

Unapproved Drugs in America: An Avoidable Public Health Threat

Salvatore Giorgianni, BSc, PharmD¹

Introduction

Unapproved drugs that have never been evaluated by the U.S. Food and Drug Administration (FDA) continue to be commercially available, and actively marketed to both consumers and healthcare providers. In some cases, these unapproved drugs continue to be prescribed and dispensed when an FDA-approved alternative is currently available; this is putting the health and welfare of men and women at risk.

Ensuring the safety as well as the efficacy of the nation's drug supply is of paramount importance. The FDA, established in 1906, with the passage of the Food and Drugs Act, provides the regulatory structure for drug review and approval and is one of the most effective consumer protection agencies in the world. While no system is perfect, the scientific process used by FDA to review product safety and efficacy is sound. Timely access to safe and effective therapies for conditions that affect the health and welfare of men and their families, is of critical importance. Through its compliance policy guide issued in June, 2006, FDA instituted a process by which it would review the safety and efficacy of the all too many unapproved drugs that continue to be marketed without adequately rigorous and scientifically based review. This effort and this review process are an equally important protection for American consumers.

Unapproved drugs are not regulated or monitored the way approved pharmaceutical products are, and because of this they may pose serious threats to the public's health. This white paper will briefly describe the process by which unapproved drugs are permitted to remain on the market even when a similar FDA-approved product is available; the FDA marketing guidance for unapproved drugs; examples of dangerous unapproved drugs; and a call to action for those who prescribe and dispense medicines to support FDA's enforcement and oversight of the marketing of unapproved drugs, particularly as approved products come to market.

Unapproved Drugs

Unapproved drugs that are available in the United States lack required FDA approval for marketing. While unapproved drugs comprise only about 2 percent of all prescription drugs on the market, they still account for nearly 72 million prescriptions per year and untold millions of patient exposures.ⁱ These products are actively manufactured, marketed, distributed, prescribed and dispensed without any of the oversight that is imposed over all approved prescription medications. Because of antiquated "grandfather" provisions, FDA estimates that there are as many as "several thousand drug products marketed illegally without required FDA approval."ⁱⁱⁱ It is unacceptable for these products to continue to be available to patients when FDA-approved alternatives are available.

¹ Belmont University School of Pharmacy, Nashville, TN USA and Advisor to Men's Health Network

Fig 1. List of Unapproved Drugs Currently Available In the U.S. Market

Acetaminophen, Codeine Phosphate and Caffeine Capsules and Tablets	Oxycodone Tablets
Amobarbital Sodium Capsules	Oxycodone Hydrochloride Oral Solution
Amyl Nitrite Inhalant	Opium Tincture
Chloral Hydrate Capsules, Syrup and Suppositories	Paregoric
Codeine Phosphate Injection, Oral Solution and Tablets	Phenazopyridine Hydrochloride Tablets
Codeine Sulfate Tablets	Phenobarbital Capsules, Elixir and Tablets
Colchicine Tablets	Phenobarbital Sodium Injection
Digitoxin Tablets	Pilocarpine Hydrochloride Ophthalmic Solution
Digoxin Elixir and Tablets	Potassium Bicarbonate Effervescent Tablets for Oral Solution
Ephedrine Sulfate Capsules and Injection	Potassium Chloride Oral Solution
Ergonovine Maleate Injection and Tablets	Potassium Gluconate Elixir and Tablets
Ergotamine Tartrate Tablets	Potassium Iodide Oral Solution
Hydrocodone Bitartrate Tablets	Salsalate Capsules
Hydrocodone Bitartrate, Aspirin and Caffeine Tablets	Sodium Fluoride Oral Solution and Tablets
Hydromorphone Hydrochloride Suppositories	Thyroid Tablets
Levothyroxine Sodium for Injection	
Morphine Sulfate Oral Solution and Tablets	
Nitroglycerin SL Tablets	

Adapted from International Journal of Pharmaceutical Compounding, March/April 2010

Lack of Awareness

Healthcare professionals who are prescribing or dispensing unapproved drugs may not be aware of the fact that these products do not have FDA approval for marketing. A 2006 nationwide study of 500 pharmacists found that 91% of them thought all of the products they dispense are FDA-approved.ⁱⁱⁱ Due to grandfather provisions going back 50 years, many non-reviewed and unapproved products remain on the market and are actively promoted, prescribed and dispensed. It is dangerous and inappropriate for the medical and pharmacy communities to remain complacent and in some cases condone this lapse in consumer protection. Dr. Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research (CDER), stated recently that "consumers are entitled to know that their drugs meet FDA standards."^{iv}

