into the pharmacy computer system to the bill being released. There are a lot of places this can go awry and leave providers billing for only a fraction of what they should be. Billing unit errors are one of the major issues reported by Medicare, which convey the false impression that a specific disease state can be treated with a much lower dose than is actually the case.

Lastly, drug administration plays a major role. It is designed to cover the costs of the use of local anesthesia; starting the IV; access to IV, catheter or port; routine tubing, syringe and supplies; preparation of the drug; flushing at completion; and hydration fluid. Each of the biologic, immunologic and chemotherapy agents administered in the infusion center qualifies for the upper-level drug administration fees, a portion of which should be transferred back to the pharmacy cost center. ❖

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.

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Vaccines

2014-15 Flu Vaccine Efficacy Low, But Still Recommended

At the end of February, the Centers for Disease Control and Prevention (CDC) reported that the 2014-15 seasonal influenza vaccine was just 18 percent effective against the dominant strain of flu — a drop from the 23 percent protection level estimated earlier in the season. What's worse is that CDC estimated the effectiveness of the injected vaccine for kids age 2 years to 8 years at just 15 percent, and the nasal spray version of the vaccine not protective in young children at all. Why is this year's flu vaccine protection rate so low? Identifying the vaccine strains' potential protective benefit is one of the most troublesome issues surrounding influenza vaccines. However, even during seasons when there is a less than ideal match, CDC still recommends the flu vaccine for everyone 6 months and older, and it emphasizes the particular importance of the vaccine for people at high risk for serious flu complications and their close contacts.

The 2014-15 Mismatch

Twice annually, the World Health Organization (WHO) consults with an advisory group of experts to analyze influenza virus surveillance data generated by the WHO Global Influenza Surveillance and Response System, and then issues recommendations on the composition of the influenza vaccines for the following influenza season. These recommendations are used by the national vaccine regulatory agencies and the pharmaceutical companies to develop, produce and license influenza vaccines months in advance so that manufactures have time to make the vaccines. But, predicting which strains of the virus to include in the influenza vaccines has been difficult both because the virus antigenically drifts (mutates) from year to year and the number of influenza subtypes A and type B that can be selected for inclusion is limited.

Until the 2013-14 season, the influenza vaccine was a trivalent vaccine (IIV3) and contained only three strains: two A strains

and one B strain. But, since the year 2000, two influenza B lineages (Victoria and Yamagata) have co-circulated, and various degrees of mismatch have occurred between the B lineage included in IIV3s and the B lineage that actually circulated, causing an increased risk of influenza-related morbidity across all age groups. Therefore, it was thought that with FDA approval of the new quadrivalent vaccine (IIV4) that added a fourth strain (a second type B strain), the chances of predicting the correct strains should improve.

For 2014–15, the IIV3 influenza vaccines contained the same vaccine virus strains as those in the 2013–14 vaccine: an A/California/7/2009 (H1N1)-like virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like (Yamagata lineage) virus. The IIV4 influenza vaccines contained those strains, as well as a B/Brisbane/60/2008-like (Victoria lineage) virus. But, this season, the mismatch occurred among one of the A strains, with influenza A (H3N2) viruses reported most frequently in almost all states. The H3N2 virus that is currently circulating drifted to look very different from the vaccine strains chosen. According to CDC, "During past seasons when influenza A (H3N2) viruses have predominated, higher overall and age-specific hospitalization rates and more mortality have been observed, especially among older people, very young children, and persons with certain chronic medical conditions compared with seasons during which influenza A (H1N1) or influenza B viruses have predominated." Unfortunately, this drifted strain was not identified until March and didn't become dominant until September, which was far too late to make new vaccines. "This is a very unusual circumstance where a new strain develops and becomes a dominant strain so quickly and after the vaccine has already been produced," said Dr. Joseph Bresee, chief of Epidemiology and Prevention Branch at CDC's National Center for Immunization and Respiratory Diseases.

On Feb. 26, WHO recommended that this year's drifted H3N2 strain, as well as updated versions of other strains be included in next season's vaccine. Trivalent vaccines for use in the 2015-2016 influenza season (northern hemisphere winter) will contain an A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like virus. Quadrivalent vaccines will contain those three viruses and a B/Brisbane/60/2008-like virus. On March 4, the Vaccines and Related Biological Products Advisory Committee voted to adopt WHO's recommendations.

2014-15 Vaccine Still Protective

While the 2014-15 flu vaccine is not a good match, CDC still recommends people get vaccinated because "antibodies made in response to one flu virus can sometimes provide protection against different but related viruses. A less than ideal match may result in reduced vaccine effectiveness against the virus that is different from what is in the vaccine, but it can still provide some protection against influenza illness." In addition, the flu vaccine contains three or four flu viruses (depending on the type of vaccine received), so even when there is a less than ideal match or lower effectivness against the virus, the vaccine may protect against the other viruses. ❖

Manufacturer News

Second Octapharma Octagam 10% Manufacturing Site Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved Octapharma's manufacturing facility in Vienna, Austria, for the production of Octagam 10% (immune globulin intravenous [human] 10% [100 mg/mL] liquid preparation), which became available in the U.S. in October. This approval means that Octagam 10% can now be manufactured for the U.S. market at FDA-licensed facilities in both Stockholm and Vienna.

In July, FDA approved Octagam 10% for the treatment of adults with chronic immune thrombocytopenic purpura, a platelet disorder that can result in easy or excessive bruising and bleeding. Octapharma has been marketing Octagam 5% (immune globulin intravenous [human] 5% [50 mg/mL] liquid preparation) to treat primary humoral immunodeficiency since 2004. Octagam 5% is also manufactured at the FDA-licensed

manufacturing facilities in Stockholm and Vienna.

"The FDA approval of Octapharma's Vienna manufacturing site for Octagam 10% is great news for patients, as it will help facilitate product availability and enhances production flexibility," said Flemming Nielsen, president of Octapharma USA. "Octapharma owns six manufacturing facilities internationally, which all utilize the latest technology and strict quality control processes." ❖

Conference

Biosimilars 20/20 Conference Scheduled for June

The Biosimilars 20/20 Conference, a two-day event that will provide an indepth look into the future of the biosimilars market and address challenges of implementation, is scheduled for June 3 and 4 at The Hub in Philadelphia, Pa. The conference will open with a session featuring an examination and five-year projections of the expected sequence of biosimilar approval for parent drugs. It will also outline key opportunities expected to emerge during biosimilars' first five years of market entry in the U.S., as well as analyze trends in Europe. Additional sessions will address perspectives from physicians and payers, the value and means of patient education, interchangeability, legal/regulatory aspects, biosimilars in the market, research and development, health information technology and its impact on biosimilars, and more. More information about the conference can be found at biosimilars.specialtycme.org. ❖

People and Places in the News

EXPANSIONS

FDA has approved Merck's new class of cancer drugs, Keytruda, for patients with advanced **melanoma** who have exhausted other therapies. Keytruda was given accelerated approval, allowing it to reach the market without the three typical phases of clinical trials needed to show a drug can prolong lives.

FACILITY

Australian specialty biotechnology firm CSL has opened the **CSL Behring biotechnology manufacturing facility** in Broadmeadows, Melbourne. The new facility will be used for producing novel **recombinant therapies** on a large scale for international clinical trials. CSL's recombinant factor development programs, which include the AFFINITY trial and the PROLONG trial for the study of therapies to treat hemophilia A and B, respectively, are central to its long-term growth plans. The company said that several candidates in these trials are showing promise, including rVIII-SingleChain, rIX-FP, and rVIIa-FP. The company has more recently developed specialist capabilities in recombinant-based research, adding to its long-standing expertise in plasma protein therapeutics. Currently, the company's R&D pipeline includes recombinant therapies for a range of rare and serious diseases, including bleeding disorders, inflammatory conditions and cancer. The first therapy to be manufactured in the new facility will be a novel blood clotting factor (rVIIa-FP) for the treatment of hemophilia. The company expects to start clinical trials of rVIIa-FP in patients later in 2014 in the U.S., Europe and Australia. ❖

Medicines

ADMA Biologics' IVIG Product (RI-002) Receives Positive Phase III Results

ADMA Biologics has received positive results on the primary and secondary endpoint evaluations from the Phase III trial for its intravenous immune globulin (IVIG) product RI-002 to treat primary immunodeficiency disease (PI). The multi-site study treated 59 PI patients with RI-002, which resulted in a total of 93 days (1.66 days per patient per year) lost from work or school due to infection; only one hospitalization due to an infection of only five days; and IgG trough levels above those required by the U.S. Food and Drug Administration (FDA) for IVIG products. In addition, there was a marked increase in all of the measured specific anti-pathogen antibodies in subjects with the greatest increase (5.3-fold) seen in the level of neutralizing antibody titers to respiratory synctial virus (RSV). The safety profile was comparable to that of other IG products.

"These Phase III results suggest that RI-002 and its unique antibody profile containing standardized high levels of anti-RSV neutralizing antibodies may demonstrate an improvement in certain clinical outcomes," said James Mond, MD, PhD, ADMA Biologics' chief medical and scientific officer. "We believe that the data from the primary and secondary outcomes analyses will enable ADMA to differentiate RI-002 from other IVIG products and offer clinicians and patients a promising alternative to current therapies for the immune deficient population." ADMA is currently assembling its Biologics License Application for planned submission to FDA during the first half of 2015. ❖

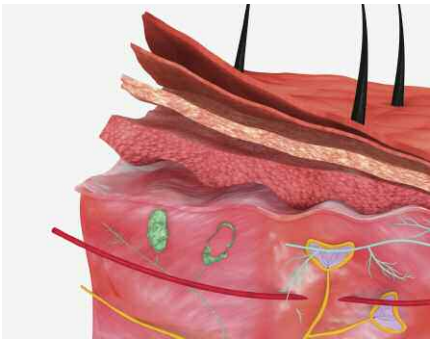
Research

New Needle-Free Vaccine Stimulates Immune Response

Recent research has found a new approach to stimulate the skin immune response to fight various pathogens with an easy-to-use needle-free vaccine.

Researchers at Charité-Berlin, Germany, and UPMC University Paris, Sorbonne Universités have been working together for 10 years to determine how to use the skin immune system to develop a new, non-invasive vaccination method. According to Annika Vogt, a researcher involved in the work from the Department of Dermatology & Allergy at Charité-Berlin and UPMC University Paris, "In this study, we show how a painless method helps such vaccines cross the skin. The method 'wakes up' skin immune cells so that they are ready to catch the vaccine and generate an immune response."

To make this discovery, Vogt and colleagues treated natural skin samples



with a novel method called cyanoacrylate skin surface stripping (CSSS). Then, they applied to the skin surface 200 nm particles that reflect the size of viruses and engineered particulate vaccines and used microscopy to compare the penetration of the particles. They found that the CSSS method enhanced the penetration of the particles to the deeper skin layers, especially to the hair follicles, and activated skin dendritic cells, which are key players in the orchestration of the skin immune system.

The results of their research suggest that the combination of an adequate skin treatment with a vaccine specifically designed to target skin immune cells could become a powerful tool for mass vaccination. And, combined with conventional injections, such skin vaccination could help in generating broader, more powerful responses in the fight against severe, chronic viral infections such as HIV. "If we learn how to better reach and communicate with skin immune cells from the outside, we would be able to develop new tools for the treatment of allergies, inflammatory skin diseases or skin cancer," said Vogt.

The research was published in the January 2015 issue of *Experimental Dermatology*. ❖

Insurance

Limiting Spending for Some Medical Services Increases

A growing number of employers and insurers are limiting how much they'll pay for certain medical services, according to a recent study. The approach, known as reference pricing, is being adopted by a growing number of very large companies, according to benefits consultant Mercer's annual employer health insurance survey. The percentage of employers with 10,000 or more employees that used reference pricing grew from 10 percent in 2012 to 15 percent in 2013, the survey found. Among employers with 500 or fewer workers, adoption was flat at 10 percent in 2013, compared with 11 percent in 2012.

An example of this is the California Public Employees' Retirement System (CalPERS), which began using reference pricing for elective knee and hip replacements, two common procedures for which hospital prices varied widely without discernible differences in quality, says Ann Boynton, CalPERS' deputy executive officer for Benefits Programs Policy and Planning. Working with Anthem Blue Cross, CalPERS set $30,000 as the reference price for those two surgeries in its preferred provider organization plan. Members who get surgery at one of the 52 hospitals that charge $30,000 or less pay only their plan's regular cost-sharing. But, if a member chooses to use an in-network hospital that charges more than the reference price, they're on the hook for the entire amount over $30,000, and the extra spending doesn't count toward their annual maximum out-of-pocket limit, says Boynton.

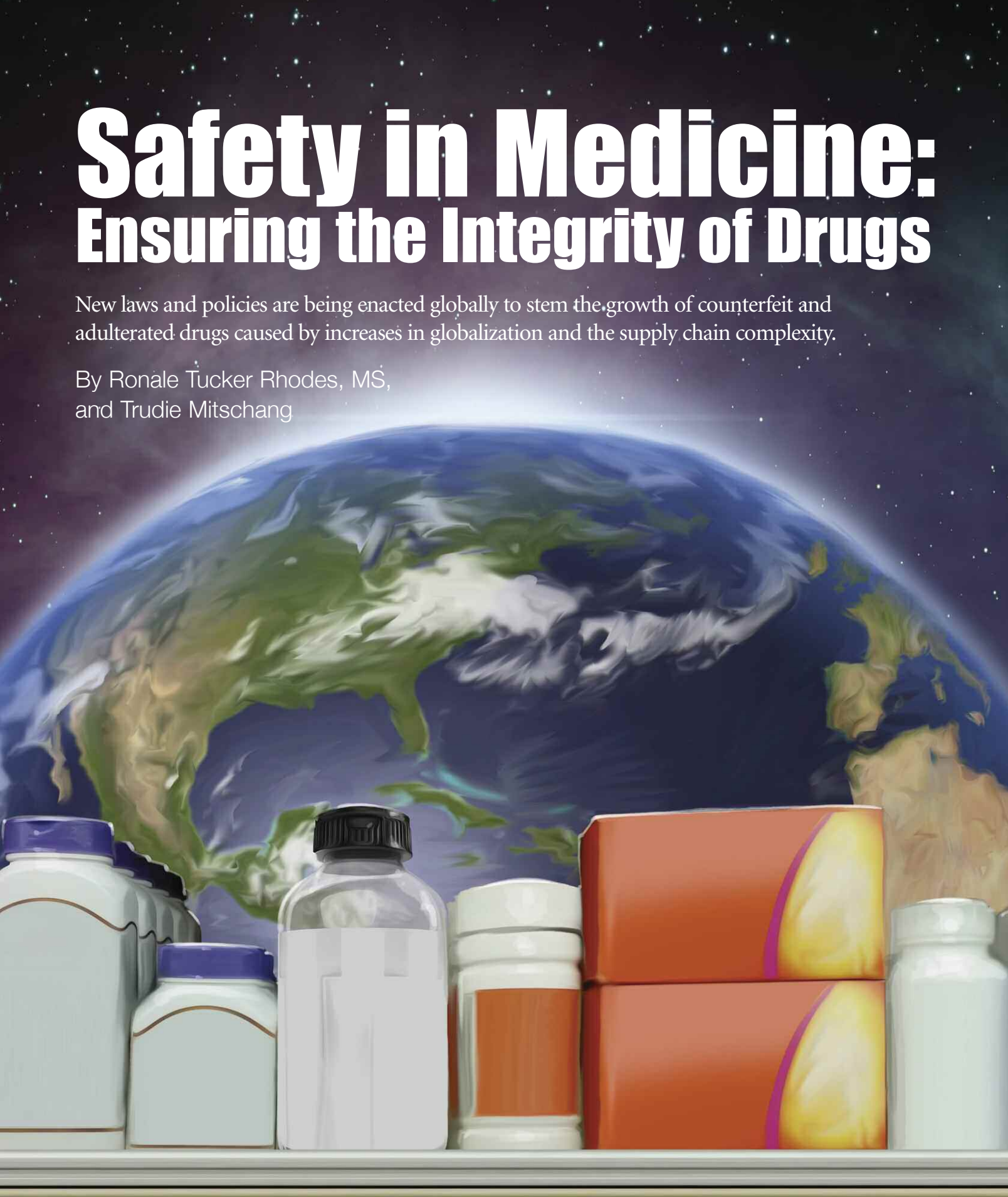
Experts say that reference pricing is most appropriate for common, non-emergency procedures or tests that vary widely in price but are generally comparable in quality. And, proponents say that because research has generally shown that higher prices for medical services don't equate with higher quality, setting a reference price steers consumers to high-quality doctors, hospitals, labs and imaging centers that perform well for that price. Yet, while others point out that reference pricing doesn't necessarily save employers a lot of money, a study released in October by the National Institute for Health Care Reform examined the 2011 claims data for 528,000 autoworkers and their dependents, analyzing roughly 350 high-volume and/or high-priced inpatient and ambulatory medical services, and found overall potential savings was 5 percent.

Reference pricing is allowed under the Affordable Care Act. But, the administration says it will continue to monitor the practice and may provide additional guidance in the future. ❖

Safety in Medicine: Ensuring the Integrity of Drugs

New laws and policies are being enacted globally to stem the growth of counterfeit and adulterated drugs caused by increases in globalization and the supply chain complexity.

By Ronale Tucker Rhodes, MS, and Trudie Mitschang



The path drugs must travel to reach a patient, known as the supply or distribution chain, is a complicated one that too often results in adulteration and counterfeiting, posing a serious threat to public health and tragic consequences around the world. The supply chain can be split into two parts. The upstream chain is the path each active and inactive ingredient and their chemical components must travel to reach the manufacturer that creates the finished drug. The downstream chain includes the repackagers, wholesale distributors, associated storage and transport companies, and the dispensers, which are independent community or chain pharmacies, hospitals or other healthcare facilities, and physicians' offices, that distribute the drugs to patients.[1] What happens at each step in these chains is directly linked to the integrity of the drugs.

Adulteration happens frequently in the U.S. due to contamination, the wrong doses or release mechanisms, or product mix-ups or mislabeling. In a study published in the *Archives of Internal Medicine* in 2012, after analyzing eight years of data from the U.S. Food and Drug Administration's (FDA's) Enforcement Reports and the MedWatch Safety Alert database, records showed 1,734 drug recalls from 2004 to 2011, 91 of which were tagged Class I recalls, meaning they had the greatest likelihood to cause patients serious harm, and even death. Of those recalls, 34 percent affected more than 100,000 units of a drug, and 64 percent had been distributed nationwide.[2]

According to the World Health Organization (WHO), global sales of counterfeit medicines in the marketplace and from online pharmacies represented an estimated $431 billion in 2012, and nearly 84 percent ($359 billion) had a direct impact on public health. Counterfeit formulations can range from random mixtures of inactive, ineffective preparations to harmful or even deadly concoctions, and all pose a very real threat to public health.[3] "We've made progress in terms of awareness, but there is still a lot that needs to be done, including federal legislation and more education for both healthcare professionals and consumers," says Katherine Eban, investigative journalist and author of *Dangerous Doses*, an in-depth exposé on counterfeiting operations within the pharmaceutical supply chain. "Drug counterfeiting is a problem that is only going to get bigger as time goes on."[4]

Bad Drugs in Recent News

Supply chain safety made headlines in 2013, and not for positive reasons. In a well-publicized story, GlaxoSmithKline announced a recall of its asthma drug Ventolin after its contract manufacturer said that the syrup bottles might have been contaminated with glass particles. Also in 2013, *The New York Times* reported that the U.S. suffered shortages of injectable drugs due to quality failures at large manufacturer plants.[4]

Between 2010 and 2012, six of the major manufacturers of sterile injectable drugs — which the federal government subjects to rigorous inspection, as opposed to compounding pharmacies that are generally overseen by states — have been warned by FDA about serious violations of manufacturing rules. Four of them closed factories or significantly slowed production to fix the problems. Nearly a third of the industry's manufacturing capacity was off line because of quality issues, according to a congressional report.[5]

Shutdowns contribute to a shortage of critical drugs, and compounding pharmacies typically step in to fill the gap as medical professionals look for alternative sources. But, compounding pharmacies have been linked to several serious health scares over the years. For instance, in what "60 Minutes" described as "the worst pharmaceutical disaster in decades," 48 people died in a meningitis outbreak that was traced back to contaminated production in a Massachusetts compounding pharmacy.[4] The types of fungus believed to be responsible for the deadly meningitis outbreak are common, found indoors and outdoors, and most people harmlessly breathe them in and the lungs filter them out. These fungi, which were identified as Aspergillus and Exserohilum, were deadly because they were injected directly into the bloodstream. There are many ways the fungi could have gotten inside the compounding pharmacy, but outside experts speculate that dirty conditions, faulty sterilizing equipment, tainted ingredients or sloppiness on the part of employees was to blame. In 2011, there were three similar incidents: At least 33 patients suffered fungal eye infections traced to products made by a compounding pharmacy in Ocala, Fla.; at least a dozen Florida patients were blinded or damaged in an outbreak linked to a compounder in Hollywood, Fla.; and the deaths of nine Alabama patients were attributed to a tainted intravenous nutritional supplement provided by a compounder in Birmingham, Ala.[5]

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After compounding pharmacies, counterfeiters step in to fill

the void. In early 2013, FDA warned doctors that a fake version of the cancer drug Altuzan was being distributed in the U.S. This particular counterfeit contained no active ingredients, making it potentially deadly for patients seeking this life-saving therapy. In 2012, a counterfeit version of the cancer drug Avastin was widely distributed in the U.S., and a fake version of the attention deficit hyperactivity disorder drug Adderall, in high demand because of a shortage, arrived in the U.S. through unethical Internet pharmacies. Avastin is an injectable drug, used often in combination with chemotherapy, to treat patients with colon, lung and other cancers. In the U.S., a 400-milligram vial of the authentic drug — the size that was counterfeited — costs $2,400, according to Genentech. The counterfeit Avastin was made of salt, starch and other chemicals, and packaged in counterfeit boxes that included French writing and Roche's name. In the U.S., the genuine product's boxes are labeled in English and bear the Genentech imprint.[6]

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The most prolific counterfeiting incident that occurred during the past 10 years involved Lipitor in 2005. In that case, three businesses and 11 individuals were charged in connection with a $42 million conspiracy that involved the distribution of counterfeit Lipitor manufactured in Costa Rica and misbranded Lipitor smuggled into the U.S. from South America, as well as for distributing stolen drugs. As a result of this case, a massive and unprecedented recall of 18 million Lipitor tablets was initiated by one of the distributors.[7]

Problems with the Supply Chain

There are many participants in the drug supply chain, including the manufacturers, wholesale distributors, repackagers, third-party logistics providers and dispensers. Manufacturers produce the drug product. Wholesale distributors sell drugs to persons other than a consumer or patient. There are three types of wholesale distributors: primary wholesale distributors that get the drug products directly from the manufacturer and sell them to other wholesalers or dispensers; authorized distributors of records that have relationships with manufacturers that are ongoing and include a written agreement specifying which products they will distribute and for which time period; and secondary wholesale distributors that acquire drug products from a wholesale distributor rather than directly from a manufacturer, some of which focus on geographic regions and others that focus on specialty markets. Repackagers remove a drug from its container and place it in another, usually smaller, container for sale to a distributor or dispenser. Third-party logistics providers take temporary physical possession of a drug, such as during transport or warehousing, under contract with manufacturers, distributors or dispensers, but they don't assume ownership of a drug. And, dispensers (independent community pharmacies, retail chain pharmacies, hospitals or healthcare facilities, doctors' offices, etc.) provide the drug to the consumer/patient.[1] At each of these stages in the supply chain, there are threats that are derived from globalized production, intentional adulteration and counterfeiting.

