What Gastroenterologists Should Know About the Gray Market, Herbal Remedies, and Compounded Pharmaceuticals and Their Regulation by the Food and Drug Administration

Eli D. Ehrenpreis, MD[1], Prasad Kulkarni, MD[2], Carol Burke, MD[3] and the FDA-Related Matters Committee of the American College of Gastroenterology

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The pharmaceutical gray market

A large number of mechanisms exist, both in the United States and globally, to regulate the research, manufacture, distribution, and postmarketing surveillance of biopharmaceuticals. In the United States, the *Code of Federal Regulations* (CFR) governs this process (1). Title 21 of the CFR governs food and drugs for three federal agencies: the US Food and Drug Administration (FDA) (Chapter I), the Drug Enforcement Administration (Chapter II), and the Office of National Drug Control Policy (Chapter III). Chapter I, Sections 200 and 300 are pharmaceutical regulations, including Current Good Manufacturing Practices (cGMPs). cGMPs are enforced in the United States by the FDA, under Section 501(B) of the 1938 Food, Drug, and Cosmetic Act (21 USC 351) (2).

In response to the development of a wholesale submarket (known as the diversion market) for prescription drugs, the US Congress passed the Prescription Drug Marketing Act (PDMA) in 1987 (3). The PDMA establishes legal safeguards for prescription drug distribution to ensure drug safety and efficacy and to discourage the sale of counterfeit, adulterated, misbranded, sub-potent, and expired prescription drugs.

Over the past several decades, the system of getting pharmaceuticals to patients, i.e., the manufacturer–distributor–supplier–retailer–consumer pathway, has become complex and difficult to regulate to maintain quality and safety at all times. A large portion of drug manufacturing has moved overseas where manufacturing costs are lower and restrictions are less stringent. Today, nearly 40% of American drugs are imported, and nearly 80% of the active ingredients in drugs on the American market come from overseas sources (4). Some drugs that are restricted or unapproved in the United States may be freely or inexpensively available overseas. The drug industry is sometimes unable to accommodate the demand for pharmaceuticals. Pharmaceutical manufacturing—from raw material to finished product—has become highly complex. Before drugs reach the consumer, involvement of raw material (including active ingredients) suppliers, producers of the finished product, package suppliers, shippers, repackagers and commercial distributors are all involved in the process (5,6). Counterfeits, diversions, and cargo theft are all part of a growing criminal enterprise that also includes the deliberate adulteration of drugs and consumer products to maximize profits. Problems include (i) the development of severe drug shortages, some in critical areas; (ii) counterfeit drugs; and (iii) the "gray market."

Traditionally, a gray market (also known as a parallel or diversion market) is the trade of a commodity through legal distribution channels that are unofficial, unauthorized, or unintended by the original manufacturer. Over the years the concept has gradually broadened to also include counterfeit drugs. The biopharmaceutical gray market has effects at four levels: hospitals (university-affiliated and private), pharmacy networks, health-care providers, and individual consumers. In the outpatient setting, gray market medications have impact when patients use sub-potent drugs that fail to achieve desired therapeutic responses. Serious consequences, such as toxic reactions or lack of drug efficacy, have been shown to occur when patients use unregulated, unsafe, or counterfeit drugs. Some of these are smuggled into the United States or purchased online (4).

An unfortunate example occurred in 2008, when more than 80 deaths were reported linked to a raw heparin ingredient imported from the People's Republic of China, processed from pig intestines. Upon investigation by the FDA and several pharmaceutical companies, the contaminant was identified as an "oversulfated" derivative of chondroitin sulfate. It was alleged that since chondroitin derivative, a non-naturally occurring

[1]Gastroenterology Division, Department of Medicine, NorthShore University HealthSystem, Evanston Illinois, USA; [2]James A. Haley Vetrans Hospital, Tampa, Florida, USA; [3]Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, Ohio, USA. **Correspondence**: Eli D. Ehrenpreis, MD, Highland Park Hospital, 777 Park Avenue West, Highland Park, Illinois 60035, USA. E-mail: ehrenpreis@gipharm.net

Table 1. Medications for which counterfeits have been identified in the United States