Unapproved Drugs vs. Generic Drugs

Though only available by prescription, these unapproved drugs are not generics. Recently the FDA has sought to clarify among the medical, pharmacy and patient communities the status of unapproved drugs, which were being routinely and mistakenly referred to as "generic" drugs.^v In a recent communication the agency explains that, unlike generic medications, when it comes to unapproved drugs, "neither their safety nor their efficacy can be assured."^{vi} The Agency explains that "generic drugs are those evaluated and approved by FDA to bioequivalence to a brand name reference product"^{vii} and that, unlike unapproved drugs, "healthcare professionals and consumers can be assured that FDA-approved generic products have met the same quality, strength, purity and stability as brand-name drugs,"^{viii} and "the generic manufacturing, packaging and testing sites must meet the same quality standards of those brand name drugs."^{ix}

History of FDA Oversight and Enforcement of Unapproved Drugs

There have been several key regulatory milestones related to unapproved drugs over the course of the past 100+ years.

1906: The original Federal Food and Drugs Act of June 30, 1906 first brought drug regulation under federal law, prohibiting the sale of adulterated or misbranded drugs.

1938: The Federal Food, Drug and Cosmetic Act - The requirement for new drugs to be approved for safety was established through the passage of the Federal Food, Drug and Cosmetic Act, or simply, “The Act.”

1962: DESI Amendment - Congress amends The Act to require new drugs to prove effectiveness and safety before being granted approval, and contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of more than 3,400 products approved only for safety between 1938 and 1962. FDA reviewed and re-evaluated these drugs, publishing their findings in the Federal Register. This process was called the “Drug Efficacy Study Implementation” (DESI).^x

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing from the market products found not to be effective, it would follow procedures and regulations from the 1938 Act that apply when an approved new drug application is withdrawn, offering hearings for manufacturers of some of the drugs it deemed less than fully effective. The FDA published its final determinations in the Federal Register. If, after the hearings, the drug was found by FDA to be ineffective, it could no longer be marketed and became subject to enforcement action. FDA’s longstanding policy allows for the drug to remain on the market “during pendency of the proceeding.” As a result, some unapproved, marketed products are still undergoing DESI review and a final determination has not yet been made with regards to their effectiveness. Others have either been deemed ineffective, or have not submitted required applications for formal review. These products are deemed by FDA to be marketed illegally.^{xi}

1983: Prescription Drug Wrap-Up - In 1983, a drug that was similar to a pre-1962 treatment (and thus “grandfathered” for marketing), E-Ferol, was associated with severe adverse reactions in 100 premature infants, resulting in 40 deaths. In response to this tragedy, a congressional oversight committee expressed its concern regarding thousands of unapproved drug products in the marketplace in a 1984 report to FDA. The Center for Drug Evaluation and Research (CDER) then instituted what came to be known as the Prescription Drug Wrap-Up, which was designed to cover all marketed unapproved prescription drugs, not just DESI products. A product subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer can establish that its drug is “grandfathered” or otherwise not new.^{xii}

2006: Compliance Policy Guide - FDA finalized its guidance in a formal document entitled “Compliance Policy Guide” (CPG), which outlines its approach to addressing medicines that are marketed without required FDA approval. The FDA’s right to enforcement action to stop the manufacture of unapproved drugs due to safety concerns was detailed in this CPG. According to the CPG, “FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow

continued marketing for some period of time after FDA determines that a product is being marketed illegally.^{xiii}

Post-2006: Since issuing its CPG, FDA has accelerated its enforcement actions and to date has removed more than 500 unapproved drugs from the market.^{xiv} Some of these are detailed in the next section.

To date, FDA has employed a “risk-based” enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns, and subsequent regulatory follow-up.^{xv} This approach makes sense and balances the need for access with reasonable procedures to protect the safety of the public.