The biggest issue with the upstream supply chain today is globalized production. FDA-regulated products originate from approximately 300,000 foreign facilities spread across more than 150 countries. Approximately 80 percent of the manufacturing sites for the active pharmaceutical ingredients used in FDA-approved drugs are outside the U.S.[8] (compared with 100 percent domestic production 15 years ago[3]), and 40 percent of finished drugs consumed in the U.S. are manufactured overseas.[8] The active ingredients are primarily made or processed by approximately 10,000 companies located in India and China, where regulatory lapses have often proved fatal.[3] Added to this is the increasing volume of drugs. The number of FDA-regulated drug shipments has more than tripled from eight million import entry lines per year a decade ago to 28 million entry lines in fiscal year 2012.[9]

According to Howard Sklamberg, deputy commissioner for Global Regulatory Operations and Policy at FDA, "In addition to the sheer volume of imports and foreign facilities, there has also been an increase in the variety of sources, shippers, methods of transportation and supply chain complexity of products. Combined, these factors create great challenges to FDA and industry in ensuring that all drugs and drug components are high quality and travel safely throughout their complex supply chains." These factors also provide opportunities for criminals to adulterate or counterfeit drugs.[10]

First, however, it should be noted that the definition of adulterated, or substandard, drugs and counterfeit drugs varies from country to country. In some countries, there is no distinction between counterfeit and adulterated drugs. That's not true in the U.S. The United States Federal Food, Drug and Cosmetic Act defines a counterfeit drug as "a drug which, or the containers or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, of a drug manufac-

turer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor."[11] Conversely, the act defines an adulterated drug as one that "fails to conform to compendial standards of quality, strength or purity." These standards include potency, sterility, dissolution, weight variation and content uniformity.[12]

Regardless of how these drugs are defined, growth in counterfeiting and adulteration "may be spurred by the economic incentives provided by an increasing volume of drugs, longer (often international) supply chains, the development of technologies that make it easier to counterfeit drugs, the involvement of international organized crime, and the ability to sell drugs directly to consumers through the Internet without face-to-face contact," says Sklamberg. "This growth also is exacerbated by the relatively low criminal penalties for distribution of adulterated, unapproved or misbranded drugs provided under the Federal Food, Drug and Cosmetic Act, compared to other types of crimes."[10]

Drugs are high-value items, and the demand for them is infinite. For the counterfeiter, the cost of ingredients can be very low if cheap substitutes are used or if they are omitted altogether. In addition, producing counterfeit drugs doesn't require building a huge infrastructure, and there are no overhead costs for quality assurance to meet good manufacturing practices standards. When prices of medicines are high and price differentials between identical products exist, there is an even greater incentive to supply cheap counterfeit drugs.[11] And, drug shortages are very attractive to counterfeiters. Many offer medications that are back-ordered or unavailable according to the manufacturer at mark-ups averaging 650 percent of the standard price for the medication, but exceeding 4,500 percent for some medicines needed to treat the critically ill.[13] Organized criminal networks are attracted by the huge profits to be made through pharmaceutical crime. They operate across national borders in activities that include the import, export, manufacture and distribution of counterfeit and illicit medicines.[14]

Along the pharmaceutical supply chain, opportunities arise for drug theft or diversion, or the introduction of counterfeit drugs. Theft of prescription drugs is a growing problem in the U.S., and the reasons are manifold, according to Partnership for Safe Medicine's board member Dr. Bryan Liang, the executive director of the Institute of Health Law Studies at California Western School of Law. "Pharmaceuticals are small and easy to store, have big margins, and limited potential for being caught," explains Dr. Liang, who describes how stolen, genuine drugs are used to "salt" shipments of counterfeits. "Salting — the process of placing real stuff [or diverted stuff] and mixing with counterfeits creates an illusion of legitimacy if inspected. Opening any box or storage container, one sees real stuff, and if one tests it, it comes out with active pharmaceutical ingredients and the real deal because it is. But the rest of the shipment is not, and hence one can salt a lot of shipments with diverted stuff."[15]

Drug diversion is the illegal distribution or abuse of prescription drugs or their use for unintended purposes. Drug theft and diversion may occur at any point as prescription drugs are distributed from the manufacturer to wholesale distributors, to pharmacies and, ultimately, to the patient. Cases of drug diversion vary widely, but the most common types include patient diversion, doctor shopping, illegal Internet pharmacies, drug theft, prescription pad theft and forgery, and illicit prescribing.[16]

Many Internet pharmacies sell drugs that are counterfeit, contaminated or otherwise unsafe. Unfortunately, consumers continue to be enticed by the availability of hard-to-find drugs and gray market pricing available through fake online pharmacies. Drugs purchased online from countries outside the U.S. can cost anywhere between 80 percent and 90 percent less than those sold in reputable U.S. pharmacies. The problem is that these drugs often come from third-world countries where there is a high incidence of counterfeiting and adulteration. And, even when consumers purchase from neighboring countries like Canada, those drugs might actually be coming from third-world countries. For instance, a 2005 FDA drug bust examined nearly 4,000 packages at airports in New York, Miami and Los Angeles, and found that 85 percent of the drugs ordered from what customers believed were Canadian pharmacies actually came from 27 other countries.[4]

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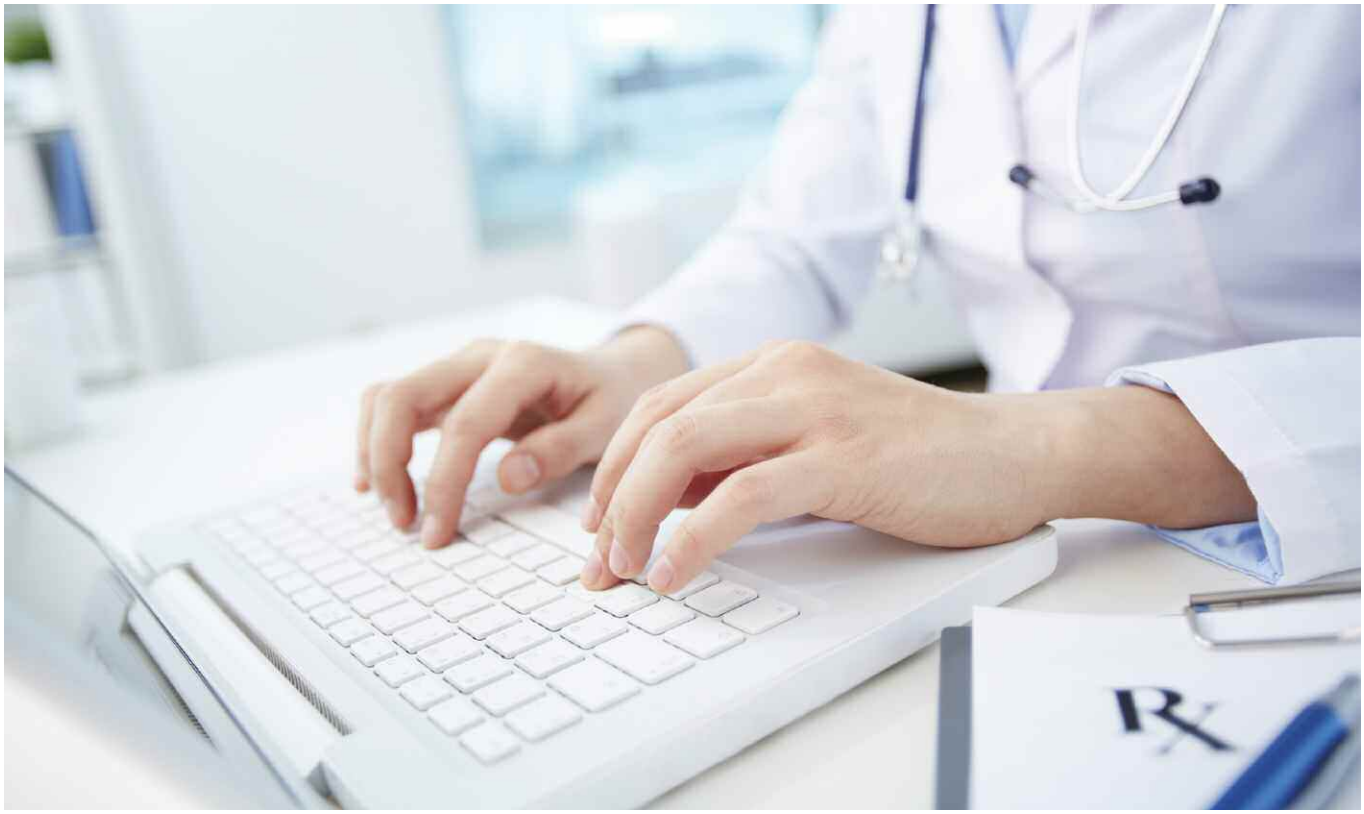
The Role of Government

Governments play a large role in policing the supply chain. In the U.S., FDA is making it a priority to investigate reports of counterfeit products through its Office of Criminal Investigations (OCI). As a result of its investigations, FDA is educating consumers and the healthcare community about the risks of, and minimizing exposure to, counterfeit and substandard drug products through recalls, public awareness campaigns and other steps. One such campaign by FDA is "Know Your Source." This program urges healthcare professionals to buy prescription drugs only from wholesale drug distributors



licensed in their states to reduce the risk of giving unsafe or ineffective drugs to patients.[17]

FDA is also working with U.S. drug supply chain stakeholders to improve its ability to prevent, detect and respond to threats of counterfeit and substandard drugs, and it is developing standards for tracking and tracing prescription drugs. FDA scientists have developed and have been testing a counterfeit detection device, CD-3, at U.S. ports of entry and elsewhere for use by FDA investigators to check for suspected counterfeit products. CD-3 is a battery-operated, hand-held tool that works much like a high-powered flashlight, and it doesn't require scientific or technical training to operate.

Internationally, all governments play a role, but some regions and the International Crime Police Organization (INTERPOL) have made significant strides. WHO estimates that less than 17 percent of its member states have well-developed drug regulations, and a third have little to no capacity to execute those regulations. Some 20 percent of nations have little to no legal provisions or capacity for regulation of the safety and reliability of medicines. Combined, 50 percent are incapable of ensuring the health of their public in terms of drug safety.

However, two regions have pooled their resources and skills to help solve the capacity issue. In Asia, the Pan American Health Organization is building laboratory centers to service the region for drug and active pharmaceutical ingredient safety analysis, and it is seeking to harmonize regulatory and enforcement laws across the region to allow transparency in surveillance and enforcement data, shared investigation power and cross-border tracking of fraudulent or contaminated drugs. In March 2012, the East African Community Medicines Registration Harmonization program was launched to encourage transparent exchange among its regulators and create financial instruments, potentially derived from stiff penalties imposed on violators, that can be used to bolster legal, inspection and enforcement capacities.[3]

In March 2013, INTERPOL, the world's largest police organization, announced its partnership with 29 of the world's largest pharmaceutical companies to create an enhanced pharmaceutical crime program to combat counterfeit medicines.[6] "With no country, no drug, no medical product immune from counterfeiting, a global effort is needed to combat this threat, which puts the lives of millions of people at risk every single day," said then-INTERPOL Secretary General Ronald K. Noble. "This support from a group of 29 companies from the pharmaceutical industry forms a bridge between the public and private sectors and will assist INTERPOL and each of its 190 member countries to more effectively tackle the problem of medical product counterfeiting."

The three-year deal will see the creation of INTERPOL's Pharmaceutical Crime Program to further build on the work of its Medical Product Counterfeiting and Pharmaceutical Crime (MPCPC) unit. According to INTERPOL, an essential part of the program is to raise public awareness of the dangers of fake drugs, particularly for people buying medicines online. WHO estimates that in more than 50 percent of cases, medicines purchased over the Internet from illegal sites that conceal their physical address have been found to be counterfeit, yet most consumers remain ignorant of this fact.[4]

Both FDA and INTERPOL are addressing illegal Internet pharmacies. Both participate in the annual International Internet Week of Action, or Operation Pangea, a global cooperative effort in partnership with international regulatory and law enforcement agencies, to combat the online sale and distribution of potentially counterfeit and illegal medical products. INTERPOL reports that as part of the 2013 annual effort, the partnership took action against more than 13,700 websites, which included the issuance of regulatory warnings and the seizure of offending websites and more than $36 million worth of illegal medicines worldwide.

OCI, in coordination with the U.S. Attorney's office for the District of Colorado, seized and shut down 1,677 illegal pharmacies' websites after purchasing drugs undercover from the sites, all of which advertised selling Canadian drugs. The agents, who were able to purchase prescription drugs without a prescription, received drugs directly from India and Singapore, and those drugs were not approved for use in the U.S., contained no directions for use and were often in unfamiliar dosage forms and of unknown quality and purity.[10]

INTERPOL has also executed criminal sweeps that have identified and removed thousands of websites engaged in illegal distribution of medicines. One website host company, GoDaddy.com, has removed 80,000 websites in two years, which is estimated to represent about 2 percent of total illegal web medicine operations. In addition, Google, Microsoft and GoDaddy are working to form a consortium that can quickly identify and remove online retailers engaged in dangerous medicine distribution.[3]

Grassroots Efforts

Healthcare professionals who purchase drugs also play a crucial role in curbing the distribution of counterfeit and substandard drugs. In 2012, the American Pharmacists Association (APhA) established a task force consisting of members of the APhA Academy of Pharmaceutical Research and Science and the APhA Academy of Pharmacy Practice and Management to assess pharmacists' roles in preventing patients from receiving counterfeit medicines. The task force published a number of recommendations, including 1) purchasing medications from known, reliable sources, 2) warning patients of the dangers of purchasing medications over the Internet, 3) confirming with distributors that products were purchased from manufacturers and other reliable sources, 4) monitoring counterfeit product alerts, 5) examining products for suspicious appearance, 6) working with the pharmaceutical industry, distributors and FDA to close gaps in the supply chain, especially for drugs in short supply, 7) using scanning technology in the pharmacy as part of a prescription verification process, 8) educating themselves, co-workers and patients about the risks of counterfeit medications, and 9) reporting suspicious medications to FDA, distributors and manufacturers.[18]

Also in 2012, the Pharmaceutical Distribution Security Alliance (PDSA) issued draft legislation language titled the Pharmaceutical Traceability Enhancement Code (RxTEC) Act, which would create a comprehensive system involving a machine-readable graphic on individual packages to support lot-level tracing of a product to its immediate previous and subsequent owners. The system would be implemented incrementally with manufacturer, repackager, wholesale distributor and dispenser requirements beginning three, four, five and six years, respectively, after enactment.[1]

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In August 2013, the National Association of Boards of Pharmacy (NABP) released a white paper titled "Wholesale Drug Distribution: Protecting the Integrity of the Nation's Prescription Drug Supply." Its intent is to address the problem of counterfeit drugs, foreign unapproved drugs and drugs diverted from the supply chain. To help safeguard the supply chain, NABP implemented updated criteria for the association's Verified-Accredited Wholesale Distributors (VAWD) accreditation program, including revised criteria allowing virtual wholesale distributors to qualify for VAWD. And, NABP stressed its support for state efforts to strengthen and work toward uniformity in prescription drug distribution laws in order to eliminate the regulatory gaps that leave the supply chains susceptible to suspect wholesalers.[19]

The Laws

Laws concerning drug integrity date back to 1906. However, the first significant law relating to the drug supply chain was the Prescription Drug Marketing Act of 1987, which was amended by the Prescription Drug Amendments of 1992. This law requires wholesalers that do not have an ongoing relationship with a drug manufacturer to provide a pedigree of a drug before wholesale distribution.[20]

Later, other laws were enacted. In 2007, the FDA Amendments Act required "the development of standards and identification and validation of effective technologies to secure the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded or expired drugs." In compliance, FDA issued *Draft Guidance for Industry Standards for Securing the Drug Supply Chain — Standardized Numerical Identification for Prescription Drug Packages* in 2009, with final guidance issued in March 2010.[1]

In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act that provided FDA with new authorities to help secure the safety and integrity of drugs imported into and sold in the U.S. For example, "the law provides FDA with the authority to administratively detain drugs believed to be adulterated or misbranded, and the authority to destroy certain adulterated, misbranded or counterfeit drugs offered for import. The law also requires foreign and domestic companies to provide complete information on threats to the security of the drug supply chain and to improve current registration and listing information, making sure FDA has accurate and up-to-date information about foreign and domestic matters."[10]

In the absence of a stronger federal pedigree law, Florida and California enacted their own pedigree laws in 2003 and 2004, respectively. Florida's law requires a paper record for legend drugs (those that are subject to the federal Food, Drug and Cosmetic Act) beginning July 1, 2006. The pedigree must include the drug's amount, dosage form and strength, lot numbers, name and address of the drug's owner and its signature, shipping information and certification that each individual receiving the drug has authenticated the pedigree papers. California's law requires an electronic record, or an e-pedigree. The e-pedigree must include the drug's source, trade or generic name, quantity, dosage form and strength, transaction date, sales invoice number, container size, number of containers, expiration dates, lot numbers, business name, address and federal manufacturer registration number or a state license number of each owner of the drug and drug shipping information, and a certification that the information in the pedigree is "true and accurate." California is implementing its e-pedigree requirements over a span of three years, starting in 2015 when 50 percent of manufacturers' products must be in compliance with the law, with the remaining 50 percent in compliance by 2016. California's law does stipulate that if a federal law is implemented, that law will supersede the state law.[20]

And, that has just happened. In November 2013, President Obama signed national e-pedigree legislation into law. The Drug Quality and Security Act (DQSA) outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the U.S. By 2023, the system will facilitate the exchange of information at the individual package level about where a drug has been in the supply chain, including enabling verification of the legitimacy of the drug product identifier down to the package level, enhancing detection and notification of illegitimate products in the drug supply chain, and facilitating more efficient recalls of drug products.

The DQSA contains two parts: Title I applies to the compounding of human drugs pursuant to a prescription, while Title II pertains to the tracking and tracing of these drugs.