Lipitor
Alli
Acomplia
Combivir
Viramune
Plavix
Viagra
Levitra
Cialis
Zyprexa
Aspirin
Tylenol phentermine
Evital
Tamiflu

molecule, costs a fraction of true heparin and mimics the properties of heparin, the contaminant was intentionally added to boost profit margins. Examples of counterfeited drugs purchased on the Internet include counterfeit oseltamivir phosphate and its branded form, Tamiflu. In 2007, Xenical (orlistat) capsules ordered over the Internet were found to be composed only of talc and starch. In January 2010, counterfeit Alli (orlistat) was discovered that did not contain the active ingredient but instead consisted of varying amounts of the stimulant sibutramine, which can lead to serious toxicity if used by people with certain cardiac diseases (7).

It is difficult to detect, investigate, and quantify counterfeiting and to know the true extent of the problem. Drug counterfeiting is known to be widespread and affect both developing and developed countries. Some estimates are: less than 1% of drugs on the market in Australia, Canada, Japan, New Zealand, the United States, and most of the European Union; about 10% in Southeast Asian countries; as much as 50% of some drugs in China; and up to 40% in underdeveloped countries such as Argentina, Colombia, and Mexico (8,9).

Table 1 shows counterfeit medicines identified in the United States. Counterfeiting of gastroenterology medications has not been identified.

Issues related to ordering medications on the Internet

Online ordering of drugs has been attractive because of discounted pricing and potential access to locally restricted drugs. Unfortunately, with this practice consumers are subject to the risks of identity theft and counterfeit medications (10,11). Buying controlled substances online without a valid prescription may be punishable by imprisonment under federal law. Websites claiming to be Canadian online pharmacies may be physically located elsewhere and selling counterfeit medicines to unwary customers. Prescriptions written by "cyberdoctors" without an actual office visit or clinical examination, using questionnaires that are administered online, are not considered legitimate by the FDA. In addition, according to federal law, importation and shipment of controlled substances to a non–Drug Enforcement Administration registrant is a felony (12).

Table 2 shows advice from the FDA to consumers on how to assess the legitimacy of online pharmaceutical purchases.

Herbal remedies

The FDA Food, Drug, and Cosmetic Act defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" (2). Drugs meeting this definition go through a variety of complex pathways during development and are scrutinized after entry into the consumer market. Dietary supplements and herbal products, on the other hand, undergo significantly less scrutiny by the FDA, particularly when entering the marketplace. The role of the FDA in regulation of these products has been formally described in detail in the Dietary Supplement Health and Education Act (DSHEA), signed by Congress in 1994 (2,13). The specifics of the DSHEA are summarized in **Table 3**.

The DSHEA was further enhanced by the Dietary Supplement and Nonprescription Drug Consumer Protection Act, enacted in 1996 (14). This act requires manufacturers to notify the FDA about deaths, life-threatening injuries, hospitalizations, disability, birth defects, and requirements for medical intervention for the prevention of any of these problems.

In June 2007, the FDA also published comprehensive regulations for Current Good Manufacturing Practices for those who manufacture, package, or hold dietary supplement products (15). These regulations focus on practices that ensure the identity, purity, quality, strength, and composition of dietary supplements.

It has been estimated that 56% of patients with inflammatory bowel disease (IBD) use complementary and alternative medicine (CAM) (16). CAM is used in 35–50% of patients with functional bowel diseases, including irritable bowel syndrome (IBS) (17,18), and 27.8% of patients with cirrhosis (19). Herbal therapies are a regular component of CAM. Although herbal treatments generally have a good safety record and a number of mechanisms have been identified that could suggest benefit from these treatments, a limited number of randomized placebo-controlled trials have been performed for gastrointestinal conditions. Thus far, randomized trials of single herbal treatments have been conducted for peppermint oil, turmeric, red pepper,

Table 2. US Food and Drug Administration Criteria for legitimacy of online pharmacies

The pharmacy is located in the United States.
The pharmacy is licensed by the board of pharmacy for the state in which the website operates. A list with contact information for the state boards of pharmacy of each state.
A licensed pharmacist is available to answer any questions regarding the drug being purchased.
The pharmacy requires a prescription from a health-care professional licensed to prescribe medications.
Contact information is available on the website.
The website carries the National Association of Boards of Pharmacy's Verified Internet Pharmacy Practice Sites (VIPPS) seal.