Recently there has been renewed interest within the Agency to step up its focus on the safety of the products it oversees. In a recent press release, the FDA’s Dr. Woodcock stated, “it is a priority of the agency to remove from the market unapproved products that expose consumers to potentially unsafe, ineffective or poor quality drugs.”^{xvi}

Fig 2. FDA Drug Marketing Approval Historical Timeline

1906	1938	1962	1983	2006
Original Federal Food and Drugs Act	Federal Food, Drug, and Cosmetic Act	DESI Amendment	Prescription Drug Wrap-up	Unapproved Drugs Initiative

Unapproved Drugs and Their Threat to Public Health

Aside from the lack of clinical efficacy and safety data to support their use, the continued manufacture and marketing of unapproved drugs following the approval of an FDA-approved alternative puts the public’s health at unnecessary risk for several reasons. When commercial interests deliberately skirt the FDA approval process, they put into interstate commerce unapproved drugs that lack the specific quality controls of an FDA-approved drug. These include purity and consistency, as well as important manufacturing oversight that ensures the appropriate amount of active drug in each tablet. In addition, unapproved drugs are not required to have dosing information that aligns with current medical practice.

As a result of unapproved drugs lacking efficacy, safety and quality controls, certain unapproved drugs have been removed from the market by FDA; several of these have been associated with patient deaths, including the following:

- Quinine Sulfate. Unapproved quinine sulfate, used to treat malaria, has been linked to 93 deaths, according to FDA. Among other adverse events, quinine sulfate has been shown to cause abnormalities in the heart’s electrical system that can lead to potentially irregular heartbeats. FDA characterized it as a drug with “a narrow margin between an effective dose and a toxic dose.” As a result of these and other findings, FDA banned all unapproved quinine sulfate products in December, 2006.^{xvii}

- *Carbinoxamine*. An unapproved sedating antihistamine, carbinoxamine was associated with 21 reports of death in children under two years of age, according to FDA data. As a result, all drugs containing carbinoxamine in combination with other cold medicines were banned in 2006.^{xviii}
- *Cough Medicines Containing Hydrocodone*. FDA banned unapproved cough medicines containing hydrocodone, a potent narcotic. Some had directions for medicating children as young as age 2, although no hydrocodone cough products have been shown to be safe and effective for children under 6.^{xix}
- *Levothyroxine sodium*. Used to treat hyperthyroidism, unapproved levothyroxine sodium was recognized by FDA as having “issues with formulation and stability” that were only uncovered when the drug was evaluated through FDA-sanctioned clinical trials.^{xx}
- *Nitroglycerin*. The FDA most recently sent warning letters to manufacturers of unapproved nitroglycerin tablets - which are used to reduce chest pain or stop a heart attack – as the agency has seen “significant quality and efficacy problems.”^{xxi} Of the nearly 4.4 million prescriptions for under-the-tongue nitroglycerin tablets in the US in 2009, about 80 percent were filled with unapproved drugs.^{xxii}
- *Injectable Colchicine*. An unapproved drug used for centuries to treat gout and Familial Mediterranean Fever (FMF), the FDA announced it had received 50 reports of adverse events associated with the use of unapproved colchicine, including 23 deaths^{xxiii}. Unapproved injectable colchicine was banned in February 2008.

Though FDA banned injectable colchicine from the market, several versions of unapproved oral colchicine, manufactured by various companies, remain on the market despite the fact that: 1) they have been linked to 169 deaths^{xxiv}; and 2) FDA approved an oral colchicine last year. Like the injectable version, oral colchicine is used to treat gout, a condition that affects as many as 5 million Americans each year, primarily men. Unfortunately, up until 2009 the only available products were not FDA approved. In 2009, URL Pharma received FDA approval of their submission for an oral colchicine product. FDA is engaged in a process for review of the continued marketing of unapproved single-ingredient colchicine products. Commercial suppliers have the option of doing the right thing and submitting New Drug Applications (NDAs) or withdrawing their unapproved colchicine products from the US market. Unfortunately, no other manufacturer has, to date, submitted the required clinical data for their colchicine product to be reviewed by FDA.

The agency's diligence in moving methodically through the list of unapproved agents and requiring evidence of safety and efficacy to be demonstrated through the usual and customary practices or removing products from the market whose commercial sponsors decline to do so, should be applauded.