Title I of the DQSA distinguishes compounders engaged in traditional pharmacy practice from those making large volumes of compounded drugs without individual prescriptions; defines FDA's role in oversight of outsourcing facilities; offers providers and patients information about compounded drugs; and clarifies current federal law regarding pharmacy compounding. More specifically, traditional pharmacies will continue to be primarily regulated by state boards of pharmacy. But, compounders that wish to practice outside the scope of traditional pharmacy practice can register as outsourcing facilities subject to FDA oversight in much the same way as traditional manufacturers. Providers and patients have the option of purchasing products from outsourcing facilities that comply with FDA quality standards.[4]

On Jan. 1, Title II of the DQSA, the Drug Supply Chain Security Act (DSCSA), took effect. However, FDA will not enforce implementation of the product tracing requirements until May 1 for manufacturers, repackagers and wholesale distributors. The requirement will go into effect on July 1 for dispensers.[21] All trading partners will be required to store the transaction information, history and statements for at least six years after the transaction date. By Nov. 27, 2017, manufacturers will be required to put a unique product identifier (a two-dimensional bar code or a radio frequency identification tag) on certain prescription drugs that can be read electronically. Repackagers will need to comply with this requirement by Nov. 27, 2018. In addition, manufacturers and repackagers will be obligated to maintain product identifier records for not less than six years.[22] Trading partners can choose, based on their facility's requirements, to maintain their records by 1) keeping printed packing slips, 2) maintaining shipping notification emails, 3) registering with a cloud-based technology platform like the TraceLink Life Sciences Cloud or 4) through electronic data interchange to receive advanced shipping notifications.

Profilnine®
Factor IX Complex

Compare the price of PROFILNINE to other complex concentrates

PROFILNINE is a mixture of vitamin K-dependent clotting factors IX, II, X, and low levels of VII and is stable for 3 years at room temperature (provided that the storage temperature does not exceed 25 °C [77 °F]).

Potency	Diluent Size	NDC Numbers
500 IU FIX Range	5 mL	68516-3201-1
1000 IU FIX Range	10 mL	68516-3202-2
1500 IU FIX Range	10 mL	68516-3203-2

Important Safety Information

PROFILNINE® (factor IX complex) is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B). PROFILNINE contains non-therapeutic levels of factor VII and is not indicated for use in the treatment of factor VII deficiency.

Because PROFILNINE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The use of factor IX concentrates has historically been associated with development of thromboembolic complications, and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis, or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. PROFILNINE should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

After repeated treatment with PROFILNINE, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. As with intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, or manifestation of allergic reactions.

During post-approval use of PROFILNINE, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis of disseminated intravascular coagulation (DIC) have been reported.

Do not administer PROFILNINE at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Please see brief summary of PROFILNINE Package Insert on adjacent page.

Mix2Vial® is a registered trademark of Medimop Medical Projects, Ltd., a subsidiary of West Pharmaceutical Services, Inc.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

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GRIFOLS

Profilnine®

Factor IX Complex

Solvent Detergent Treated/Nanofiltered

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

DESCRIPTION

Factor IX Complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine does not contain heparin and contains no preservatives. Profilnine contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.

Profilnine is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment have been incorporated into the Profilnine manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step. The ability of the manufacturing process to eliminate virus from Profilnine was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvovirus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloped viruses.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo[a]	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Non-Env	Hepatitis B	NT	NT	≥ 5.3

[a] Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

INDICATIONS AND USAGE

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).

Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such products can potentially transmit disease: therefore the risk of infectious agents cannot be totally eliminated. The physician must weigh the risks and benefits of using this product and discuss these issues with the patient. Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX complex concentrates is recommended.

The use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. Profilnine should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Exercise caution when handling Profilnine due to the limited risk of exposure to viral infection. Discard any unused Profilnine vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse components.

Information for Patients

After repeated treatment with Profilnine, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. Patients must be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients must be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care if these symptoms occur.

Pregnancy Category C

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

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 have not been established. However, across a well controlled half-life and recovery clinical trial in patients previously treated with factor IX concentrates for Hemophilia B, the two pediatric patients receiving Profilnine responded similarly when compared with the adult patients.

ADVERSE REACTIONS

As with other intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling lethargy, hives, or manifestation of allergic reactions.

In addition, during post-approval use of Profilnine, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) have been reported. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

* Unit refers to International Unit in the labeling of Profilnine.

Rx only

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U.S. License No. 1694

3039440-BS
Revised: November 2013

By Nov. 27, 2017, manufacturers will be required to provide product tracing information in an electronic format for certain transactions.[23] However, by Nov. 27, 2023, all trading partners will need to be able to exchange transaction information, history and statements in an interoperable electronic manner.[22]

Also as of May 1, manufacturers, wholesale drug distributors, repackagers and many dispensers (primarily pharmacies) will be required to provide information about a drug and who handled it each time it is sold in the U.S. market; establish systems and processes to be able to verify the product identifier on certain prescription drug packages; quarantine and promptly investigate a drug that has been identified as suspect; and establish systems and processes to notify FDA and other stakeholders if an illegitimate drug is found. Wholesale drug distributors will be required to report their licensing status and contact information to FDA, which will be made available in a public database. And, third-party logistic providers will be required to obtain a state or federal license.[21]

Yet, despite these new laws, there is still the issue of inadequate penalties that needs to be addressed. The Federal Food, Drug and Cosmetic Act, which was enacted in 1938 and regulates civil and criminal penalties related to distributing counterfeit or adulterated drugs, has yet to be revised to increase penalties for counterfeiting and adulteration of drugs. As FDA's Sklamberg points out, "Given the high profit potential of trafficking in counterfeit and unapproved drugs and the relatively low penalties for noncompliance, bad actors still have incentives to find ways to circumvent the new requirements.… Title 18 Counterfeiting, designed to protect the trademark holder, carries with it a 20-year maximum penalty for counterfeit pharmaceuticals. However, risky conduct such as trafficking in foreign unapproved or adulterated drugs, carrying with it the same risk to the public health, is subject to a one- or three-year penalty — same risk to public health, dramatically different results."[10]

A Globalized Effort

As the threats posed by a globalized marketplace and the complexity of the supply chain continue to grow, more needs to be done to protect the public from counterfeit and adulterated drugs. Because of the high profits associated with illegal drug trafficking, this problem will likely never be eradicated. But, the new laws at the state and federal levels, and the grassroots efforts put forth by healthcare organizations, are steps in the right direction. Ultimately, it will take the joint efforts of all — government, healthcare organizations, prescribers, dispensers and patients — to protect consumers in America and abroad. ❖

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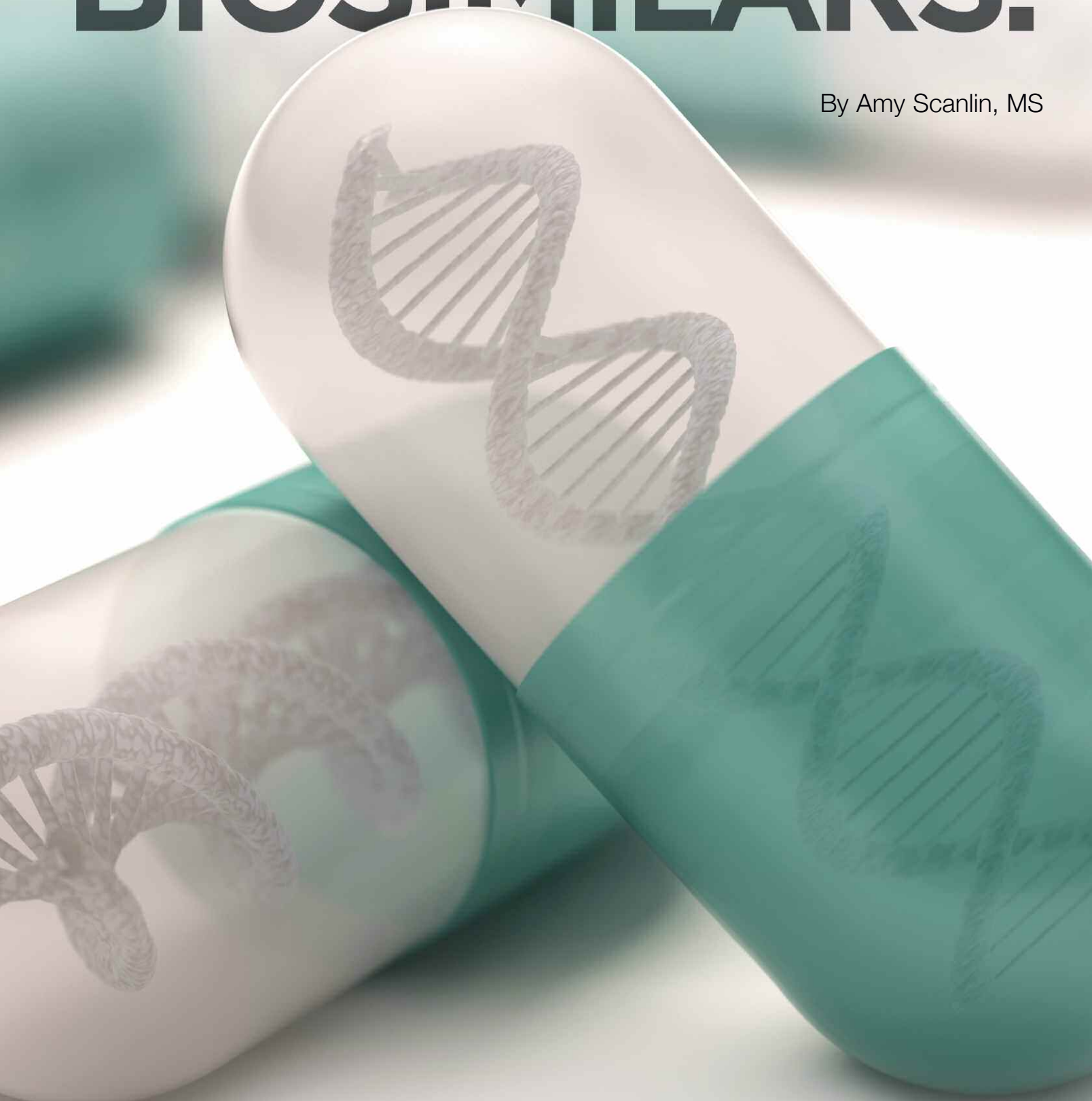
BIOSIMILARS:

By Amy Scanlin, MS



The Race for Approval

As the approval of biosimilars looms, debate continues over whether they should be substituted for biopharmaceuticals, how to legislate them and how they should be named.

While the scientific advances in the field of biologics move forward, so too does legislation to regulate many aspects of biosimilars and interchangeable biologics, although at a seemingly much slower pace. However, with 21 biologic products (biopharmaceuticals) losing their patent protection by 2019 in the U.S. alone,[1] the race for approval and development is gaining speed.

Sales in biologics, which include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins,[2] make up about a quarter of the $320 billion in drug sales in the U.S. annually,[3] and according to the Generic Drug Association, the rising costs of biologics are outpacing any other aspect of healthcare.

Thanks to the Biologics Price Competition and Innovation (BPCI) Act within the Patient Protection and Affordable Care Act, an abbreviated U.S. Food and Drug Administration (FDA) approval process for the licensure of biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product has been created.[4] The BPCI Act allows FDA to declare a biosimilar interchangeable provided that it is expected to produce the same results in all patients and, with continued use, the safety and efficacy risks are no greater if a patient were to be switched to a biosimilar than if they had stayed on the innovator drug.[1]

FDA defines biosimilars as "highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

While only one biosimilar product has been approved, a few more are under consideration and even more are in development stages. Approvals of biosimilars and subsequent marketplace competition are expected to have a significant impact, much like the approval of generics (a term that applies only to bioequivalents of an already approved small molecule drug), with savings ranging anywhere from $42 billion to $108 billion in the first 10 years alone.[5]

Are Biosimilars Interchangeable?

The fact that biologics are derived from living cells makes them, of course, incredibly complex, and unlike generic drugs, that complexity makes them impossible to replicate. Even nearly imperceptible changes to the cells when making a biosimilar can lead to variances in how a body responds to the drug.

According to the American Society of Health-Systems Pharmacists, infections and immune system disorders are the most common safety problems associated with biopharmaceuticals, although allergy, anaphylaxis and serum sickness are rare because of improvements in purity. Understandably, there is concern about switching from an innovator biopharmaceutical to a biosimilar because the safety profile for the biosimilar will likely be unclear at the time of FDA approval, and any potential adverse events are unlikely to be detected prior to marketing the product. However, the expectation is that most serious adverse events would likely be identified during the testing phase of the innovator product. Even so, due to the nature of biosimilars, any adverse events could differ from those of the innovator drug in clinically significant ways.[6]

While only one biosimilar product has been approved, a few more are under consideration and even more are in development stages.

Whether a biosimilar can be considered "interchangeable" with a biologic is a question of intense debate and is one factor driving the question of approvals. Kristofer Baumgartner, a spokesperson at FDA's Center for Drug Evaluation and Research (CDER), says, "There is an additional standard to meet for an interchangeable biological product. In addition to demonstrating biosimilarity, a manufacturer must show that

the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient. When a product will be administered more than once to an individual (as many biological products are), the manufacturer must also demonstrate that the risk in terms of safety or reduced effectiveness of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

The fact that biologics are derived from living cells makes them, of course, incredibly complex and impossible to replicate.

Still, Larry Lamotte, vice president of public policy at the Immune Deficiency Foundation (IDF), which serves immunodeficient patients who rely on treatment with the plasma product immune globulin (plasma products are one of the most complex biologics), urges caution: "The one thing we know is minute changes [in biosimilars] from a reference product can create differences in tolerability in patients. Our patients are already at increased risk of everything else in the world, and we would not want them running risks with a new drug. Biosimilars must meet the same safety requirements as their reference product."

The International Role in Biosimilars

For years, biosimilars have been approved for use in the European Union, Canada, Japan and other countries, but FDA has thus far been slow to respond in kind. FDA is looking at the issue of biosimilars not only in the U.S., but also how they are viewed and used internationally. Baumgartner explains that collaboration via forums with international regulatory colleagues is enabling discussions of potential areas of alignment on scientific approaches to biosimilar development in an effort to support multinational development programs. "For example," he says, "FDA collaborates with the European Medicines Agency (EMA) and Health Canada to encourage alignment on scientific approaches to biosimilar product development through the EMA-FDA-Health Canada Biosimilar Cluster. Under the Confidentiality Commitments, the regulatory agencies share experiences and best practices to provide biological product developers assurance, when possible, that data developed for one regulatory authority could be acceptable to another regulatory authority. Recently, Japan's Pharmaceutical and Medical Devices Agency (PMDA) asked to join the cluster. In addition, EMA and FDA can discuss and jointly advise biosimilar applicants on specific development programs through the Parallel Scientific Advice procedure when an applicant makes such a request."

Several regulatory agencies, including FDA, EMA and PMDA, are involved with the International Pharmaceutical Regulators Forum, chaired by the Korean Ministry of Food and Drug Safety, which has established a working group on biosimilars. The working group's goal "is to understand the legal requirements and constraints across many regulatory regions and determine the potential for alignment of scientific approaches."

"It is through these interactions that FDA, EMA and other regulatory agencies are exploring approaches to developing guidance that facilitates multinational development programs for biosimilar products by aligning scientific recommendations and, when possible, leveraging existing data," says Baumgartner.

There is expected to be high international demand for U.S. biosimilar products once processes have been finalized, approvals have been given and production is underway.

The Notification of Substitution Debate

The BPCI Act did not address notification, and it is an issue that is raising a heated debate. Therefore, due to a concern that the statutes applying to generic drugs may be misapplied to biosimilars that are not identical, some states are already expanding on their laws concerning pharmaceutical substitution. Since late 2013, 23 states have considered legislation that establishes standards for substitution of biosimilar products to replace original biologic products. As of this writing, only eight states have enacted statutes. Virginia was the first state to pass a law on biosimilars, with North Dakota following. California passed a bill that passed in both chambers but was then vetoed by the governor. Thirteen other states filed bills that did not pass. And, New Jersey carried over its 2014 bills to 2015.[7]

While the provisions of the state statutes differ, they do have several things in common:[7]

- FDA must first approve any substitution product as interchangeable for a biological product.
- The prescriber can prevent substitution by stating "dispense as written" or "brand medically necessary."
- The prescriber must be notified of any allowable substitution made at a pharmacy.
- The patient must be notified that a substitution has been made (and, in some cases, patient consent is required prior to the substitution).

• The pharmacist and physician must retain records of substituted biologic medications.

• The state must maintain a public list of permissible interchangeable products.

In some states, pharmacists who make a substitution in compliance with the law are provided immunity.

Groups that oppose notification requirements cite statistics that show states with patient consent laws for generic drugs typically have a 25 percent lower substitution rate than states that don't.[8]

The Naming Debate

There also is considerable debate concerning the naming of biosimilars, because a name can make or break a biosimilar's ability to be interchangeable with its innovator biologic. Once again, the BPCI Act did not specifically address how biosimilars would be named. And, groups on both sides of the argument are petitioning FDA to side with them as millions of healthcare dollars are at stake.

Currently, small molecule drugs and their generics carry the same United States Adopted Names (USAN) or International Nonproprietary Name (INN). However, it is still undetermined whether biosimilars will carry the same USAN/INN as their branded counterparts.[9]

On one side of the issue are those who are lobbying for the names to be the same. They say a unique name would be confusing to physicians, pharmacists and patients and could inhibit the prescribing of a biosimilar. In a letter to FDA in July, generic drug makers, Express Scripts and 30 other organizations argued that the INN, administered by the World Health Organization (WHO), has been used with biosimilars in Europe since 2006, as well as other parts of the world, and thus far, there have been no issues of traceability or pharmacovigilance. Not using the INN, they say, would make U.S. biosimilar product names different from those in the rest of the world.

On the other side of the issue are those who argue that a unique name should be given to biosimilars because they are, in fact, not identical. In August, specialty physicians urged FDA to not use the same names, citing the difficulty in copying biologics and, therefore, the difficulty in accurate traceability of adverse events. They argue that even though the products may be safe and effective, they also may differ. Those differences, however small, can have a significant impact on the patient's response. "It is absolutely necessary for names to be distinct and non-proprietary. You can't track adverse events without a distinct name," says Lamotte.

It will be up to FDA to determine if the INN will be used for biosimilars in the U.S. In 2006, FDA sent a position paper to WHO in favor of INN, but with distinct suffixes, which is similar to how Japan handles naming. But, critics of the addition

of suffixes to names say those suffixes could be a challenge for pharmacies because they could be dropped from an electronic drop-down menu or may not fit into the electronic prescription database fields.[1]

Another issue is the rate at which biosimilars are substituted by pharmacists, which will likely be determined by the naming convention. For example, the American Medical Association recommends that prescriptions of current generic drugs contain the USAN-assigned name for the drug. If this recommendation were followed, a biosimilar with a different USAN designation would not be listed on the prescription, making it less likely to be substituted.[8]

The Purple Book

Recently, FDA published its first edition of the *Purple Book* (similar to FDA's *Orange Book* for the pharmaceutical industry), which lists all approved biologics. As biosimilars are approved, they will be added to the *Purple Book* so healthcare professionals are able to view them. The *Purple Book* will use a four-part standard to define biosimilar interchangeability:

• Highly similar with a fingerprint-like similarity
• Highly similar
• Similar
• Not similar

The Regulatory Affairs Professional Society notes that the term "biosimilar" will likely be the catch-all term for non-interchangeable biosimilar products, and the four-part standard appears to indicate that not all approved biosimilar products will be considered interchangeable.[10]

The Way Ahead

Since there are no final guidelines at this time, it is likely that approvals will occur on a case-by-case basis. The first biosimilar, Zarxio (filgrastim-sndz), was approved in early March. Zarxio, which is biosimilar to Amgen Inc's Neupogen (filgrastim) that was originally licensed in 1991 for treating cancer, is approved for the same indications as Neupogen.[11]

IDF is petitioning for FDA to prohibit immune globulin therapies from being considered as interchangeable until there is a greater understanding of how they will affect patients. According to IDF, "FDA must recognize that there are tremendous variations in the complexity of biologics and the substantial differences in therapeutic responses to biologics from patient to patient. IDF also urges that at which time biosimilars are approved, they are identified with unique names."[12]

Since there are no final guidelines at this time, it is likely that approvals will occur on a case-by-case basis.

Concerned with making sure a strong voice advocates for immunodeficient patients, the Patients for Biologics Safety & Access (PBSA) coalition was launched in October. A consortium of 22 patient advocacy organizations, including IDF, the Jeffrey Modell Foundation, the American Autoimmune Related Diseases Association and the Platelet Disorder Support Association, is lobbying for adequate patient safety pathways as FDA considers biosimilars and interchangeable biologics.[13] "Patients need continued access to safe biologic medicines," says Marcia Boyle, president and founder of IDF, "and as the FDA creates a regulatory pathway to market for biosimilars, we want to make sure the voices and interests of patients are front and center."