St. John's wort, and artichoke leaf for IBS (19–21); aloe vera gel, *Boswellia serrata*, curcumin, and wheat grass juice for IBD (22–24); and milk thistle for liver disease (19). Combinations of herbs have also been studied for IBS and functional dyspepsia (25). Combinations of multiple Chinese herbs have also undergone clinical trials for IBS and IBD. Chinese herbal remedies have been used for the treatment of cirrhosis, nonalcoholic fatty liver disease, hepatocellular carcinoma, metastatic cancer of the liver, viral hepatitis, and schistosomiasis. Interestingly, consumption of two or more cups of coffee or tea daily appears to protect against chronic liver disease (26). A meta-analysis has been performed evaluating the quality of studies on herbal remedies for IBD (27). This study suggested that the majority of these treatments do not have proven efficacy because of identified methodological problems. Meta-analyses of herbal treatments for IBS and chronic liver diseases have not been performed.

Gastroenterologists should also be aware that some herbal remedies that have been used for nondigestive conditions are potentially toxic to the liver. These are listed in **Table 4** (28).

Compounded pharmaceuticals

Compounded pharmaceuticals are medications prescribed by a legally authorized prescriber and prepared by a pharmacist or physician by combining, mixing, or altering ingredients to create a medication to meet the unique needs of an individual patient. Compounding is used to alter medication formulations (e.g., from solid to liquid), to avoid unessential ingredients (gluten, povidone), to alter medication dosage or concentration, to enhance palatability or compliance with flavoring, or to provide medications no longer available from manufacturers.

In the United States, compounding pharmacies are licensed and regulated by their respective State Board of Pharmacy. Compounded drugs are regulated through the Food and Drug Administration Modernization Act (FDAMA) of 1997. The active pharmaceutical ingredients used by compounding pharmacies must be manufactured by an establishment registered under the FDAMA, and each bulk drug substance must be accompanied by a valid certificate of analysis. Pharmacists may not compound drugs using bulk products that have been withdrawn from the market because of lack of safety or effectiveness; compound a drug regularly or in inordinate amounts (quantities that exceed 5% of the total prescription orders dispensed or distributed by the pharmacy or physician); or dispense drug products that are copies of a commercially available drug. Pharmacies are restricted from advertising or promoting the compounding of any particular drug or drug class.

Table 3. Summary of the Dietary Supplement Health and Education Act

1.	"A dietary supplement is a product taken by mouth that contains a 'dietary ingredient.' Dietary ingredients in these products may include: vitamins, minerals, herbs, other botanicals, amino acids, enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in forms including tablets, capsules, liquids, or powders."
2.	Regulation of dietary supplements by the FDA uses a system separate from regulation of drugs.
3.	The FDA (not manufacturers of dietary supplements) is responsible for monitoring for safety issues regarding these products.
4.	Dietary supplements are allowed to have "statements of support." These statements may not claim improvements of diseases but instead may suggest that the product improves a deficiency, alters or helps to maintain normal functioning of an organ or the entire body, or can improve general well-being. Statements of support require manufacturers to provide a proclamation about their reliability to the secretary of the Department of Health and Human Services within 30 days of placing the product on the market.
5.	Accompanying literature about the product is considered a form of product labeling and is allowed if it has no false or misleading information, is not supporting a specific brand of the product, and presents a "balanced" assessment of scientific literature on the product and/or its ingredients. Literature must be in a separate physical location from where the product is displayed for sale.

The FDA issued a Compliance Policy Guidance on compounding in 2002. It enumerates how the agency intends to address compounding and whether to take enforcement action when a pharmacy's activities raise concerns ordinarily associated with drug manufacturing. The FDA defers to state authorities regarding less significant violations. However, significant violations of the new drug, adulteration, or misbranding provisions may result in FDA-initiated regulatory action including issuance of warning letters, seizure, injunction, and/or prosecution (29).