Risks of Unapproved Drug Prescribing

Healthcare providers, pharmacists, and patients continue to prescribe, dispense and utilize unapproved drugs for various reasons, including familiarity with the unapproved drug, lack of awareness of the product's approval status or price benefits vs. FDA-approved alternatives. However, this practice may place patients at unnecessary risk from drug-drug interactions, lack of standardized dosing guidance, potential overdose among special populations requiring dosing adjustments, and drug purity or potency problems associated with lack of FDA-approved manufacturing and quality control practices that may result in too much or too little active ingredient. FDA itself has stated that:

“While a patient or prescriber may believe that a drug is safe or effective because of individual experience, such subjective experiences can be misleading and insufficient to establish safety and effectiveness. Instead, FDA relies on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with the risks and benefits of taking placebo or another accepted therapy. Carefully designed clinical trials have repeatedly demonstrated that the safety and effectiveness of drugs cannot be adequately established from anecdotal evidence or consumer or prescriber preferences.”^{xxv}

The inherent issues and concerns about the use of unapproved drugs present a serious dilemma for patients and healthcare practitioners alike. However, healthcare practitioners must also weigh the potential liability and malpractice implications of prescribing and dispensing such products that may result in patient injury.

Patients must also consider the fact that, despite the potential risk that unapproved drugs represent, maintaining access to medications, such as nitroglycerine sublingual tablets, which may cause harm if abruptly discontinued by the patient without consulting with the prescriber poses a particular concern. For this reason the FDA has urged consumers using unapproved nitroglycerin to “continue taking their medication and consult a health care professional for guidance on alternative treatment options.” Those taking unapproved nitroglycerine sublingual tablets should contact their prescriber or pharmacist and discuss how to obtain an approved product. Prescribers and pharmacists should seek out patients under their care that may be receiving this, or any unapproved product with an FDA approved alternative available, and get them switched to an approved product

Cost of Unapproved Drugs

With the renewed focus on drug costs as part of the ongoing health care reform debate, it is important to consider the costs of unapproved drugs on the healthcare system and in the context of the safety risks they represent. Research has shown that unapproved drugs have been linked to serious side effects leading to hospitalization and patient harm. Furthermore, this results in far more expense to individual patients and the healthcare system in general.

The cost of unapproved drugs hits taxpayers as well, as conflicting federal laws allow for the funding of hundreds of these unapproved treatments through the Medicaid program. An Associated Press (AP) analysis of federal data in 2008 found that Medicaid paid at least \$200 million from 2004 to 2007 for more than 100 unapproved drugs, used mainly for conditions like the common cold.^{xxvi} In response, Sen. Charles Grassley (R-Iowa), in

January of 2010 introduced legislation (“The Strengthening Program Integrity and Accountability in Health Care Act”) that includes a provision “to ensure that the Medicaid program does not provide reimbursement for covered outpatient drugs that are not approved by the FDA under a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), or drugs grandfathered under prior FDA determinations.”^{xxvii}

In addition, the provision would:

“. . . prohibit a state from making a payment for any covered outpatient drug unless the state first verifies with FDA that such a covered outpatient drug is being legally marketed. It would also require FDA to establish a public registry of all drugs that are not approved under an NDA or ANDA and include the drug, the person who listed the drug, and the authority that does not require the drug to receive approval via NDA or ANDA.”^{xxviii}

Millions of privately insured patients are also taking unapproved drugs, as private insurance plans cover them. Their availability, according to AP, may create a “false sense of security.”

Summary

In the past several weeks, the media scrutiny over FDA actions against the manufacturers of unapproved nitroglycerin tablets, and concern expressed by many physicians who unwittingly prescribed them with no way of knowing whether patients have suffered unnecessarily, has once again put the issue of unapproved drugs back into the spotlight. Adding to that in some instances these unapproved drugs, for which FDA had “recorded problems with” in the past, are still being dispensed by some pharmacists. This is, despite the fact that an FDA-approved nitroglycerin therapy is commercially available.^{xxix}

This recent increase in regulatory scrutiny is a promising sign, but more remains to be done:

- Call on **FDA** to continue to accelerate its focus on unapproved drugs by 1) moving quickly to exercise its enforcement authority toward the manufacturers of unapproved drugs by removing unapproved products from the market, particularly in instances where a similar FDA-approved drug exists and serious safety or patient care issues may be involved; and 2) more vigorously enforcing existing policy toward manufacturers of unapproved drugs in a consistent manner
- Urge **manufacturers of unapproved drugs** to do the right thing and participate in the FDA regulatory process as a measure to not only protect themselves and healthcare professionals but most importantly the safety of the public
- Urge **health care providers** and professional associations to become knowledgeable about unapproved drugs and to avoid their use when an FDA-approved version becomes available
- Call on **patients** to discuss with their physicians and pharmacists whether unapproved drugs are included as part of their healthcare regimens, to

understand the risks and benefits of using unapproved drug therapies, and to seek out alternative treatments wherever possible.