To date, FDA's CDER has received more than 60 requests from companies wishing to discuss biosimilar development for more than 13 different reference products, not to mention Investigational New Drug (IND) applications for biosimilar development programs.[1] The efforts and concerns for determining a safe and effective regulatory pathway for these products have never been greater. "Right now, we are in a black hole," says Lamotte. "If there are biosimilars that are proved safe and effective, then we are all for that. But we just need some rules for the road and something that provides confidence and trust that these biosimilars will be safe and effective."

"Substitutability helped spur the growth of the generic drug industry at an earlier time and is similarly essential to help foster competition in the biologic drug market," adds Baumgartner. "Ultimately, such competition will spur innovation, improve consumer choice and drive down medical costs. The high standards for approval of biosimilar and interchangeable products mean that patients and healthcare professionals can be assured that, when these products go to market, they will meet the standards of safety, efficacy and high quality that everyone expects and counts on." ❖

AMY SCANLIN, *MS, is a freelance writer and editor.*

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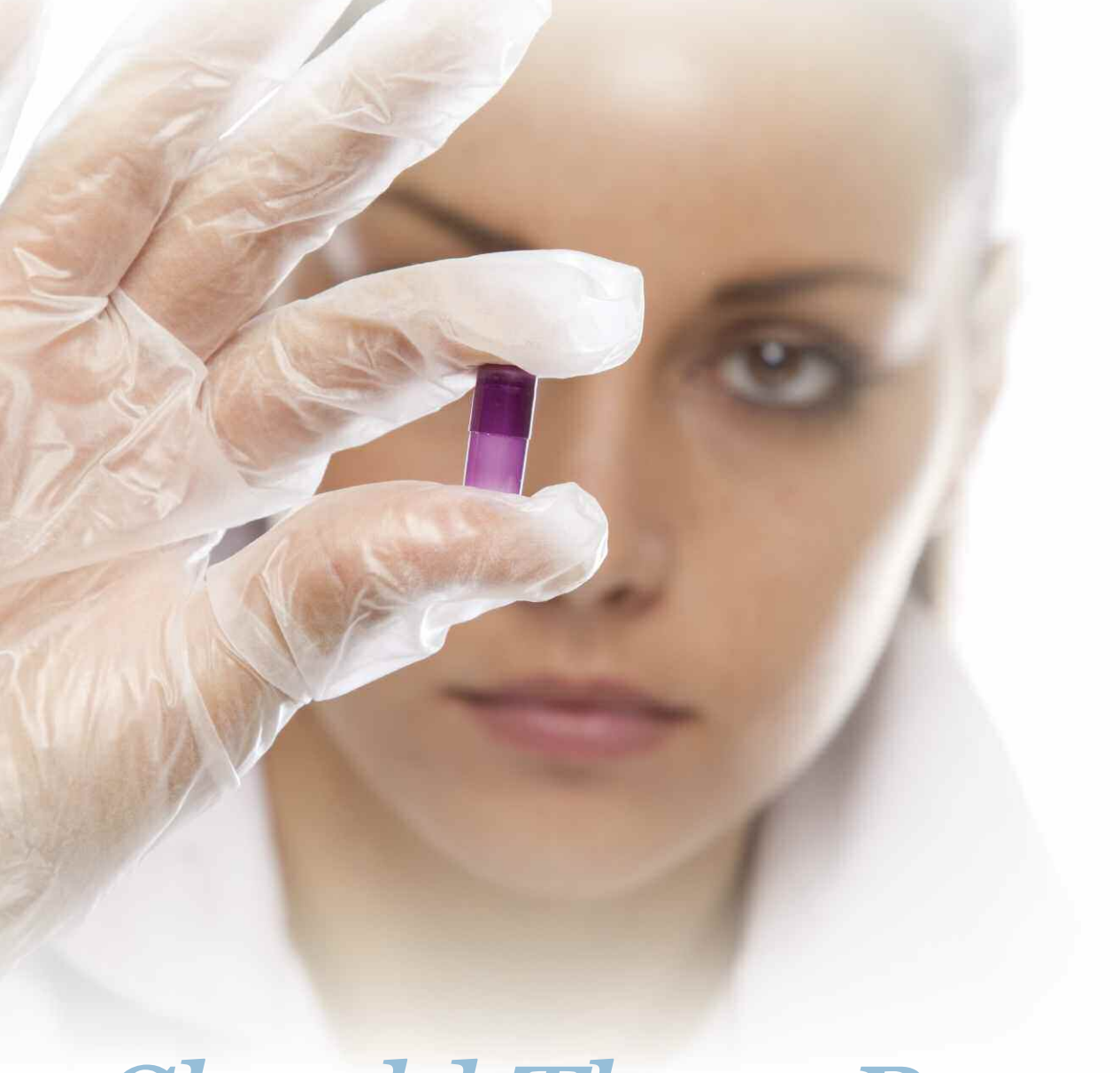


Should There Be a 'Right to

The debate surrounding right-to-try laws to allow patients access to potentially life-saving drugs hinges on safety and ethical concerns.

By Kevin O'Hanlon

More than four years after Frank Burroughs' daughter Abigail died of throat cancer, the U.S. Food and Drug Administration (FDA) approved for use a drug her doctors had hoped could have saved her life. Before she died in 2001, Abigail was being treated at Johns Hopkins Hospital in Baltimore after conventional treatments had failed. Her oncologist suggested that a developmental cancer drug (Erbitux) showed promise, but that FDA approval was far off. The FDA approved Erbitux for use for treating cervical cancer more than three years after Abigail's death. It approved the drug for treatment of throat cancer about a year after that.

Right-to-Try Laws

The loss of his 21-year-old daughter prompted Burroughs to co-found the Abigail Alliance. The Virginia-based organization is trying to help patients with life-threatening illnesses get access to experimental drugs that have undergone so-called Phase 1 FDA testing[1] — the first clinical trial stage where it is determined if the drugs are harmful — but still face years of clinical trials before being approved. The Abigail Alliance is helping to push for so-called "right-to-try" laws — now passed in Arizona, Colorado, Louisiana, Michigan and Missouri — to allow patients to gain access to such potentially life-saving drugs.

Lawmakers in at least 20 states have either introduced or indicated that they will introduce right-to-try legislation this year, according to the Goldwater Institute, a conservative, Arizona-based public policy advocacy/research organization that is one of the champions of the right-to-try movement. Such laws allow a doctor and a patient — provided approved

Try'?

treatment options have been exhausted — to ask a drug company for access to an experimental drug. Colorado's law, for example, does not mandate that pharmaceutical companies make the drugs available. And it does not require insurance companies to pay for such treatments.[2] "You can identify these drugs that are showing genuine solid efficacy early ... in clinical trials," Burroughs said. "It's an issue of the right to fight for your life."

FDA's Role

FDA has not taken a position on any state's right-to-try legislation. But spokeswoman Stephanie Yao said the agency has a long history of supporting patient access to experimental new treatments by working with drug companies through two pathways:

- enrollment of patients in clinical trials that may eventually lead to FDA approval of the product, and
- through an expanded access program that provides patients with serious or immediately life-threatening conditions when there is no comparable or satisfactory alternative.[3]

The right-to-try movement has spawned concerns over safety, debate over medical ethics and legal action.

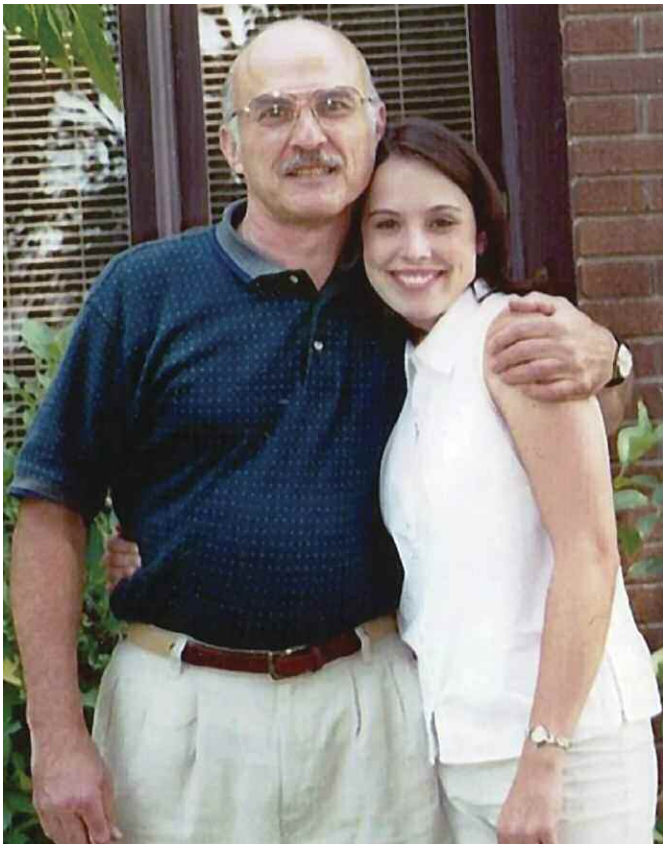
Yao said FDA's oversight of the process provides important protections for individual patients while also helping to ensure the collection of the data needed to support FDA approval of safe and effective therapies. "While the FDA is supportive of patient access to experimental new treatments when appropriate, we believe that the drug-approval process represents the best way to [ensure] the development of and access to safe and effective new medicines for all patients," she said.

FDA does not formally track the amount of time it takes to respond to an expanded access request. But data for fiscal years 2010 through 2014 show that FDA has allowed more than 99 percent of expanded access submissions to proceed.[4] "The agency often allows these submissions to proceed quickly and, in the case of emergencies, over the phone," Yao said. She stressed that the 99 percent figure reflects the number of requests submitted to FDA, not the number of patients seeking access to experimental drugs. The figures do not reflect how many patients or physicians do not submit a request because a company refused to provide the drug. "The FDA cannot make a drug company provide a drug to a patient" Yao said.

FDA says expanded access can be granted on a case-by-case basis for an individual patient and to intermediate-size groups of patients (two to 99) who otherwise do not qualify to participate in a clinical trial and for large groups of patients (100 or more) who do not have other treatment options available.[5]

Safety Concerns and Medical Ethics

The right-to-try movement has spawned concerns over safety, debate over medical ethics and legal action.



Frank Burroughs' daughter, Abigail, died from throat cancer. More than four years later, an experimental drug that they tried to have Abigail treated with but were denied was approved by the U.S. Food and Drug Administration.

In 2008, the U.S. Supreme Court refused to hear an appeal of a federal appeals court ruling (in a case filed by the Abigail Alliance) that said patients do not have a constitutional right to try drugs before FDA approval. R. Alta Charo, a professor of law and bioethics at the University of Wisconsin-Madison, said allowing patients to use drugs after only preliminary testing puts them at risk of being harmed by the drug — or by the fact that the drug is useless and they "have missed the chance to take something better."

FDA's drug-access protocol has been revised several times to make access less logistically complicated. And Yao said if it is still deemed too cumbersome, it can be revised again. In fact, the agency, as recently as 2013, has solicited new comments on the program.

Though manufacturers can't sell a drug until it has been approved by FDA, they can ask to be reimbursed for their cost if used on an experimental basis. So "they have little or no incentive to provide it at cost to patients who make demands via the right-to-try laws," Charo said. For example, drug companies may not yet have large supplies of such drugs because they are making only enough for their clinical trials — and scaling up the manufacturing can be expensive. "And without knowing an approval is in the offing from FDA, it is an expense that may never be recouped," she said, adding that FDA is entitled to information about how the drug worked in every patient who takes it.

Since patients using experimental drugs will not be the same as those in clinical trials — who have been screened for complicating factors — there is a good chance they will have a variety of adverse events, each of which "must be reported to FDA and considered in the approval process unless clearly unrelated to the drug," Charo said. That, then, can complicate and slow the process of seeking approval.

Dr. David Gorski of the Science-Based Medicine blog is not a fan of right-to-try laws, which he called "placebo legislation." "They make legislators feel better but don't actually do anything," said Dr. Gorski, an associate professor of surgery at the Wayne State University School of Medicine in Detroit, managing editor of Science-Based Medicine and chairman of the board of directors of the Society for Science-Based Medicine. Dr. Gorski specializes in breast cancer surgery and also serves as the medical director of the Alexander J. Walt Comprehensive Breast Center and as cancer liaison physician for the American College of Surgeons Committee on Cancer.

According to Dr. Gorski, FDA control of drug approval trumps state law, but "there is always the danger that the FDA won't protect its authority in this matter, and that's what right-to-try advocates are counting on. Right-to-try laws are far more likely to harm a patient than help, given that the bar is very low. A drug only need have passed a Phase I clinical trial and still be under clinical trials to qualify." And, said Dr. Gorski, since most Phase I studies only use fewer than 30 patients, "it's patently absurd to refer to this … as having 'passed safety testing.' "

He said the real goal of right-to-try is to "chip away at the regulatory power of the FDA, based on a fantasy view that there are lots of cures out there if only the FDA would get out of the way and let the free market work its magic. Add to that the fact that these laws provide no financial support, and it is not difficult to imagine patients going broke chasing these cures. Worse, right-to-try gives them no recourse if they are harmed, as patients can't sue."

Sascha Haverfield, vice president of scientific and regulatory affairs at the Pharmaceutical Research and Manufacturers of America, said her group has "serious concerns with any approach to make investigational medicines available that seeks to bypass the oversight of the Food and Drug Administration and clinical trial process, which is not in the best interest of patients and public health." Haverfield said successful completion of the clinical trial process is necessary to demonstrate that an investigational medicine is safe and effective, which is required to obtain FDA approval.

The FDA process for a patient to gain access to an investigational drug through expanded access was established in close consultation with patients, physicians and the biopharmaceutical industry, Haverfield said. "Legislation at the state level, however well-intentioned, is unlikely to add any meaningful new approaches that can optimize the federal expanded access process overseen by FDA." Therefore, it is critical that all stakeholders — patients, physicians, biopharmaceutical companies, academia and FDA — come together to identify ways to improve the existing federal expanded access process and modernize the clinical trial, drug development and FDA review processes "by harnessing 21st century science to accelerate the availability of new medicines for the patients who need them," Haverfield added.

Proponents Keep Pushing

Kurt Altman, national policy advisor and general counsel for the Goldwater Institute, said proponents of right-to-try "are under no grand illusion that miracle cures exist. They do not guarantee a right to cure. The laws simply give patients the right to try to prolong their lives. They are based on reality, not fantasy."

Right-to-try does not hamper the clinical trial process — but rather may even complement it, Altman added. "Investigational medicines that are available to terminal patients through right-to-try continue to make their way through the clinical trial process, where additional information is collected," he said. And, he stressed that if a drug is removed from the clinical trial process, it is no longer available to patients under right-to-try. "In this way, right-to-try patients get the same access that members of the clinical trials get, while doctors and scientists collect even more information," he said.

Proponents also argue that federal regulations that violate constitutional liberties can never trump state laws. "It is well-established that the U.S. Constitution was designed to provide a floor of protection for individual rights, not a ceiling," Altman said. State constitutions may provide additional and greater protections to individuals. For example, many states protect speech to a greater extent than the U.S. Constitution, and others provide greater privacy rights. "The right-to-try (laws are) designed to provide the expanded individual right to life by ensuring a right to medical self-preservation," Altman said. "That right is a liberty so inherent and vital that no government can place limitation on it through regulation or otherwise. Although these medicines may have unknown adverse effects, some even severe, all terminal illnesses have one certain adverse effect: death."

Burroughs said that every drug for cancer and other serious life-threatening illnesses that the Abigail Alliance has pushed for earlier access in its 13-year history is now approved by FDA. "There is not one drug that we pushed for earlier access to that did not make it through the clinical trial process," he said. "Many lives could have been saved or extended if there had been earlier access to these drugs."

While Altman said the FDA's Expanded Access — or compassionate use — program may be an option, "it isn't a very viable one" for most terminal patients. "That's because even the FDA's own literature estimates that it takes over 100 hours for a doctor simply to complete the initial paperwork required," Altman explained. "The bureaucracy is so burdensome that fewer than 1,000 compassionate use requests are received by the FDA annually. Meanwhile, over 400,000 people in the United States die from cancer each year."

Proponents argue that federal regulations that violate constitutional liberties can never trump state laws.

According to Burroughs, federal action is needed: "The U.S. Congress needs to get the FDA to move forward and get promising — keyword 'promising' — investigational drugs out there to people fighting for their lives sooner. Tens of thousands of people are dying each year that don't have to. Good grief. It's this risk-benefit issue. These people have no choices but that. We're not talking about a new toe fungus cream. We're talking about people's lives."

"These patients do not have decades to wait for a drug that could help them now," Altman adds. "The reality is that when facing a terminal illness, every day, hour, minute and second matters." ❖

KEVIN O'HANLON *has been a writer and editor for some 30 years, including stints with the Associated Press,* Cincinnati Enquirer *and* Omaha World-Herald. *He lives in Lincoln, Neb.*

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Foodborne Illness: A Continuing Threat to Public Health

With more than 250 foodborne illnesses identified, it is often difficult to diagnose when a person has been infected to ensure proper treatment is prescribed.

By Jim Trageser

A mid-20th-century doctor looking back at his own career recalled that, during his medical training in the early 1900s, he and other students were called over to a specific cadaver by the training physician. They were told that they should take a look at the lung cancer in the donated body because they might not ever see another case in their careers, whereas they could expect to see hundreds of cases of stomach cancer, at the time one of the most common types of malignancies. Of course, the introduction and marketing of pre-rolled cigarettes led to a stunning increase in lung cancer rates, while stomach cancer rates have plummeted in the United States and other developed nations thanks to the widespread adoption of refrigeration[1] (made possible due to the development of dependable electricity supplies) and food safety practices.

If stomach cancer is not as rare today as lung cancer was in the 19th century, its radically lower rate is nevertheless emblematic of the state of foodborne illnesses in general in the developed world: They still happen but are today the exception rather than the rule. Recent lurid media coverage of foodborne illnesses might lead one to believe that it represents a growing epidemic. However, the Centers for Disease Control and Prevention's (CDC) FoodNet program shows that most types of foodborne illnesses have declined since the late 1990s.[2]

If serious foodborne illnesses are rarer than ever in the developed world, mild cases are still all too common, and the potential for deadly consequences is always present: One in six Americans (48 million) will contract a foodborne illness this year[3] — with 128,000 of those cases requiring hospitalization and roughly 3,000 of them ending up fatal. Outside the developed areas of the world, foodborne illnesses remain a major public health threat. Without widespread use of refrigeration or proper food-handling procedures, food spoilage is a much bigger issue. A recent report from the World Health Organization estimated 2.2 million deaths a year from diarrhea alone.[4]

Although over-the-top media coverage may be partially responsible for the public perception that food poisoning is on the rise, there is also the fact that modern transportation — in which fresh food can be quickly distributed farther from its point of origin than ever — can lead to foodborne illness outbreaks covering more territory than was possible in earlier generations. A recent outbreak of *Listeria* contained in caramel-covered apples from a California producer led to infections in 11 states.[5] And, even more recently in March, five patients at Via Christi St. Francis hospital in Wichita, Kan., contracted Listeria after consuming milkshakes with a single-serving Blue Bell ice cream product called Scoops. Three of those patients died.[6]

What Are Foodborne Illnesses?

While most diseases are defined by either the causative agent or the part of the body affected, foodborne illness refers to the entryway by which the disease enters the body. The national nonprofit advocacy organization STOP Foodborne Illness defines a foodborne illness as "an infection or irritation of the gastrointestinal (GI) tract caused by food or beverages that contain harmful bacteria, parasites, viruses or chemicals." At the same time, botulism attacks the nervous system,[7] prions cause brain-wasting disease,[8] and hepatitis A attacks the liver[9] — and all are clearly foodborne diseases. Therefore, a better definition might simply be *any* infection or poisoning caused by food or beverages containing harmful bacteria, parasites, viruses, toxins or chemicals. This is why there aren't very many specialists in food poisoning — and why diagnosing a serious case of food poisoning can be challenging.

CDC reports that more than 250 types of foodborne illnesses have been identified.

The major causes of foodborne illnesses are:

- bacteria
- viruses
- parasites
- toxins
- prions
- non-organic causes (poisons)

CDC reports that more than 250 types of foodborne illnesses have been identified,[3] with causes ranging from defective proteins (prions) to bacterial toxins (*Clostridium botulinum*), mold to protozoa, and tapeworms to *Trichinella spiralis*.

Most cases of foodborne illness are entirely preventable. Bacteria, viruses and parasites in food sources can be killed by properly cooking food and eating it promptly. Refrigeration and freezing can slow or even prevent bacteria growth, while washing hands and keeping food covered can prevent outside bacteria from being introduced to food. Even pathogens like prions and toxins that cannot be killed or neutralized through cooking can be kept out of the food supply if standard food-handling procedures (clean processing facilities, proper temperature control) are followed.

