

# 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.

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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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> "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."<sup>4</sup>

### 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.<sup>4</sup>

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.<sup>5</sup>

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.<sup>4</sup> 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

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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.<sup>5</sup>

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.<sup>6</sup>

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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.<sup>7</sup>

### **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.<sup>1</sup> 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. (compared with 100 percent domestic production 15 years ago<sup>3</sup>), and 40 percent of finished drugs consumed in the U.S. are manufactured overseas.<sup>8</sup> 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.<sup>3</sup> 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.<sup>9</sup>

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.<sup>10</sup>

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.”<sup>11</sup> 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.<sup>12</sup>

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.”<sup>10</sup>

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.<sup>11</sup> 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.<sup>13</sup> 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.<sup>14</sup>

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.”<sup>15</sup>

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.<sup>16</sup>

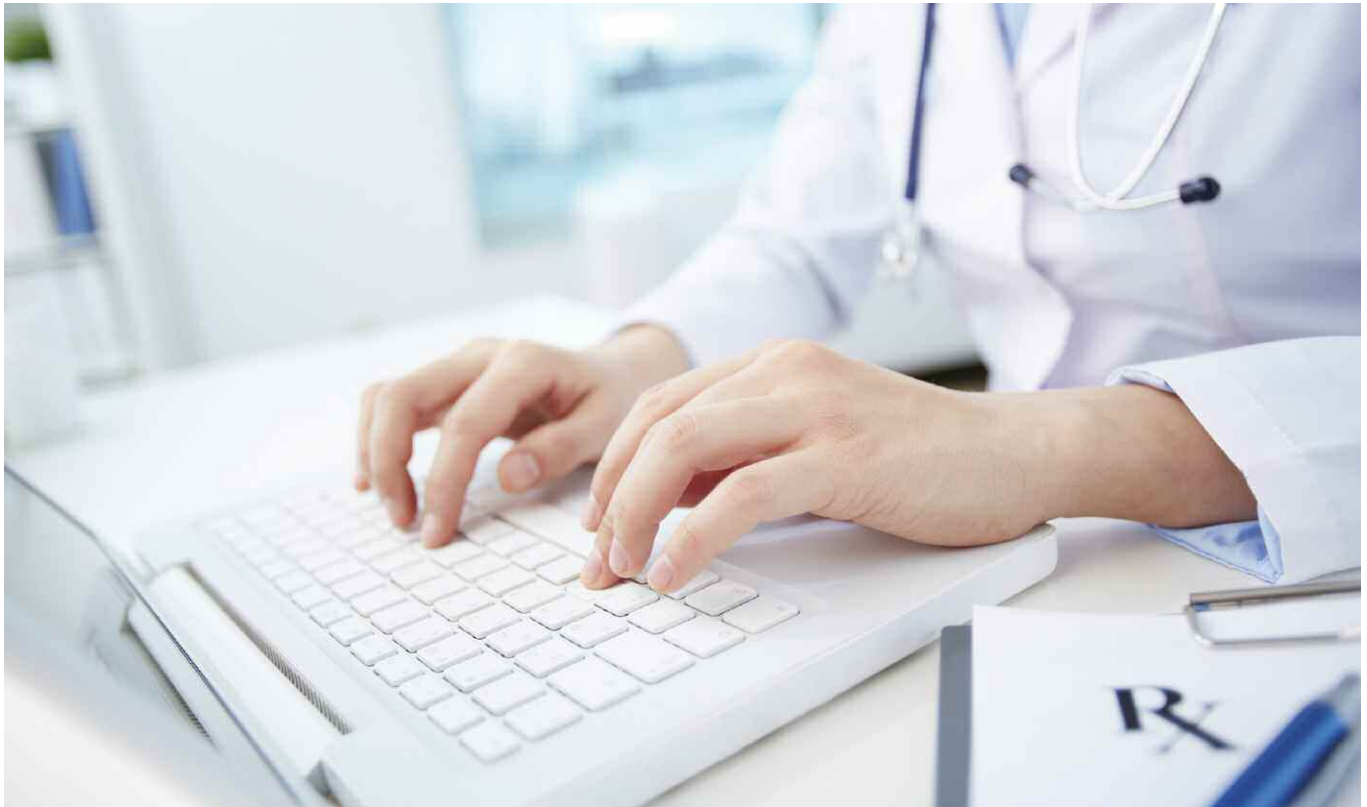
Many Internet pharmacies sell drugs that are counterfeit, contaminated or otherwise unsafe. Unfortunately, consumers continue to be enticed by the availability of hard-to-find drugs and gray market pricing available through fake online pharmacies. Drugs purchased online from countries outside the U.S. 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.<sup>4</sup>

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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.<sup>17</sup>

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.<sup>3</sup>

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.<sup>6</sup> "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.<sup>4</sup>

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.<sup>10</sup>

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.<sup>3</sup>

### **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.<sup>18</sup>

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.<sup>1</sup>

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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.<sup>19</sup>

## 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.<sup>20</sup>

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.<sup>1</sup>

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.”<sup>10</sup>

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 com-

pliance by 2016. California’s law does stipulate that if a federal law is implemented, that law will supersede the state law.<sup>20</sup>

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.<sup>4</sup>

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.<sup>21</sup> 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.<sup>22</sup> 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<sup>®</sup>

## 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<sup>®</sup> (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 or 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<sup>®</sup> is a registered trademark of Medimop Medical Projects, Ltd., a subsidiary of West Pharmaceutical Services, Inc.



For more information: Grifols Biologicals Inc.  
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# Profilnine<sup>®</sup>

## Factor IX Complex

Solvent Detergent Treated/Nanofiltered

### BRIEF SUMMARY

#### CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

#### DESCRIPTION

Factor IX Complex, Profilnine<sup>®</sup>, 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	Virus Type	Model For:	Virus Reduction (log <sub>10</sub> ) Process Step		
			1 <sup>st</sup> 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 <sup>a</sup>	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

<sup>a</sup> 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](http://www.fda.gov/medwatch).

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

#### Rx only

# GRIFOLS

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U.S. License No. 1694

3039440-BS  
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By Nov. 27, 2017, manufacturers will be required to provide product tracing information in an electronic format for certain transactions.<sup>23</sup> 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.<sup>22</sup>

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.<sup>21</sup>

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."<sup>10</sup>

## 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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