Protecting access while protecting safety is the right thing to do for all Americans.

References

- ⁱ AP IMPACT: "Gov't Pays for Risky Unapproved Drugs," R. Alonzo-Zaldivar, F. Bass (Nov. 23, 2008)
- ⁱⁱ "Marketing Unapproved Drugs Compliance Policy Guide," US Department of Health and Human Services, FDA Center for Drug Evaluation and Research, June 2006, p.2
- ⁱⁱⁱ "Hundreds of Unapproved Drugs Sold by Prescription," USA Today (Sept. 19, 2006)
- ^{iv} "FDA Orders 2 Companies to Stop Marketing Unapproved Nitroglycerin Tablets," U.S. Food and Drug Administration Press Release (March 16, 2010)
- ^v "HHS Response Letter Regarding Concerns Over Current Market Prices of Approved Oral Colchicine," Janet Woodcock, Director, Center for Drug Evaluation and Research (March 3, 2010)
- ^{vi} Ibid
- ^{vii} Ibid
- ^{viii} Ibid
- ^{ix} Ibid
- ^x "Marketing Unapproved Drugs Compliance Policy Guide," US Department of Health and Human Services, FDA Center for Drug Evaluation and Research, June 2006, p. 8
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf> (accessed March 9, 2010)
- ^{xi} Ibid, p.9
- ^{xii} Ibid, p.10
- ^{xiii} "Marketing Unapproved Drugs Compliance Policy Guide," US Department of Health and Human Services, FDA Center for Drug Evaluation and Research, June 2006, p.5
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf> (accessed March 9, 2010)
- ^{xiv} "Purging the Pharmacy of Unapproved Drugs," Natasha Singer, New York Times, March 26, 2010.
- ^{xv} Ibid
- ^{xvi} "FDA Orders 2 Companies to Stop Marketing Unapproved Nitroglycerin Tablets," U.S. Food and Drug Administration Press Release (March 16, 2010)
- ^{xvii} "FDA Advances Effort Against Marketed Unapproved Drugs," U.S. Food and Drug Administration Press Release (Dec. 11, 2006) <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108799.htm> (Accessed March 17, 2010)
- ^{xviii} "Questions and Answers about Unapproved Drugs and FDA's Enforcement Action Against Carbinoxamine Products," U.S. Food and Drug Administration document, June 8, 2006
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActions>
- ^{xix} "Hundreds of Unapproved Drugs Sold by Prescription," USA Today (Sept. 19, 2006)
- ^{xx} "Questions and Answers on Levothyroxine Sodium Products," U.S. Food and Drug Administration document, October 3, 2007
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161266.htm> (accessed March 5, 2010)
- ^{xxi} "FDA Orders Two Companies to Stop Marketing Unapproved Nitroglycerin Tablets," U.S. Food and Drug Administration Press Release March 16, 2010
- ^{xxii} "FDA Says Millions Got Unapproved Heart Pills," New York Times, March 26, 2010
- ^{xxiii} Dr. Charles Lee, medical officer at the Division of New Drugs and Labeling Compliance in the FDA Center for Drug Evaluation of Research, as quoted in "FDA's Action Against Marketing Unapproved Drugs," ReachMD XM157, U.S. Food and Drug Administration Podcast, October 17, 2008 (transcript available at: <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm079097.htm>, accessed April 5, 2010)
- ^{xxiv} "Information for Healthcare Professionals: New Safety Information for Colchicine," U.S. Food and Drug Administration Alert, July 30, 2009
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm174315.htm> (accessed March 5, 2010)
- ^{xxv} "HHS Response Letter Regarding Concerns Over Current Market Prices of Approved Oral Colchicine," Janet Woodcock, Director, Center for Drug Evaluation and Research (March 3, 2010)
- ^{xxvi} AP IMPACT: "Gov't Pays for Risky Unapproved Drugs," R. Alonzo-Zaldivar, F. Bass (Nov. 23, 2008)
- ^{xxvii} "Sen. Grassley Fights Fraud, Waste and Abuse in Medicare, Medicaid, CHIP,"
<http://finance.senate.gov/press/Gpress/2010/prg012810.pdf>
- ^{xxviii} Ibid
- ^{xxix} "FDA Says Millions Got Unapproved Heart Pills," Natasha Singer, New York Times, March 26, 2010