Symptoms, Diagnosis and Treatment

Most physicians will go their entire careers without ever seeing a patient suffering from botulism, Creutzfeldt-Jakob disease or tetrodotoxin poisoning. On the other hand, with one in six Americans contracting some sort of foodborne illness every year, all doctors will treat a case of food poisoning from time to time.

Fortunately, the least dangerous cases are also the most plentiful — and just a handful of CDC's 250 sources of food poisoning are responsible for the vast majority of incidents in the U.S. Between them, norovirus, *Salmonella*, *Campylobacter, Staphylococcus aureus* and *Clostridium* account for some 91 percent of all food poisonings in the U.S. *Toxoplasma gondii* and *Escherichia coli (E. coli)* join norovirus, salmonella and *Campylobacter* in jointly causing 88 percent of foodborne illness-related hospitalizations, while *Listeria* replaces *E. coli* on the list of the top-five fatality-inducing foodborne illnesses in the U.S.[3]

The symptoms and diagnoses of these various agents can vary widely — as do, obviously, the treatments.

Viruses

CDC reports that almost 60 percent of all cases of food poisoning in the U.S. are caused by the norovirus.[3] The virus attacks the stomach and intestines, causing inflammation that leads to cramping, nausea, diarrhea and vomiting. Infection usually lasts 72 hours or less. There are currently no antivirals available to treat norovirus, but most cases are not severe and are treated as with the flu: rest and plenty of liquids. CDC estimates that approximately 580 to 800 deaths a year in the U.S. are attributable to norovirus, mostly patients who are already weakened.[10]

Regular hand-washing before handling food and cooking food until it has an internal temperature above 140 degrees Fahrenheit are the best ways to prevent transmission of norovirus through food. The norovirus can be diagnosed by an RNA lab test of a stool sample.

Bacteria

Bacteria can cause disease either through infection, in which the bacteria themselves attack the host body's cells, or through poisoning, in which the bacteria produce waste that is toxic to the host.

Salmonella causes more food poisonings in the U.S. than any other bacteria — being thought responsible for about 11 percent of all foodborne illness cases.[3] As with the norovirus, the *Salmonella* bacteria attack the cells of the host's stomach and/or intestines.[11]

There are two species of the *Salmonella* bacteria: *Salmonella bongori*, which is native to reptiles,[12] and *Salmonella enterica*, which is naturally found in cattle and poultry (including chicken eggs).[13] A subspecies of *S. enterica* is the cause of typhoid fever,[14] which still kills about 160,000 people around the world every year[15] (although almost none in the developed world; only about 5,700 cases are reported in the U.S. each year, with about three-quarters of them contracted during overseas travel[16]).

Symptoms of *Salmonella* are typical for those of any bacterial or viral food poisoning: abdominal cramps, diarrhea, vomiting, fever, headache and dehydration. Most cases are mild, and patients will self-treat without any medical intervention: rest, liquids and possibly a fever reducer. The infection usually runs its course in four to seven days.[14]

Serious cases — particularly those affecting infants, the elderly and those with weakened systems — may be treated with antibiotics. Diagnosis is made by inspecting a stool sample.[17] Antibiotics used in treating salmonella include fluoroquinolones, third-generation cephalosporins and ampicillin. However, due to increased drug resistance seen in *Salmonella* bacteria, it is now recommended that antibiotics be used only in the most serious cases.[18]

Salmonella infections can be prevented by proper cooking of food, avoiding raw or undercooked foods, and washing hands thoroughly before handling food.

E. coli is a type of bacteria in the same family as *Salmonella*. These bacteria are one of the best-known types of foodborne illness-causing agents among the general public. Native to the digestive tracts of most warm-blooded organisms, *E. coli* are mostly harmless when left alone in the intestines. However, these bacteria can be transferred to the meat during meat processing. The strain *E. coli* O157:H7 is particularly virulent, causing cramps, bloody diarrhea and vomiting — and can also lead to kidney failure.[19]

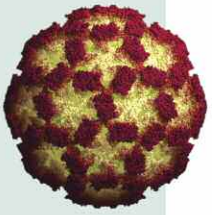
E. coli can be ingested through raw produce or undercooked meat. A diagnosis is made through testing of a stool sample. There is not currently an antibiotic to treat an *E. coli* infection. Rest and fluids will help speed the body's own recovery, and if the kidneys are attacked, dialysis may be employed to help.[19]

Campylobacter jejuni is the second most-common bacterial cause of foodborne illness in the U.S. Like *S. enterica*, *Campylobacter jejuni* is found naturally in poultry, and it causes about 10 percent of all cases each year. As with *Salmonella*, CDC believes most cases are never reported.[20] Diagnosis is made by laboratory examination of a stool sample.

In *Campylobacter jejuni* infections, the bacteria attack the cells of the digestive system, causing diarrhea, fever, vomiting, nausea, dehydration, headache and muscle pain.[20] However, some cases can lead to the development of Guillain-Barré syndrome. Researchers believe that the antibodies the immune system makes to fight *Campylobacter jejuni* bacteria attack the body's own nerve cells after the infection has been defeated,[21] which can lead to muscle weakness, paralysis and even death.[22] This is extremely rare, however, and in most cases the *Campylobacter* infection runs its course in less than a week. In severe cases, or when the patient has high risk factors, the infection can be treated with azithromycin and fluoroquinolones. Again, drug resistance has been increasing in *Campylobacter*.

Listeriosis is the third most deadly of the bacterial food-

Major Causes of Foodborne Illnesses



Viruses

Norovirus

Bacteria

Salmonella

Escherichia coli

Campylobacter jejuni

Listeria monocytogenes

Clostridium difficile

Clostridium perfringens

Clostridium botulinum

Staphylococcus aureus

Shigella

Toxins

Tetrodotoxin

Poisonous mushrooms

Prions

Single-protein molecules

Poisons

Artificial contaminants

Parasites

Cyclospora cayetanensis

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Toxoplasma gondii

Cryptosporidium

Trichinella spiralis

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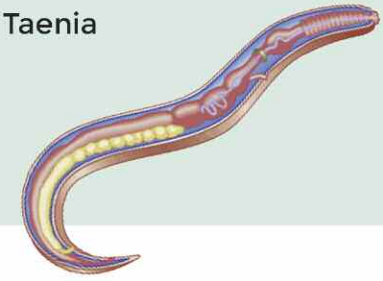
Taenia



borne infections,[3] caused by the bacteria *Listeria monocytogenes*, a naturally occurring organism found in soil and water. This bacteria can be spread to humans through improperly handled or undercooked food. *Listeria* exists naturally in the environment all over the globe, and all humans are exposed to it. Generally, the elderly and others with compromised immune systems are the most likely to develop an infection. Symptoms include muscle ache, stiff neck, fever, diarrhea, confusion, loss of balance and/or confusion.[23] Expecting mothers are also at heightened risk and can pass the disease to their babies. Diagnosis is generally made from a sample of spinal fluid. The recommended treatment is the antibiotic ampicillin, although trimethoprim/sulfamethoxazole, erythromycin, vancomycin, and the fluoroquinolones have also been used.[24]

Clostridium is a family of some 100 species of bacteria that causes a range of diseases from the rare but dangerous botulism to the healthcare-associated *Clostridium difficile* (*C. difficile*).

Clostridium perfringens causes about one-tenth of all cases of food poisoning in the U.S. It grows naturally, including in the digestive tracts of many animals, where it can be transferred to the meat during processing. The bacteria produce a toxin in the intestines of its host that causes the symptoms, which are generally cramping and diarrhea.[25] Most infections last less than 24 hours, and CDC recommends against treating it with antibiotics. Diagnosis is made by a lab test on a stool sample.

The dangerous but rare botulism food poisoning is caused by toxins in food where *Clostridium botulinum* has lived. The toxins affect the nervous system of humans who eat contaminated food, causing paralysis that can lead to death. *Clostridium botulinum* occurs naturally in the soil, including in areas where food crops are grown. Cooking food will kill the bacteria but not the toxins already created. CDC reports that fewer than 25 cases of foodborne botulism occur each year in the U.S., and most are the result of consuming home-canned foods that were improperly prepared (not using pressurized canning equipment to kill the bacteria before it can grow and excrete the toxin).[26]

The symptoms of botulism poisoning are drooping eyelids, double or blurry vision, slurred speech, difficulty swallowing and/or muscle weakness.[27] Treatment will include use of an antitoxin kept on hand by CDC for distribution. Depending on the severity of the exposure, a patient may require a ventilator to assist with breathing until the paralysis begins to decrease, which can take weeks or even months. Total recovery takes years.[26]

Another bacteria that produces toxins that cause illness is *Staphylococcus aureus*, a common germ that lives on the skin and in the noses of otherwise healthy people. When the *Staphylococcus aureus* gets into food during preparation, however, it can create seven different compounds poisonous to humans.[28] About 3 percent of cases of food poisoning in the U.S. are due to this agent.

Fortunately, the symptoms — appearing as soon as 30 minutes after eating contaminated food — are generally mild: nausea, vomiting, abdominal cramps and diarrhea. Few cases are formally diagnosed, according to CDC, because they can be treated with the usual rest and liquids. If a case is severe, or a wide foodborne outbreak is suspected and a diagnosis is warranted, a lab test of a stool sample can detect either the bacteria or the toxins. Antibiotics are not recommended.[28]

A rarer bacteria-caused foodborne or waterborne illness is *Shigella*. Most commonly seen in preschool-aged children, often in healthcare settings, it is generally passed when preparing food after contact with an infected person's feces.[28] The symptoms are generally confined to diarrhea that may contain blood. Most cases clear up within a week. More serious cases can be treated with trimethoprim-sulfamethoxazole, which is sold under the names of Bactrim, Septra or Cotrim. Due to increasing resistance to antibiotics seen in *Shigella*, the Mayo Clinic advises reserving antibiotic treatment for severe cases or for those patients with weakened immune systems.[29]

Parasites

Parasites are multicellular (tapeworms, roundworms) or large single-celled organisms (amoeba) that are ingested in food and then transfer to the host's body to find their sustenance and safety. Most of these infections are the result of eating undercooked food or drinking untreated water.

The largest foodborne disease outbreak reported in the United States in 2013 was for *Cyclospora* in two possibly distinct outbreaks in Iowa-Nebraska and Texas.[30] *Cyclospora cayetanensis*, which generally causes watery, explosive diarrhea, is caused by a single-celled organism that can only be diagnosed by examining a stool sample with a microscope.[30] Treatment consists of the application of the antibiotics trimethoprim-sulfamethoxazole.[32] The infection is usually traced to ingesting raw vegetables or to drinking untreated water. Recent outbreaks have been linked to produce imported to the U.S., although the U.S. Food and Drug Administration (FDA) reports that little is presently known about the microbe, including its natural habitat.[33] It was virtually unknown before 1990.

Another single-celled organism that can cause infection in humans through contaminated meat or water is *Giardia duodenalis*. Symptoms are similar to those of bacterial GI infections: cramping, nausea, diarrhea and dehydration.[33] As with most parasitic infections of the digestive tract, diagnosis is made by examining a stool sample in a lab. Treatment is generally with metronidazole, tinidazole or nitazoxanide, all of which will kill the parasite. None of these should be prescribed to pregnant women, however, due to the risks to the baby.

Toxoplasma gondii is a single-celled organism that can reproduce only while in the digestive tract of a cat.[33] However, the infective reproductive cysts can be ingested by other animals, and humans can contract it through eating undercooked wild game, pork or lamb or by drinking untreated water. Most people who contract it will have no or very mild symptoms, including swollen lymph glands and muscle aches. However, unborn children exposed to it through their mother's infections can develop serious, even fatal, complications. Those with compromised immune systems such as HIV patients can also develop very severe complications. (CDC has targeted toxoplasmosis as one of its five neglected parasitic infections.[34]) Once ingested, the parasite leaves the digestive tract and moves to muscle and nerve tissue. Diagnosis is performed by a blood test, looking for specific antibodies that indicate the presence of the parasite. Treatment consists of the antibiotics pyrimethamine and sulfadiazine, although most healthy patients will not need antibiotics.[34]

Cryptosporidium is a single-celled organism with a shell that can survive for long periods of time outside of a host. It is also resistant to chlorine (bleach). While generally transmitted via water, it can infect food during improper preparation.[35] The symptoms are diarrhea and dehydration, and diagnosis is made by an exam of a stool sample. Most patients will recover with rest and fluids, while more severe cases can be treated with nitazoxanide.

Trichinosis is caused by the *Trichinella spiralis*, a roundworm ingested in undercooked wild game or, much left often today, domestic pork. The roundworms will complete their reproductive cycle in the intestines, then launch larvae into the bloodstream, where they will embed in muscle tissue, forming cysts.[36] The first symptoms are similar to other types of foodborne illness: GI distress (cramping, vomiting and diarrhea). However, subsequent symptoms include eye swelling, headaches, aching joints and muscles, and general weakness. Because the worms migrate, a stool test may return a false negative; therefore, blood tests and muscle biopsies are more often used for a diagnosis.[37] The antibiotics thiabendazole and mebendazole will kill the live adults in the digestive tract, but there is no treatment to kill the encysted larvae in muscle tissue.[38]

Anisakiasis is a roundworm found in fish and squid, and is contracted when eating infected fish or squid that have not been fully cooked.[39] Symptoms are generic: abdominal cramping, nausea, diarrhea and vomiting. An endoscopic examination is used to diagnose an infection, and surgical removal of the worms is necessary in severe cases; mild cases will generally resolve on their own. However, the worm can migrate out of the digestive tract into the liver and even lungs, requiring surgical intervention in these cases.[40]

Diphyllobothrium latum is the largest parasite that can infect humans. A tapeworm, this species can grow up to 30 feet long.[41] It is ingested in undercooked fish, and diagnosed through an examination of a stool sample. However, it is often asymptomatic for years, even decades, living in the host's intestine and shedding millions of eggs a day.[42] If symptoms do appear, they may include unexplained weight loss, abdominal pain or diarrhea. The worms can drop segments that migrate to the gallbladder or bile duct, causing infections to those organs.[43] Praziquantel is most often prescribed for tapeworms. The drug causes the head of the tapeworm to detach from the intestinal wall, and the worm is then passed with the next bowel movement.

Taeniasis is a tapeworm infection caused by any one of three species of the genus *Taenia*. It is contracted by eating undercooked beef or pork infected with tapeworm, which then attaches to the host's intestines.[44] Symptoms are similar to those of the fish tapeworm: abdominal discomfort and weight loss. But as with other tapeworms, many people are unaware they are infected for years or decades. If oncospheres hatch in the intestines, they may migrate to muscle tissue or even the brain, causing cysticercosis, which can lead to seizures.[45] As with other tapeworms, praziquantel is most often prescribed, along with niclosamide.

Toxins

While several of the bacteria listed above produce compounds that are poisonous to their human hosts after they are ingested, other toxins can be ingested that already exist within food. Perhaps the most infamous is tetrodotoxin, found in the puffer fish and related species popular in Japan and Japanese cuisine. Tetrodotoxin is confined to the liver and sex organs of the fish, and chefs in Japan must go through years of rigorous training and testing before they can prepare these species for human consumption.[46] The toxin is heat-stable (so cooking will not neutralize it), and it is a deadly neurotoxin: There is no antidote, and as paralysis spreads through the body, the victim remains conscious the entire time.[46] The symptoms — tingling and loss of muscle control — begin within minutes of ingestion, and the final outcome depends only on the size of the exposure.

Poisonous mushrooms continue to be a foodborne danger throughout the world, even in developed countries where hobbyists try to harvest wild species that may resemble edible or psychoactive varieties. As FDA warns, "there is no general rule of thumb for distinguishing edible mushrooms and poisonous toadstools."[47] Most toxins produced by mushrooms are heat-stable, meaning that cooking does not make them safer.

Because the symptoms vary by the species of poisonous mushroom, the government classifies mushroom poisonings into four physiological categories: protoplasmic (causing general decay of cells, resulting in organ failure), neurotoxins (affecting the nervous system), GI irritants (causing non-lethal discomfort such as nausea, diarrhea and cramping) and disulfiram-like toxins (which are only dangerous if consumed with alcohol).[47]

Poisonous mushrooms continue to be a foodborne danger throughout the world.

Of these four categories, the protoplasmic and neurotoxins are the most dangerous. One class of protoplasmic toxins, amanitins, is the only one that has a clinical test available commercially.[47] The challenge for medical and emergency personnel is that, most often, a patient isn't seen until a day or two has passed since ingestion, and the test has a two-hour turnaround. The amanitins can quickly lead to permanent, irreversible liver damage. Symptoms from these mushrooms often don't appear for 12 hours after ingestion, at which time patients may experience persistent, violent vomiting, abdominal cramping and watery diarrhea. After a few hours, the symptoms will ease, leading patients to think they are well. Then, jaundice will manifest three to five days later, at which time a rapid decline in patient health may lead to coma and even death.

Prions

There is no general scientific consensus on just what prions are. They are smaller even than viruses, containing only a single protein molecule. What makes prions both dangerous and infectious is that they are misfolded proteins, and when near other similar proteins, they will cause them to misfold as well.[48]

Researchers have been aware of prion disease for several centuries, since ranchers first noticed a disease in sheep called scrapie. The affected sheep slowly became deranged, and it was clearly an infectious disease spreading from one sheep to another. Cows, too, can suffer from prion disease, most specifically bovine spongiform encephalopathy, popularly known as "mad cow disease." The misfolded proteins tend to most

resemble proteins on the surface of a nerve or brain cell, meaning that animals (including humans) with prion infection tend to suffer debilitating and ultimately fatal brain-wasting disease.

Prions are heat-stable, so cooking does not destroy them. The prions in an animal's nervous system can be spread to the meat during the slaughtering and processing of the animals, which is how some humans developed variant Creutzfeldt-Jakob disease (vCJD) from eating infected meat.[49] Symptoms of vCJD are similar to those of CJD, which is not believed to be associated with ingesting prions from infected food sources but is likely caused by spontaneous deformation of the proteins for unknown reasons.[49] Patients will suffer significant personality changes, anxiety, depression, impaired thinking and blurred vision. Life expectancy is a little over a year from the onset of symptoms. There is no cure or treatment available.[50] However, careful monitoring of livestock populations and improved care and feed protocols (no more mixing unused beef into cattle feed, or mutton into sheep feed) have mostly eliminated prion disease from our food sources.

Not only are nearly all cases of foodborne illnesses preventable, but most foodborne illness outbreaks are now required to be reported to public health authorities.

Poisons

With much of our food supply being processed or packaged by automated factory equipment, occasionally artificial contaminants are introduced into our food, and many of these can act as toxins to the human body. If produce isn't properly rinsed, pesticide residue may remain. Trace amounts of artificial hormones may also remain in meat and poultry and have deleterious effects on those who consume them. Harvesting machines may accidentally introduce lubricants onto crops headed for the table, or canning equipment may have cleaning residue.[51]

FDA maintains information on different chemicals that can accidentally enter the food supply. Local poison control centers and emergency rooms have information on nearly all of these compounds, their symptoms and appropriate treatments.

Prevention and Research

Not only are nearly all cases of foodborne illnesses preventable, but most foodborne illness outbreaks are now required to be reported to public health authorities.[52] If a physician suspects the possibility of food poisoning, they are able to check with local public health authorities or the CDC's FoodNet to see if a foodborne illness has been reported in that area. If so, the physician can then follow up with the patient to see if he or she may have been exposed to the reported outbreak, which can provide guidance in determining the diagnosis and treatment.

Refrigeration, proper cooking and cleanliness remain the best ways to prevent foodborne illness. The food supply in the U.S. is regulated both by law and by industry guidelines. From livestock ranches to lettuce farms, from distribution centers to refrigerated railcars and semitrailers, from grocery stores to farmers markets to restaurants, there are both written regulations and well-understood best practices that help protect our food chain from disease-causing agents.

When a patient does contract a foodborne illness, particularly from a meal prepared at home, it may be advisable to review basics of food safety with them:

- Always fully cook meat, poultry and eggs (a meat thermometer is the only way to be sure a meal is fully cooked); learn the temperature each kind of meat should be cooked to ensure safety.[53]
- Always wash hands with hot water and soap before handling any food, or when handling dishes or utensils that will touch food.
- Keep produce and meats refrigerated when not in use. Don't leave food to thaw on the countertop or leave prepared food out longer than a few hours (it's not just meat — even fresh produce that has been sliced can host dangerous pathogens if left at room temperature for more than a few hours).
- Be sure the refrigerator is working properly and that it is chilled to 40 degrees Fahrenheit or cooler.[54]

It's important to remind patients that food left out too long at room temperature may be infected by bacteria that produce poisons that won't be removed by cooking and that remain dangerous even if the bacteria are killed by heating (cooking) the food.[54]

CDC has designated foodborne illnesses as one of its "winnable battles," and is putting considerable resources into further strengthening the protective measures surrounding our food supply.[55] Among the strategies being used to combat foodborne illnesses are:

- Improved communication with state and local health agencies
- New technology in public health labs to help identify sources of food-based infection more quickly
- Better food surveillance systems and improved data sharing when an outbreak is reported or detected[56]

Given that food fit for humans is also food fit for bacteria, viruses, mold, parasites and just about anything living, it is

unlikely that we can ever wholly eradicate foodborne illness. But by working with ranchers, farmers, distributors, grocers, restaurateurs and the general public in emphasizing the importance of following proven best practices in food handling, and combining that with improved detection and communication, it does seem likely that we can continue to reduce incidences of foodborne illness and ensure they remain the rare exception to our safe food supply. ❖

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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.