Examples of compounded pharmaceuticals

Alternative formulations of known medications such as troches, lollipops, topicals, suppositories, eye and ear drops, nasal sprays, and sterile injections are compounded medications. Compounded medications encountered by gastroenterologists include intravenous solutions, total parenteral nutrition, BMX solution (diphenhydramine, viscous lidocaine, Maalox), injectable sclerosing solutions such as sodium tetradecyl sulfate, "GI cocktails," and domperidone. In 2004, letters were issued by the FDA stating that "all drug products containing domperidone (whether compounded or not) violate the Federal Food, Drug, and Cosmetic Act (the Act) because they are unapproved new drugs and misbranded. In addition, distribution within the U.S., or importation of domperidone-containing products, violates the law. FDA informed the warning letter recipients that further violations of the Act may result in enforcement actions including seizure and injunction" (30).

Because patients with severe gastroparesis or gastrointestinal motility disorders may be refractory to standard therapy, the FDA encourages physicians interested in prescribing domperidone to open an Investigational New Drug (IND) Application, a request for FDA authorization for an unapproved use of a drug. This allows for importation, interstate shipment, and administration of drugs lacking approval in the United States.

Oversight of the compounding industry is provided by state and federal authorities, and concerns of safety and efficacy, product stability, sterility, false claims, improper compounding, and pharmacy fraud have been uncovered. In 2002, FDA researchers sampled 29 products from 12 Internet compounding pharmacies. Nine products were sub-potent, and one was contaminated. Three others failed an initial test but were not retested. By comparison, 1–2% of drugs from manufacturers fail to meet standards (31). In 2011 the Alabama Department of Public Health reported an

Table 4. Selected herbal remedies with potential hepatotoxicity

English name	Latin name
Black cohosh	*Cimicifuga racemosa*
Chaparral	*Larrea tridentata*
Chinese skullcap	*Scutellaria baicalensis*
Germander	*Teucrium chamaedrys*
Kava	*Piper methysticum*
Mistletoe	*Viscum album*
Pennyroyal	*Mentha pulegium*
Senna	*Cassia angustifolia*
Valerian	*Valeriana officinalis*
Chinese herbal preparations	

outbreak of *Serratia marcescens* bacteremia from contaminated total parenteral nutrition (TPN) bags in six Alabama hospitals (32). Nineteen patients from six hospitals were adversely affected after receiving the contaminated TPN produced by a single compounding pharmacy. Nine of the affected patients died, although the Centers for Disease Control and Prevention have not confirmed that the deaths were directly caused by the contaminated TPN.

Recently, an outbreak of aspergillus meningitis affecting almost 500 patients, with 34 deaths in 19 states, was attributed to contaminated injectable methylprednisolone produced by a compounding pharmacy in Framingham, Massachusetts. Other aspergillus infections ascribed to the contaminated injections include epidural abscesses, vertebral osteomyelitis, and soft-tissue infections. The contaminations appear to have been due to failure of the compounding pharmacy, the New England Compounding Center, to follow safe manufacturing practices. In addition, it appears to have violated general principles of compounding. By definition, compounding pharmacies make up medications for a single patient, but the New England Compounding Center appears to have been functioning as a drug manufacturer while avoiding the FDA's strict manufacturing regulations (33). In response to the outbreak, FDA chief Margaret Hamburg has suggested tighter regulation of compounded drugs by the agency.

Managing the problem

To reduce the potential for the use of "gray market" sources for drug products to address patient needs due to drug shortages, the FDA has introduced a number of measures to minimize the impact of these shortages, including regular updates to the Current Drug Shortages and Counterfeit Medicine lists on their website and advisory posts on the latest additions to these (34). The FDA has also formally established a Drug Shortage Program with assigned staff who manage drug shortage situations and work with internal and external stakeholders, including drug manufacturers, to prevent, alleviate, and resolve shortage situations. Education of practitioners and consumers about proper purchase of drugs and potential toxicities of CAM is pursued on a continued basis. The FDA has established a Counterfeit Alert Network, a coalition of the health profession and consumer groups. A recent presidential executive order directed the FDA to broadly enforce reporting requirements for manufacturers with low supplies of individual drugs, expedite review of new drug suppliers, and work with the Justice Department to prosecute excesses in the pricing of drugs.

CONFLICT OF INTEREST

Guarantor of the article: Eli D. Ehrenpreis, MD.

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