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 years of age and older.

DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL)

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%). In adults 50 through 64 years of age, the most common (≥10%) injection site reactions were pain (32%) and tenderness (37%); the most common (≥10%) solicited systemic adverse reactions were headache (17%), fatigue (13%), and muscle pain (11%). In adults 65 years of age and older, the most common (≥10%) injection site reaction was pain (19%); the most common (≥10%) solicited systemic adverse reactions were fatigue (13%) and headache.

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

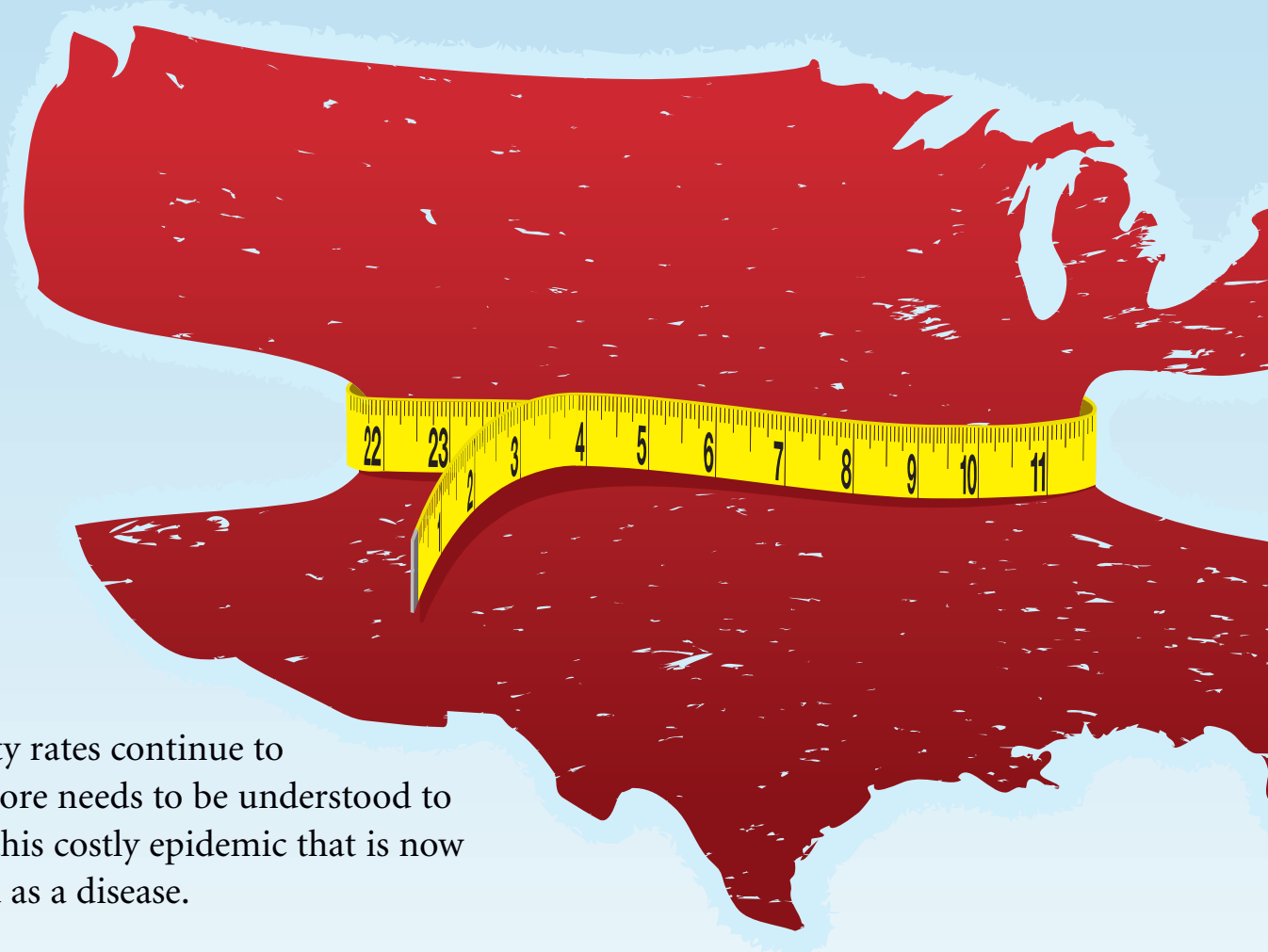
Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, or children. A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871. Revised: October 2014

*Flublok demonstrated a higher antibody response to the A strains during 2 clinical trials in adults ≥50 years old. The B strain antibody response was comparable to traditional trivalent vaccines.

FB14044

Myths and Facts: **Obesity**

By Trudie Mitschang



As obesity rates continue to climb, more needs to be understood to combat this costly epidemic that is now classified as a disease.

Some blame it on our sedentary lifestyles and "American"-sized menus. Others claim calorie-laden carbs, sugary snacks and nutrient-deficient processed foods are the leading culprits. Food additives, artificial sweeteners and even antibiotics have also been linked to America's growing girth, but the reality is that whatever the reasons are for the upward climb of our collective body mass index (BMI), America as a whole has become overwhelmingly obese.

According to the Centers for Disease Control and Prevention, more than one-third of American adults are classified as obese.[1] Obesity is linked to more than 60 chronic diseases,[2] including heart disease, stroke, type 2 diabetes and certain cancers. And, as waistlines increase, so do healthcare costs. Researchers estimate that if obesity trends continue, obesity-related medical costs could rise by $43 billion to $66 billion each year in the United States by 2030.[3]

While the link between obesity and disease is not new, the recent classification of obesity as a disease itself is still being debated. In June 2013, the American Medical Association (AMA) announced its controversial decision to classify obesity as a stand-alone disease requiring specific medical interventions to promote treatment and prevention. "Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans," said AMA board member Patrice Harris, MD. "The AMA is committed to improving health outcomes and is working to reduce the incidence of cardiovascular disease and type 2 diabetes, which are often linked to obesity."[4]

The new classification has far-reaching implications, influencing everything from provider reimbursement, public policy and patient stigma to the International Classification of Diseases coding.[5] As healthcare providers are increasingly tasked with

taking a broader view of obesity causes, interventions and treatment plans, it's important to look at some of the common but erroneous beliefs about obesity, and separate fact from fiction.

Separating Myth from Fact

Myth: Slow and steady wins the weight-loss race: Gradual weight loss is better than rapid weight loss when it comes to long-range results.

Fact: According to recent studies, people who lose weight quickly are as likely to keep it off as those who slim down at a moderate pace. A meta-analysis of randomized, controlled trials that compared rapid weight loss (achieved with extremely low-energy diets) with slower weight loss (achieved with low-energy diets) showed that there was no significant difference between the two different diet plans and outcomes at the end of the long-term follow-up. In fact, within some weight-loss trials, more rapid and greater initial weight loss has been associated with lower body weight at the end of long-term follow-up.[6] Researchers also noted that a recommendation to lose weight more slowly might cause participants to lose momentum and interfere with the ultimate success of weight-loss efforts.

Myth: Setting realistic goals for weight loss is important because otherwise patients will become frustrated and lose less weight.

Fact: Although from a behavioral standpoint this theory makes sense, studies show no consistent negative association between ambitious goals and program completion or weight loss. Some data point out that people achieve more by setting more challenging goals.[7] Several studies have shown that more ambitious goals are sometimes associated with better weight-loss outcomes. Furthermore, two studies showed that interventions designed to improve weight-loss outcomes by altering unrealistic goals resulted in more realistic weight-loss expectations but did not improve outcomes.[8]

Myth: Breast-feeding helps prevent future obesity for the breast-fed baby.

Fact: Although breast-feeding has advantages for both mother and child, data does not confirm that it protects against obesity. This myth stems from a World Health Organization (WHO) report stating that individuals who were breast-fed as infants are less likely to be obese later in life. WHO later found clear evidence of publication bias in the published literature it synthesized,[9] and follow-up studies with improved controls provided no compelling evidence that breast-feeding had any influence on obesity.[10]

Myth: Obesity is a result of poor education regarding proper diet and nutrition.

Fact: According to a physicians' health study, 44 percent of male doctors in the U.S. are overweight.[11] Another study by the University of Maryland School of Nursing found that 55 percent of nurses surveyed were classified as overweight or obese.[12] These statistics suggest that if healthcare providers who have ample exposure to health and nutrition information struggle with obesity, clearly the problem is not rooted simply in a lack of information. On the other hand, race and socioeconomic status do play a role in obesity statistics. Among non-Hispanic black and Mexican-American men, those with higher incomes are more likely to battle obesity than those with low income, and overall, higher-income women are less likely to struggle with obesity than low-income women.[13]

Myth: Eating more fruits and vegetables encourages weight loss.

Fact: Fruits and vegetables are healthy food choices but may not encourage weight loss, according to a study in *The New England Journal of Medicine*.[14] The common wisdom suggests that since fruits and vegetables contain fiber, they will keep you full longer and encourage you to eat less. But a report in the *International Journal of Obesity* noted that regularly consuming fruit, whether solid fruit or fruit juice, did not encourage people to eat less. The study concluded that the recommendation for increased consumption of fruits and vegetables may be well-founded but should not be based on a presumed beneficial effect on regulation of BMI.[15]

Myth: Obesity is genetically, not behaviorally, influenced.

Fact: A cohort study was used to investigate the extent to which people with a genetic susceptibility to obesity can change their weight with exercise. The research was based on previous genetic studies that had identified 12 possible positions on 11 genes where DNA sequencing differences could influence BMI. However, although the studies showed an association between variations in the genetic sequence and BMI, the variations seemed to have a very small effect on a person's risk of obesity. Previous research suggested that lifestyle played a greater role in determining BMI, and the new study aimed to investigate this theory in more detail. Researchers found that although some genes increased the likelihood of having a higher BMI, an active lifestyle proved these "genetically predisposed" individuals were less likely to be overweight. Conversely, an inactive lifestyle increased the amount of weight the individuals were likely to gain.[16]

Myth: School-based physical education classes play an important role in reducing or preventing childhood obesity.

Fact: Physical education, as typically provided in a school setting, has not been shown to reduce or prevent obesity. Findings in three studies that focused on expanded time in physical education indicated that even though there was an

increase in the number of days children attended physical education classes, the effects on BMI were inconsistent across sexes and age groups. Two meta-analyses showed that even specialized school-based programs that promoted physical activity were ineffective in reducing BMI or the incidence or prevalence of obesity.[17] Researchers did agree that certain levels of physical activity (a specific combination of frequency, intensity and duration) could potentially be effective in reducing or preventing obesity in children and adolescents, but whether that level is achievable in a traditional school has yet to be explored. Research also concluded that while weight-management programs in schools, daycare or other places away from the home are convenient, programs that involve a child's parents and take place at home are likely to be more effective in the long run.

Myth: Obesity is a leading cause of breast cancer.

Fact: This statement is only partially true. Current evidence suggests that heavier body weight does not increase breast cancer risk before menopause and may even slightly lower risk. But, research by leading cancer organizations has concluded that there is convincing evidence that being obese or overweight may be linked to increased risk of breast cancer in post-menopausal women.[18] The higher risk of breast cancer for women who gain weight is likely due to higher levels of estrogen, since fat tissue is the largest source of estrogen among women who are post-menopausal. Since being overweight increases a woman's risk of post-menopausal breast cancer, cancer researchers are exploring whether weight loss can actually lower the risk.

Myth: Overweight children will outgrow their excess weight. It's just "baby fat."

Fact: Children and adolescents who are obese are likely to be obese as adults and are, therefore, more at risk for adult health problems such as heart disease, type 2 diabetes, stroke, several types of cancer and osteoarthritis. One study showed that children who became obese as early as age 2 were more likely to be obese as adults.[19] In the United States alone, childhood obesity has more than doubled in children and quadrupled in adolescents over the past 30 years. The percentage of children aged 6 years to 11 years who were obese increased from 7 percent in 1980 to nearly 18 percent in 2012. Similarly, the percentage of adolescents aged 12 years to 19 years who were obese increased from 5 percent to nearly 21 percent over the same period. These statistics are worrisome; some have predicted that the current generation of youth could become the first to have a shorter life expectancy than their parents. In a study published in *The New England Journal of Medicine*, researchers stated: "If the prevalence of obesity continues to rise, especially at younger ages, the negative effect on health and longevity in the coming decades could be much worse. It is not possible to predict exactly when obesity among the young will have its largest negative effect on life expectancy. However, in the absence of successful interventions, it seems likely that it will be in the first half of this century, when at-risk populations reach the ages of greatest vulnerability."[20]

Myth: Hypothyroidism is a primary cause of obesity.

Fact: Decreased thyroid function, or hypothyroidism, is commonly associated with weight gain. But contrary to popular belief, effective treatment to restore normal thyroid hormone levels is not associated with clinically significant weight loss in most people. Following an eight-year study, researchers from Boston University Medical Center noted that because obesity and hypothyroidism are very common, there are many patients who have both conditions. As a result, these patients (and sometimes their physicians) often assume the hypothyroidism is causing the obesity even though this may not be the case. The study showed that only about half of hypothyroid patients lose weight after successful treatment of their hypothyroidism.[21]

Treating Obesity: A Look Forward

It's been nearly two years since the American Medical Association officially classified obesity as a disease, but healthcare providers remain divided in their opinions of the decision. Some argue that the problem of obesity in America has reached dire proportions: 78 million adults and 12 million children are obese — figures many regard as an epidemic. With that in mind, recognizing obesity as a disease may help change the way the medical community tackles this complex health issue. Proponents of the classification say recognizing obesity as a disease has the potential to spur new interventions and treatments for patients struggling with weight loss, and encourage improved dialogue between patients and their doctors about available behavioral, medicinal or surgical options. Still, opponents of the change say calling obesity a disease lessens personal responsibility and may provide less incentive to curb unhealthy eating habits or adopt healthier lifestyles. They worry the disease designation will create a victim mentality that will only lead to more overeating and weight gain.

New Guidelines and Treatment Recommendations

In November 2013, the American Heart Association, American College of Cardiology and the Obesity Society issued updated guidelines to more actively treat obese patients and encourage weight loss. The guidelines reflect the latest information that scientists have about weight-loss treatment plans, with a special emphasis on preventing heart disease and stroke, the nation's No. 1 and No. 5 killers.[22]

One of the biggest changes in the new guidelines is that the criteria have been expanded to include more categories of overweight and obese people. The current weight-loss guidelines recommend behavioral treatment for 140 million American adults — 65 percent of the population.[23] Of these, 116 million would be candidates for adjunctive pharmacotherapy, and 32 million could be considered for bariatric surgery. "This huge

number of Americans recommended for weight-loss therapy reinforces the need for broad, sweeping transformations in obesity management in the primary-care setting," stated Dr. Donna Ryan, a coauthor of the guidelines and a spokesperson for the Obesity Society. "The good news is that there are evidence-based treatments readily available."

Children and adolescents who are obese are likely to be obese as adults and are, therefore, more at risk for adult health problems.

The new guidelines recommend that all obese patients pursue weight-loss therapy. Overweight individuals need to have only one as opposed to two cardiovascular risk factors to qualify, with one of the key risk factors being excessive weight around the waist. The guidelines also include evidence-based recommendations for lifestyle management, including behavioral strategies, pharmacotherapy and metabolic (bariatric) surgery. The guidelines are expected to provide a tool to help physicians identify and treat patients who may not have achieved prior success with diet and exercise alone.

In January, the Endocrine Society issued a clinical-practice guideline for the pharmacological management of obesity, providing clinicians with yet another tool to help improve weight-loss treatment outcomes.[24] The guidelines state that medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. The authors also stress that providers should be mindful that medications prescribed for chronic diseases such as diabetes and depression can have effects on weight, noting that "knowledgeable prescribing of medications, choosing whenever possible those with favorable weight profiles, can aid in the prevention and management of obesity and thus improve health." ❖

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Severe PIs: Cutting-Edge Science Turns Tragedies to Cures

For decades, donor blood stem cell transplantation has been the only potential cure for severe primary immunodeficiency disorders, but it has been limited by failure and serious complication risks. Now, a trifecta of scientific advances is transforming the prognosis for children once defenseless against life-threatening infections.

BY KEITH BERMAN, MPH, MBA

If you are of a certain age, you may remember heart-wrenching images and a long-running — and ultimately tragic — story about a Texas boy whose 12 years of life inside a plastic isolation bubble introduced Americans to the plight of children born with severe combined immunodeficiency (SCID). David Vetter, dubbed the "bubble boy" in countless news features, lived in a succession of sterile chambers to avoid the fate of his older brother, who had succumbed in infancy from complications of overwhelming infection from the same disorder.

From his mother, David inherited a defective version of the IL-2 common chain receptor gene (IL2RG) that she carried on one of her two X chromosomes. David's X-linked disorder, SCID-X1, affects only boys and accounts for 40 percent to 50 percent of all SCID cases. Any of at least 300 different mutations can disable the IL2RG gene, which encodes a protein critical for regulating growth and maturation of T and B lymphocytes and other immune cells responsible for killing bacteria, viruses, fungi and other invasive pathogens.

The next most common form, ADA-SCID, accounts for 15 percent to 20 percent of cases and equally affects boys and girls. In this instance, the genetic defect results in a non-functional enzyme called adenosine deaminase (ADA), which, like SCID-X1, leads to profoundly low numbers of T lymphocytes (T cells), B lymphocytes (B cells) and natural killer cells.

Altogether, more than 20 recognized forms of "classical SCID" are characterized by a very low T-cell count with near-absent responsiveness to immunogenic stimuli. These patients not only have profound deficits in cellular immunity, but also have very poor antibody response when they come in contact with bacteria, viruses and other pathogens that infants with normal immune function (for their age) can readily fight off. Without immune reconstitution or the kind of extreme measures

used to protect David Vetter, nearly all of these children will die from overwhelming infection by the second year of life.

With an incidence estimated at just one in 30,000 to 60,000 live births, children with SCID are referred to major academic medical centers that have well-trained specialists who can manage infections and order prophylactic antibiotic and immune globulin (IG) therapy, and map out a definitive treatment plan. For most patients with classical forms of SCID, definitive treatment is to attempt to reconstitute the immune system by intravenously administering functional hematopoietic stem cells (HSCs) sourced from donor bone marrow, peripheral blood or umbilical cord blood. Ideally, these cells engraft in the bone marrow and restore cellular and antibody-mediated immunity.

The (Improving) Promise of Cure: Donor HSCT

In 1968, pediatricians at the University of Minnesota were the first to infuse HSCs from the bone marrow of a human leukocyte antigen-matched sibling to achieve immunological correction of an infant with X-linked SCID.[1] Over the ensuing four and a half decades, specialists have turned to HSC transplants (HSCTs) as a potentially life-saving treatment for SCID with mixed results. Some infants have experienced partial or complete restoration of immune function, while others have suffered engraftment failure or serious complications, including graft versus host disease (GVHD) and toxicity from preparative immunosuppressive "conditioning."

A number of factors (Table 1) appear to influence the prospects for successful HSC engraftment and survival. Prominent among them are 1) the type of stem cell donor, 2) the "conditioning" regimen prior to transplantation that facilitates donor cell engraftment, 3) recipient age at transplantation and 4) recipient infection status at transplantation.

For many years, availability of limited numbers of transplant procedures, together with combinations of these presumptive "risk factors" that vary from one SCID patient to the next, largely frustrated efforts of clinicians to discern which of them importantly impacted long-term survival after HSCT. Finally, a collaborative network of 25 U.S. and Canadian institutions — the Primary Immune Deficiency Treatment Consortium (PIDTC) — tasked itself with retrospectively gathering and analyzing demographic, treatment and long-term survival data from 240 infants with classical SCID who had undergone allogeneic (human donor) HSCT over a 10-year period from Jan. 1, 2000, through Dec. 31, 2009. This large case series, published in 2014, yielded a trove of valuable information to aid HSCT treatment planning.[2]

Prior to their procedure, 171 of the 240 infants — just more than 70 percent — had already suffered a documented infection.

Table 1. Key Risk Factors That Can Influence Long-Term Survival Prognosis in SCID Patients Undergoing Allogeneic HSCT

Risk factor	Examples
Type of stem cell donor	Matched sibling donor Matched family donor Matched unrelated donor Mismatched unrelated donor Haploidentical donor
Preparative conditioning regimen prior to transplantation	None Immunosuppression Reduced-intensity myeloablation Full-intensity myeloablation
Infective status at time of transplantation	No infection history Infection resolved Active infection
Age at transplantation	Specific to each individual

Well over half — 62 percent — of those infected infants were still suffering from their infection at the time of transplantation. Bacterial infections were the most common, followed by the yeast-like fungus *Pneumocystis jirovecii* (the causative organism for *Pneumocystis* pneumonia) and respiratory and DNA viruses. Most infants were diagnosed as the result of one or more severe infections from which they struggled to recover, even with the use of aggressive antibiotic therapy.

Most striking about the PIDTC survival analysis (Table 2) was that the entire cohort of infants transplanted under age 3.5 months had the highest long-term survival (94 percent; 64 of 68 children surviving). There was a similar 90 percent five-year survival rate (21 of 23 surviving) for infants *older than* 3.5 months at transplant who had no history of infection. The five-year survival rate was 82 percent (48 of 58 surviving) in the cohort of infants older than 3.5 months who had experienced a clinical infection that fully resolved by the time of transplantation. But the survival rate plummeted for infants older than 3.5 months who also had an *active infection* at the time of transplantation: just 50 percent (45 of 91) were alive after five years.

While infants receiving HSCs from a matched sibling donor also had an excellent survival outcome (97 percent), the unfortunate fact is that fewer than 15 percent had access to a matched sibling donor. All the rest of the 240 infants in this case series were forced to accept HSCs from a mismatched related donor (79 percent five-year survival when no immunosuppressive conditioning was used; 66 percent when it was used) or other

Table 2. Effects of Age, Infection Status, Donor Type and Conditioning Regimen on 5-Year Survival in SCID Patients Treated with HSCT[2]

Risk factor	Defined parameters	5-year survival (95% confidence interval)
Age, infection status at transplantation	0 – 3.5 months (any infection status)	**94%** (85 – 98%)
	>3.5 months, no infection	**90%** (67 – 98%)
	>3.5 months, infection resolved	**82%** (70 – 90%)
	>3.5 months, active infection	**50%** (39 – 61%)
Donor type, conditioning regimen	Matched sibling donor, any conditioning regimen	**97%** (79 – 100%)
	Mismatched related donor, no conditioning	**79%** (67 – 98%)
	Mismatched related donor, with conditioning	**66%** (70 – 90%)
	Other related or unrelated donor, any conditioning	**74%** (39 – 61%)

related or unrelated donors (74 percent five-year survival). By contrast, infants transplanted under age 3.5 months had a very high five-year survival experience despite the fact that the majority received less optimal mismatched related or unrelated donor HSCs, and at least some had a prior infection history or active infection at the time of their procedure.

The PIDTC data convincingly show that infants with SCID should undergo an HSCT procedure within the first 3.5 months of life, ideally before a first severe infectious illness. But as infants with SCID appear entirely healthy at birth, this presents a challenge. Usually nothing appears amiss directly up to the first hospitalization with severe and potentially life-threatening infection, when finally a battery of tests reveals the absence of a functioning immune system. Thus, diagnosis of SCID has historically been reactive — usually *after* a first or second severe opportunistic infection. The median age of the PIDTC SCID cohort, for example, was nearly 140 days at diagnosis; the median age at transplant was six months, by which time the health of most infants had already been harmed by opportunistic infection.

Newborn TREC Screening Jump-starts SCID Therapy

Seemingly on cue, a practical population-based newborn screening for SCID arrived to detect this occult disorder: the T-cell receptor excision circle (TREC) assay. First used in patients with HIV and hematological malignancy, the TREC assay was adapted to utilize the dried blood spots already universally obtained by heel-stick from infants in the first days of life to screen for metabolic diseases, cystic fibrosis, hypothyroidism and hemoglobin disorders. The TREC copy number is a biomarker for the output of T lymphocytes (lymphopoiesis) from the thymus. A very low TREC value identifies infants with SCID, who have profoundly decreased circulating naïve T cells, SCID-like disorders including "leaky SCID" and Omenn syndrome, and other non-SCID conditions associated with low T-cell counts.

How reliable is the TREC assay for identifying the rare case of SCID among the many thousands of unaffected babies? In 2008, Wisconsin became the first state in the U.S. to screen all newborns. The results of infant screening over the first three years (Figure 1) essentially tell the story. The specificity of the TREC assay — the proportion of healthy individuals correctly identified as test-negative — was a remarkable 99.98 percent. This is important, as too many "false positives" would unnecessarily create parental worry and drive up costs for fruitless additional testing. Equally if not more important was its 100 percent sensitivity: TREC screening identified every case of SCID.[3]

Of the 207,696 infants tested, 0.035 percent had an abnormal TREC screen. On further testing, normal T-cell counts were found in 53 percent of the infants with abnormal screen, but the remainder had varying levels of T-cell lymphopenia (low T-cell count). Of the patients with severe T-cell lymphopenia identified by the TREC assay, further testing determined that 58 percent had various secondary causes (e.g., a congenital anomaly, lymphatic abnormality or metabolic disorder), 15

percent had reversible T-cell lymphopenia, 12 percent had 22q11 chromosomal deletion syndrome and 15 percent — five newborns — had laboratory-confirmed SCID. Four of those five were referred for HSCT, and the fifth (with ADA-SCID) was placed on adenosine deaminase (ADA) replacement therapy.[4] At last report, all five SCID patients are alive, and those who received a donor stem cell transplant are alive and well.[5]

In May 2010, the U.S. Secretary of Health and Human Services added the TREC assay to the Uniform National Newborn Screening Panel. Unrelenting advocacy by the Jeffrey Modell Foundation, the Immune Deficiency Foundation and other groups has convinced 42 states to adopt TREC newborn screening, of which 28 are already up and running and 14 others expect to be sometime in 2015.[6] Just eight states — Alabama, Arizona, Indiana, Kansas, Louisiana, Montana, Nevada and Vermont — have yet to approve, fund and implement TREC screening for all newborns.

Transplants for PI Disorders Other Than SCID

The uniform lethality of SCID in infancy demands that clinicians and families accept some risks in pursuit of a realistic potential cure. This same principle applies for a number of other rare primary immunodeficiency (PI) disorders. Prominent among those often treated with HSCT are the following:

• *Chronic granulomatous disease (CGD)* is an inherited disorder of neutrophil function caused by mutations of an enzyme critical for phagocytic killing of intracellular pathogens. Severe and prolonged infections of the lungs, lymph nodes and skin are frequently found at diagnosis. Life expectancy is short, with only about one-half of affected individuals still alive by age 30.[7] First performed in the mid-1980s, HSCT remains the only curative therapeutic option.

While selection of which CGD patients would benefit from HSCT is still debated, those with signs and symptoms suggesting a guarded prognosis may be the most appropriate candidates.[8] After HSCT using well-matched donors, 18 of 20 children and young adults in a recent case series were alive at four to 117 months (median 61 months), with normal neutrophil function. Colitis affecting 10 of these patients resolved, and all seven with growth failure experienced catch-up growth.

• *Wiscott-Aldrich syndrome (WAS)*, an X-linked recessive disorder that affects about four in every one million male births, is associated with a life expectancy of less than 20 years. Most patients die of infections, malignancy, autoimmune-related illness or bleeding complications.[9]

Five-year survival following HSCT, which is the only curative therapy for WAS, now stands at about 90 percent. Patients with matched sibling donors have the best overall prognosis, but a recent analysis reveals 1) comparably high survival rates for boys under age 5 years who receive either an unrelated donor transplant or an HLA identical sibling transplant and 2) a 73 percent five-year survival rate for boys transplanted after age 5 years, suggesting that the transplantation option may be worth considering for those with good clinical status.[10]

• *X-linked lymphoproliferative disease (Duncan syndrome)* is a rare PI disorder affecting one to two boys per million. Mortality is high in part due to a unique susceptibility to Epstein-Barr virus, which can result in fulminant fatal disease. Once again, HSCT is the only curative treatment.

A multicenter study of 91 patients — 43 treated with HSCT and 48 not transplanted — documented an overall survival of 81 percent in the HSCT group and 62 percent in the non-transplanted group. Still under debate is whether a newly diagnosed child who is asymptomatic should receive HSCT therapy, as intravenous IG (IVIG) treatment can be instituted promptly; there is general consensus among experts that those with a matched sibling donor should be transplanted.[8]

The uniform lethality of SCID in infancy demands that clinicians and families accept some risks in pursuit of a realistic potential cure.

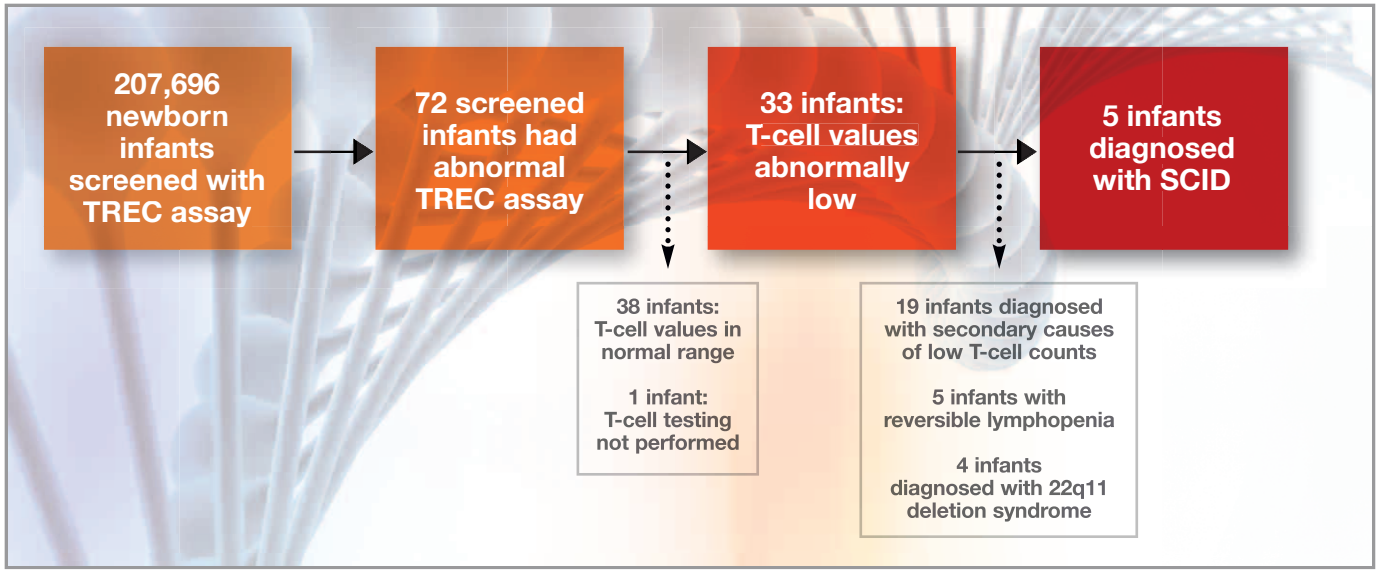
Several other PI syndromes for which HSCT has been shown to dramatically improve the prospects for long-term survival include *hemophagocytic lymphohistiocytosis (HLH)*[11] and *IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)*.[12,13]

Gene Therapy: The Promise of Cures Becomes Reality

Donor HSCT is clearly curative for the majority of infants with SCID. But major problems persist. GVHD and other transplant-related complications commonly occur in the large share of infants for whom there is no fully matched sibling or family donor. Many children continue to have poor B-cell function and remain dependent on long-term IG therapy. Incomplete immune reconstitution following transplantation leaves many children at ongoing risk for serious opportunistic infections; residual immunodeficiency after partially HLA-incompatible HSCT is still responsible for an estimated 30 percent mortality rate at one year post-transplantation.[14]

For many years, immunologists have appreciated that — if achievable without introducing new health risks — the ideal

Figure 1.
Outcome of TREC Screening of All Live Births in the State of Wisconsin for Severe Combined Immunodeficiency (SCID), 2008 – 2011



curative therapy is to harvest bone marrow from the patient and "transduce" his or her own (autologous) HSCs by using special viral "vectors" to insert normal copies of the mutated gene. These normal genes can in turn produce the critical missing functional protein causing the immunodeficiency disorder.

Two small early trials, one in France[15] and another in the United Kingdom,[16] proved that autologous CD34-positive hematopoietic bone marrow stem cells transduced with a gammaretroviral vector delivering IL2RG and reinfused into patients with SCID-X1 resulted in a sustained restoration of both cellular and humoral immunity.

Unfortunately, less than three years after their triumphant findings were published in *Science* in 2000, the French investigative team reported two cases of leukemia. Eventually, five of 20 SCID-X1 patients developed leukemia, attributed to "insertional mutagenesis" that resulted when gammaretroviral vectors activated a known T lymphocyte oncogene. In January 2003, the U.S. halted more than two dozen gene therapy studies that utilized those vectors.

Several years later, researchers returned to the clinic with redesigned vectors to ferry functional genes, including novel "self-inactivating" gammaretroviral vectors and lentiviral vectors incorporating safety features intended to minimize the risk of inducing leukemia. A wave of early trial results strongly suggest that gene therapy is safe and curative in patients with SCID-X1 and ADA-SCID.

Gene therapy for SCID-X1. In a report on parallel trials in the U.S. and Europe,[17] autologous bone marrow-derived HSCs transduced by a self-inactivating retroviral vector carrying a normal copy of the IL2RG gene were reinfused into nine infant boys with confirmed SCID-X1, including profound deficiency of autologous T cells. All were over age 3.5 months at the time of treatment; the median age was 8 months. All nine patients either lacked an HLA-identical related or unrelated donor or had an active treatment-resistant SCID-related infection. One patient with preexisting severe systemic adenoviral disease died before he could be fully reconstituted with vector-modified CD34-positive HSCs. Another who received a graft with a low number of vector copies did not show evidence of vector DNA uptake and later received a mismatched umbilical cord blood transplant.

At a median follow-up of 29 months, all eight treated boys were still alive, and seven of the eight experienced T-cell proliferative capacity in the normal range, and associated functionality that led to resolution of their infections. No severe adverse events related to the gene-transfer vector or cell manipulations were reported in any of the children. At a median of 33 months of follow-up, there was no occurrence of leukemia. These children are scheduled to be followed and periodically tested over the next 15 years.

Gene therapy for ADA-SCID. In 2009, a multinational team

reported that nine of 10 children receiving autologous HSCs transduced with a retrovirus carrying the functional ADA gene experienced immune reconstitution with increases in T-cell count and normalization of T-cell function.[18] At a median follow-up of four years, all 10 patients were alive, with no reports of leukemia or other serious adverse outcomes. Eight no longer required ADA replacement therapy. The number of severe infections decreased from 0.93 per 10 person-months before gene therapy to 0.13 following gene therapy; the median number of hospitalization days dropped from 45 to two.

A separate clinical study in the UK subsequently affirmed that, when it works, gene therapy for ADA-SCID resolves the profound T- and B-cell immunodeficiency and appears to all but eliminate the risk of severe opportunistic infections.[19] In an extraordinary announcement last November, Dr. David Kohn, the lead investigator of two trials of a gene therapy regimen developed at UCLA, reported that all 18 treated infants with ADA-SCID have been cured.[20] The UCLA team plans to seek FDA approval for its gene therapy regimen.

What Comes Next

In this new era of TREC screening, clinicians can now identify infants with SCID at birth and employ HSCT to reconstitute a functional immune system during the critical first few months of life, with improved prospects for partial or complete cures. HSCT is already the gold standard treatment for SCID, but going forward we can expect to see fewer treatment failures and higher overall long-term survival statistics. This experience may additionally help clinicians make further refinements to HSCT therapy for other severe PI disorders, potentially leading to its use in more patients with better outcomes.

Donor HSCT is clearly curative for the majority of infants with SCID.

Remarkably, at the same time, new clinical research suggests that gene therapy is finally poised to realize its curative potential for infants diagnosed with SCID-X1, ADA-SCID and someday, hopefully, other genetically well-characterized PI conditions as well.

In the very near future, clinicians may find themselves in the position of making patient-by-patient decisions about when to perform HSCT and when to turn to gene therapy for SCID or certain other severe PI disorders. Given the stakes involved for these precious new beings and their parents, it is a future they can look forward to. ❖

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Sleep Disorders: A Patient's Perspective

BY TRUDIE MITSCHANG

Narcolepsy is often misdiagnosed and frequently misunderstood. Most individuals experience symptoms for an average of three to five years before receiving an accurate diagnosis, although 10- to 15-year delays are not uncommon.

Melissa Patterson was a teen when she was first diagnosed with narcolepsy.

ON THE EVENING of her homecoming football game, high school freshman Melissa Patterson found herself sitting at home with electrodes attached to her head and a recorder strapped to her waist. The once-active teen had complained of sudden and puzzling symptoms, including unexplained muscle weakness and extreme drowsiness. Following a neurological exam, her doctor ordered a 24-hour EEG. Although results were inconclusive, Melissa was prescribed medication for epilepsy. A self-described "gifted but academically lazy" student, Melissa would spend the next year exhausted, frustrated and socially ostracized. "I was spending so much time battling exhaustion and trying to get my work done, I had no time or energy left to make friends or even socialize," she recalls. "I was bullied viciously for falling asleep all over the place and for being a complete klutz in gym class. I felt completely isolated."

By the latter half of ninth grade, it was clear the epilepsy medications were ineffective. Melissa's neurologist recommended she enroll in a sleep study, and a short time later, Melissa and her family received the shocking news: Melissa had narcolepsy.

Understanding Narcolepsy

Narcolepsy is a neurological disorder that causes excessive daytime sleepiness (EDS), affecting about one in 2,000 people nationwide. Patients diagnosed with narcolepsy may also experience brief episodes of muscle weakness known as cataplexy, vivid dreamlike hallucinations, brief episodes of paralysis when falling asleep or upon awakening (sleep paralysis), and fragmented nighttime sleep. Narcolepsy typically develops during the teen years and, though manageable with treatment, symptoms persist for a lifetime.[1]

In recent years, research has suggested that an immune system dysfunction may be a key trigger for narcolepsy. And, a growing body of research has produced evidence of a strong genetic component to the disorder. The latest results of studies into the origins of narcolepsy in the brain provide significant new information on both fronts. A recent study conducted by scientists at the Center for Integrative Genomics at Switzerland's University of Lausanne pinpoints a specific, immune-related genetic variation as a near-certain prerequisite for the condition.[2]

Melissa's narcolepsy presented with almost all of the common symptoms; in addition to EDS and cataplexy, she experienced both hypnagogic and auditory hallucinations, and disrupted nighttime sleep. "Once I was diagnosed, the first thing my doctor did was prescribe stimulants to combat the EDS. The stimulants were effective, but I learned the disruption in the sleep/wake cycle that causes narcolepsy also impacts nighttime sleep," she explains. "People with narcolepsy often suffer from insomnia, night terrors and other sleep disturbances, in addition to getting very little restorative, slow wave sleep. In my case, I was getting maybe four or five hours on a good night."

Learning to Accept a New Normal

When it came to identifying an effective treatment plan, Melissa says she had an advantage because her father is a pediatrician. The year she was diagnosed, her dad attended a Narcolepsy Network conference in Seattle and returned with a list of drug recommendations for Melissa's doctor to try. One of the medications was brand new and fairly controversial marketed under the name Xyrem. Although it was not approved for pediatric use, her doctor agreed to try it. Melissa says, "It's not an ideal medication, but it gave me my life back."

Melissa's full daily treatment regimen also includes modafinil (Provigil), a psychostimulant used to treat EDS; Concerta (methylphenidate), a central

nervous system stimulant usually prescribed to treat ADHD; and the antidepressant venlafaxine HCl (Effexor).

Melissa credits the Narcolepsy Network, an organization she now works for, with helping her family navigate those difficult early years. Because narcolepsy is so rare, it can be difficult for people to share information effectively, so in essence, everyone winds up reinventing the wheel during diagnosis and treatment. Melissa says patient support groups are vital because they help people network and link together so that the narcolepsy experience is less isolating.

In the decade since her diagnosis, Melissa says narcolepsy does impact her life, but it's not the most significant influence anymore. Despite her challenges, she graduated from college and graduate school (with a 3.5 or above GPA), participated in extracurricular activities and even served in student government. Today, she has a master's degree in public policy, and she now uses her degree by working for the Narcolepsy Network. "At this point, I have a small group of really good friends, so all in all, I'd say I have a pretty good life both because of and in spite of narcolepsy," says Melissa. "I love having a job that allows me to give back to an organization that did so much for me."

According to Melissa, the stigma of narcolepsy is still very real, and part of what drives her career is her desire to help educate people about a rare and very misunderstood condition. Narcolepsy patients have long been the subject of misunderstanding and insensitive, inaccurate or humorous portrayals in the media. In 2014, Honda Motor Co. produced a You Tube spot promoting its Honda Fit compact that poked fun at a driver living with narcolepsy. Amid public outcry, the spot was quickly pulled, but the damage was done. Across the nation, patient groups responded angrily, saying the ad "disrespects the 200,000 Americans struggling with this lifelong, incurable sleep disease."

Melissa understands. "I want people to know it's not just falling asleep in your soup. There are lots of other symptoms and issues associated with it," she says. "Disrupted night sleep, 'brain fog,' automatic behaviors — these are all things patients with narcolepsy live with but are rarely mentioned. You have to treat all aspects of the condition, not just the EDS." ❖

Melissa now works for the Narcolepsy Network, which she says allows her to give back to an organization that did so much for her. She is pictured with Eveline Honig, Narcolepsy Network executive director (center), and Tiffany McCullough, a Narcolepsy Network member (left).

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

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Sleep Disorders: A Physician's Perspective

Dr. Peter A. Fotinakes has made it his life's commitment to treat sleep apnea, which is his passion.

DR. PETER A. Fotinakes first encountered sleep medicine in 1977 during his first year at UC Irvine Medical School, when his mentor, Dr. Jon Sassin, lectured on a newly described medical condition called sleep apnea. Five sleep apnea patients attended that lecture to discuss how they were "cured" by having a tracheostomy, the only known treatment at the time. Their miraculous response to treatment prompted Dr. Fotinakes to make sleep medicine his life's commitment. Sleep medicine has evolved since those early days, and today, Dr. Fotinakes serves as the medical director at St. Joseph Hospital Sleep Disorders Center in Orange, Calif., and as a diplomate of the American Board of Neurology.

BSTQ: You've described sleep as a "new frontier" in medicine. What do you mean?

Dr. Fotinakes: Until about 50 years ago, most physicians viewed sleep as a period of inactivity with little impact upon general health. With the discovery of narcolepsy, sleep apnea, circadian rhythm disorders and insomnia, we now understand that sleep has a profound impact on life and health. Narcolepsy is now understood to be a neurodegenerative disorder of hypocretin cells in the hypothalamus of the brain that may be related to an autoimmune reaction or exposure to exogenous toxins. Sleep apnea produces nonrestorative sleep and excessive daytime sleepiness and increases the risk of hypertension, cardiovascular disease and cerebrovascular disease. Recent prevalence studies indicate that 26 percent of adults between 30 years and 70 years old require treatment for sleep apnea. We now have better ways of treating circadian rhythm disorders with bright light exposure and wake-promoting medications. Also, the U.S. Food and Drug Administration recently approved a new medication to treat non-24-hour sleep-wake disorder, a circadian rhythm disturbance associated with ocular blindness. William Dement, MD, one of the fathers of sleep medicine, aptly said, "After 50 years of research, as far as I know, the only reason we need to sleep … is because we get sleepy." There is still much to learn about why we sleep and what sleep does for us and to us.

BSTQ: What are the most common disorders you treat in your clinic?

Dr. Fotinakes: The most common sleep disorder seen in a general clinical practice is insomnia, but the most common sleep disorder seen within a sleep disorders center is sleep apnea. That's because most insomnia is transient and affects people for such short periods that they don't rise to the level of a specialty referral. Furthermore, general practitioners often treat these patients with sleeping medications that effectively treat sleeplessness but often lead to problems in chronic insomniacs. Sleep apnea requires specific testing to determine if it rises to the level to require treatment. Treatment often involves nasal continuous positive airway pressure (CPAP), which requires a certain level of expertise to improve and perpetuate compliance.

BSTQ: What are the most prevalent misconceptions about sleep disorders?

Dr. Fotinakes: Patients are often unaware of their sleep disturbance because they are asleep when their symptoms occur. The prevalence of snoring is so high in the general public that it is often viewed more as a humorous nuisance than what it truly is, a symptom of a serious condition. Insomniacs are keenly aware of their

condition, because they are awake as they suffer through the night. Many insomniacs seek a quick-fix with a medication, without understanding the underlying problem and how to deal with it without medications. Insomnia is more often a symptom of another problem than a condition unto itself.

BSTQ: When should a patient be referred to a sleep disorders center?

Dr. Fotinakes: Usually this occurs when their sleep disturbance requires specialized testing that is best performed in an accredited sleep disorders center. Accreditation ensures that testing is performed within the guidelines of the American Academy of Sleep Medicine, and patients will receive evaluation by a board-certified sleep specialist and registered sleep technologists. Most people are referred for sleep testing related to the diagnosis of sleep apnea, periodic limb movements and narcolepsy. Primary care physicians also refer insomniacs who fail to improve after six months or have complicating features associated with their sleep disturbance.

BSTQ: What happens during the assessment and diagnosis process?

Dr. Fotinakes: As with most medical conditions, the medical evaluation begins with a history and physical focused upon health issues that impact sleep. Most insomniacs do not require overnight testing in the laboratory and are better served by a clinical evaluation that includes a sleep diary and a medical/psychological assessment. People with nonrestorative sleep and daytime sleepiness often require overnight testing to screen for conditions such as sleep apnea, periodic limb movements and narcolepsy.

BSTQ: Many patients who present with sleep issues are prescribed medications. What is your opinion on this treatment tactic?

Dr. Fotinakes: Prescription sleeping pills work great, but that's the problem. They are an easy fix for a complicated condition. More often, chronic insomnia is a symptom of an underlying medical or psychological condition, and it's better to treat the underlying condition than it is the symptom. Prescription sleeping medication should be reserved for short periods of insomnia. If the sleep disturbance extends beyond four to six weeks, then another mode of treatment should be entertained. Most prescription sleeping medications affect the GABA receptor in the brain, which is the same receptor affected by benzodiazepine medications (Valium-type drugs). As such, even though they have a different chemical structure from benzodiazepines, they share the same potential side effects. These side effects include habituation and tolerance. Very often, insomniacs who take these medications beyond six weeks have developed a tolerance to their effects and experience rebound insomnia from the medication 24 hours after the last dose, which is when they are trying to sleep. They are, in effect, only treating medication withdrawal and not the cause of their insomnia.

BSTQ: Are there any new studies on sleep disorders or treatment options in the pipeline that show promise?

Dr. Fotinakes: The most prevalent focus in sleep medicine has been how to deal with the huge segment of the population that suffers from sleep apnea. In an attempt to reduce costs and streamline care, the industry has developed home sleep studies and automated CPAP units. While it is tempting to sidestep a large segment of the evaluation and treatment, it is difficult to fully eliminate the human element, so the automated systems may not be indicated in 30 percent of treatable sleep apnea patients who may remain undiagnosed or inappropriately treated if insurance companies relegate diagnosis and treatment to a fixed algorithm to cut costs. ❖

With the discovery of narcolepsy, sleep apnea, circadian rhythm disorders and insomnia, we now understand that sleep has a profound impact on life and health.

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

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BioResearch

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

IVIG to SCIG Switch in CIDP & MMN Patients: Improved Tolerability and Patient Satisfaction

Eight consecutive patients on long-term, hospital-based intravenous immunoglobulin (IVIG) therapy to treat chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (n=4) and multifocal motor neuropathy (MMN) (n=4) were switched to home-based subcutaneous immunoglobulin (SCIG). Patients were selected on the basis of a relatively low dosing requirement, problems experienced with IVIG, and their willingness to switch to SCIG. Reasons cited for wishing to switch from IVIG included adverse effects attributable to IVIG (neutropenia, n=3; nausea or headache, n=2; allergy requiring treatment, n=1); unacceptable fluctuations in weakness as IVIG wore off (n=1); poor intravenous access (n=2); distance from home to hospital (n=2); and missing work for hospital visits (n=1). Several patients cited more than one reason.

After a mean of 33 months on SCIG therapy (range 18 to 64 months), seven patients remained neurologically stable, with six on a similar mean weekly immunoglobulin dose relative to their original IVIG dose. At final follow-up, the mean weekly SCIG dose ranged from 8.0 grams to 24.0 grams.

Seven of the eight patients reported a "good" outcome, citing substantial benefits relating to nausea and headache (four patients), travel convenience (four patients), venous access problems (three patients) and avoidance of wearing-off fluctuations (two patients). Adverse effects of SCIG were generally mild and infrequent. The mean score in response to the question "Overall how strong is your preference for IVIG or SCIG?" (visual analogue scale [VAS]; prefer IVIG = 0, prefer SCIG = 100) was 93 (standard deviation, 7). For seven of the eight patients, the investigators concluded that "SCIG gave improved tolerability and patient satisfaction with similar efficacy compared with IVIG."

Hadden RDM and Marreno F. Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: improved tolerability and patient satisfaction. Ther Adv Neurol Disord *2015;8(1):14-19.*

Higher Dosages of 25% Albumin Associated with Lower Incidence of Cerebral Ischemia and Infarction in Pilot ALISAH Study

The "Albumin in Subarachnoid Hemorrhage" (ALISAH) pilot clinical trial, conducted at the Baylor College of Medicine in Houston, assessed the neuroprotective effects of varying dosages of 25% human albumin. Vasospasm, delayed cerebral ischemia (DCI) and cerebral infarction were evaluated in 20 patients who received seven consecutive daily infusions of 0.625 g/kg (Tier 1), 20 who received 1.25 g/kg (Tier 2), and seven who received 1.875 g/kg (Tier 3).

Transcranial Doppler ultrasound (TCD) showed vasospasm in 75% (n=15), 55% (n=11) and 29% (n=2) of subjects in dosage Tiers 1, 2 and 3, respectively. DCI was present in 20% (n=4), 15% (n=3) and 14% (n=1) of subjects in the three escalating dosage tiers. Cerebral infarctions occurred in 45% (5/9), 27% (3/18) and 25% (1/4) of subjects who had follow-up head CT scans in dosage Tiers 1, 2 and 3, respectively.

The investigators concluded that higher dosages of 25% albumin were associated with a lower incidence of TCD vasospasm and cerebral infarction at 90 days follow-up, in a dose-dependent manner.

Suarez JI, Martin RH, Calvillo E, et al. Effect of human albumin on TCD vasospasm, DCI, and cerebral infarction in subarachnoid hemorrhage: the ALISAH study. Acta Neurochir Suppl. *2015;120:287-90.*

4-Factor Prothrombin Complex Concentrate Superior to 3-Factor Version for Reversal of Coumarin Anticoagulation in Rat Model

In an established preclinical bleeding model, reversal of coumarin anticoagulation with Kcentra, a four-factor prothrombin complex concentrate (4F-PCC), was shown to be superior to three-factor prothrombin complex concentrates (3F-PCCs), according to findings reported by CSL Behring investigators. Treatment with 4F-PCC was able to fully reverse bleeding, achieving an average bleeding time of 676 seconds. Prior to 4F-PCC therapy, animals had been anticoagulated with coumarin to induce an increase in median bleeding time from an average of 823 seconds to 1,800 seconds; in parallel, prothrombin time (PT) was prolonged from 8.9 seconds to 29.9 seconds prior to treatment.

In addition to normalizing bleeding time, 4F-PCC treatment reversed elevated PT, bringing it down to 15.1 seconds. In contrast, two commercialized 3-PCCs were not able, or were only partially able, to reduce coumarin-induced bleeding; average post-treatment bleeding times were 1,398 and 1,708 seconds. This also corresponded with inferior reductions in PT, with minimum levels of 23.8 and 29.5 seconds.

The investigators concluded that the replenishment of all vitamin K-dependent coagulation factors (factors II, VII, IX and X), including factor VII found in 4F-PCC, may result in superior efficacy compared with the use of 3F-PCC for reversal of coumarin anticoagulation.

Herzog E, Kaspereit F, Krege W, et al. Four-factor prothrombin complex concentrate (4F-PCC) is superior to three-factor prothrombin complex concentrates (3F-PCC) for reversal of coumarin anticoagulation. American Society of Hematology Annual Meeting. Oral and Poster Abstract 1472. Saturday, Dec. 6, 2014.

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BioProducts

New products in the marketplace.

Clinical Trial Patient Monitoring

A U.S. Food and Drug Administration-cleared biosensor is now available to help improve monitoring during clinical trials. HealthPatch MD, a small patch worn on the chest, enables 24-hour remote patient monitoring without inhibiting regular activities of clinical trial participants. The biosensor has two components: the reusable sensor module and the disposable patch. It detects the following vital signs and biometric measurements: single-lead ECG, heart rate, heart rate variability, respiratory rate, skin temperature, body posture, including fall detection/severity, and steps. The patch is particulate- and water-resistant.
Vital Connections, (408) 963-4600, www.vitalconnect.com/healthpatch-md

Safer Vaccine Administration

West Pharmaceutical Services has been given U.S. Food and Drug Administration clearance for its NovaGuard SA (staked-needle automatic) safety system that prevents needlesticks by providing a mechanism that can be activated to cover the needle immediately after injection. The system includes a tamper-evident needle shield, a break-resistant design that does not put pressure on the flange during assembly, and an indicator that makes the needle nonfunctional if the shield has been damaged. It comes packaged in bulk to facilitate the assembly process without the risk of pre-activation. The system is compatible with prefilled ISO standard glass syringes.
West Pharmaceutical Services, (800) 231-3000,
www.westpharma.com/en/events/Pages/7832-RN-NovaGuard-Platform.aspx

Needle Safety Device

Raumedic AG and Cambridge Design Partnership have created RauSafe, a needle safety device that uses a telescopic sleeve activated after injection to cover the needle and protect healthcare workers from needle-stick injuries. The safety system is activated after the injection by simply pushing it forward. As soon as the needle is fully enclosed, the system latches permanently in the final position, which the user can hear and feel. The needle stick protection system can also be adapted to various existing syringes on the market and is built in a compact way that it is frequently possible to retain the standard packaging. The device recently received the DeviceMed award for most innovative medical device at COMPAMED 2014, the international trade fair for the medical engineering supply industry. RauSafe is currently available for license.
RaumedicAG, www.raumedic.com/news/news-detail/raumedic-rausafeR-wins-the-devicemed-award-at-compamed-2014/

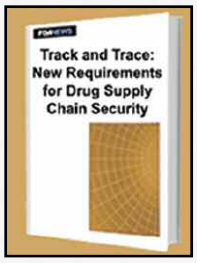
First Pathogen-Reduction System to Treat Plasma

The INTERCEPT Blood System for plasma, the first pathogen-reduction system for use by blood establishments in the preparation of plasma to reduce the risk of transfusion-transmitted infections, has been approved by the U.S. Food and Drug Administration (FDA). The system, marketed by Cerus Corp., can be used to reduce pathogens in plasma derived from whole blood and plasma obtained by apheresis, a collection process that separates red blood cells from plasma and then returns the red cells to the donor. Examples of some of the pathogens that could be reduced using the system include HIV, hepatitis B and C viruses and West Nile virus. The inactivation of certain potential pathogens in plasma treated with the system is achieved through a photochemical process involving a controlled exposure to ultraviolet light and amotosalen, a chemical that facilitates the inactivation process. The plasma is then purified to remove the chemical and its byproducts. "The approval of devices like the INTERCEPT Blood System allows blood establishments to prepare plasma that carries a lower risk of transmitting infectious pathogens through transfusion," said Karen Midthun, MD, director of FDA's Center for Biologics Evaluation and Research.

Plasma prepared using the INTERCEPT Blood System was evaluated in eight clinical studies with 704 patients, and the data to support the use of plasma treated with the system were obtained from clinical trials conducted in various clinical settings, including acquired clotting disorders associated with liver disease and thrombotic thrombocytopenic purpura. Adverse events experienced by patients who received plasma prepared using the system were comparable to those experienced by participants who received plasma that had not been treated with it.
Cerus Corp., interceptbloodsystem.com

BioResources

Recently released resources for the biopharmaceuticals marketplace.



Track and Trace: New Requirements for Drug Supply Chain Security

Author: U.S. Food and Drug Administration

This guide presents the new rules and technical standards for track and trace. It includes tips on how to classify an enterprise to determine which deadlines must be complied with, a roadmap to help companies anticipate how the new rules will change over time, an explanation of technical serialization and identifier requirements, how a company can determine whether it's dealing with ADRs (authorized distributors of record) and other newly required steps before sending or receiving drugs from another party, and more.

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Stopping the Ebola Outbreak

Author: American Association for Accreditation of Ambulatory Surgery Facilities

The AAAASF has developed a sheet that provides a facility preparedness checklist for Ebola, as well as facts about the virus in the United States.

http://news.cision.com/aaaasf/r/aaaasf-provides-out-patient-facilities-with-ebola-checklist,c9656277

Reduce Human Error in Drug and Device Manufacturing

Author: U.S. Food and Drug Administration

This report discusses why investigations of human error often end without learning what led to the error and how to prevent it from happening again. It explores root cause analysis techniques and how to apply them to workers, as well as systems, and includes the following tools: cognitive load tool, root cause determination tool, predictive load tool, human error prediction tool assessment form, task criticality assessment tool, human error — floor assessment checklist, human error assessment tool, process vs. procedure analysis tool, SOP template to prevent human error, and on-the-job training test template.

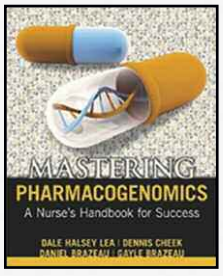
info.fdanews.com/B-Reduce-Human-Error-in-Drug-and-Device-Manufacturing_Landing-Page?hittrk=14N05&utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=56801380

Considerations of the FDA's Impact on Competition in the Drug Industry

Author: Alex Brill (sponsored by the Pharmaceutical Care Management Association)

This paper is intended to explore government involvement in drug pricing by examining how the U.S. Food and Drug Administration (FDA) affects, perhaps unintentionally and unknowingly, the prices of prescription drugs, and to encourage the agency to investigate and evaluate the impact it has on both brand versus generic competition and brand versus brand competition within the drug industry. The paper argues that "as policy experts examine the causes and consequences of high drug prices, greater attention should be paid to the FDA's impact on competition. Possible steps for lawmakers and the FDA to take to facilitate competition in the pharmaceutical industry include a more vigorous effort in support of biosimilars, faster review times for drug applications, legislation to prohibit misuse of Risk Evaluation and Mitigation Strategies (REMS), and adequate FDA resources to ensure that expedited approvals for certain novel drug applications do not impede the approval of competing brand drug applications."

www.pcmanet.org/images/stories/uploads/2014/mga%20pcma%20white%20paper%20nov%202014.pdf



Mastering Pharmacogenomics: A Handbook for Success

Author: Dale Halsey Lea, MPPH, RN, CGC, FAAN, Dennis J. Cheek, PhD, RN, FAHA, Daniel Brazeau, PhD, and Gayle Brazeau, PhD

Four of the top leaders in genetics, genomics and pharmaceutical research have put their minds together to create an informational guide to the inner workings of pharmacogenomics and how it could help prevent many diseases and relieve side effects and current treatments. Their new book provides both students and practitioners with an understanding of the basic principles of human genetics and genomics. Both academic and clinical professionals — specifically nurses — can apply this knowledge base to challenges in optimizing drug therapy and patient care.

www.nursingknowledge.org/sttibooks

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective April 1, 2015, through June 30, 2015.

Product	Manufacturer	HCPCS	ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$72.70	$71.53
CARIMUNE NF	CSL Behring	J1566	$57.90	$56.97
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$71.09	$69.95
GAMMAGARD LIQUID	Baxter	J1569	$78.41	$77.16
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$57.90	$56.97
GAMMAKED	Kedrion	J1561	$79.81	$78.53
GAMMAPLEX	Bio Products Laboratory	J1557	$72.76	$71.59
GAMUNEX-C	Grifols	J1561	$79.81	$78.53
OCTAGAM 5% & 10%	Octapharma	J1568	$81.11	$79.81
PRIVIGEN	CSL Behring	J1459	$74.90	$73.70

*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: PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	3 g, 6 g, 12 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PI	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: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxter	IVIG: PI, ITP, CLL, KD	2.5 g, 5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Laboratory	IVIG: PI, ITP	5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PI	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Baxter	SCIG: PI	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PI	1 g, 2.5 g, 5 g, 10 g, 25 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PI, 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
PI 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 mL multi-dose vial	5 years and older*	90658/Q2035
		0.5 mL single-dose syringe		90656
GlaxoSmithKline	FLULAVAL (IIV3)	5 mL multi-dose vial	3 years and older	90658/Q2036
	FLULAVAL QUADRIVALENT (IIV4)	5 mL multi-dose vial	3 years and older	90688
		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 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 years and older	90673
Sanofi Pasteur	FLUZONE (IIV3)	5 mL multi-dose vial	3 years and older	90658/Q2038
			6-35 months	90657
		0.5 mL single-dose syringe	3 years and older	90656
	FLUZONE QUADRIVALENT (IIV4)	5 mL multi-dose vial	3 years and older	90688
			6–35 months	90687
		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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