



Pilot Study of Internet Drug Availability, Pricing, and Quality

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Abstract

Background

Internet-sourced drugs are often considered suspect. The World Health Organization reports that drugs from websites that conceal their physical address are counterfeit in over 50 percent of cases; the U.S. Food and Drug Administration (FDA) works with the National Association of Boards of Pharmacy (NABP) to regularly update a list of websites likely to sell drugs that are illegal or of questionable quality. Some pressure groups and politicians have called for banning Internet drug purchasing—even while others laud it as a convenient, cost-effective way for consumers to access drugs.

Methods and Findings

This study examines drug purchasing over the Internet, by comparing the sales of five popular drugs from a selection of websites stratified by NABP or other ratings. The drugs were assessed for price, conditions of purchase, and basic quality.

Prices and conditions of purchase varied widely. Some websites advertised single pills while others only permitted the purchase of large quantities. Not all websites delivered the exact drugs ordered, some delivered no drugs at all; many websites shipped from multiple international locations, and from locations that were different from those advertised on the websites.

All drug samples were tested against approved U.S. brand formulations using Raman spectrometry. Many (13) websites substituted drugs, often in different formulations from the brands requested. These drugs, some of which were probably generics or copy versions, could not be assessed accurately. Of those drugs which could be assessed, failures ranged from 0% (0 out of 24) at “approved” websites to 8% (1 out of 12) at websites “highly not recommended” by the NABP. One of the two drugs received from “not recommended” and “highly not recommended” websites that could not be linked directly to a website for purchase because the packaging lacked appropriate labeling failed spectrometry testing.

Conclusions

Some websites did not comply with purchaser requests for brand-name drugs, which limited the ability to assess quality. Of those which could be assessed, most drugs (except Viagra) passed spectrometry testing. Of those which failed, few could be identified either by a country of manufacture listed on the packaging, or by the physical location of the website pharmacy. If confirmed by future studies on other drug samples, then U.S. consumers may be able to reduce their risk by relying on tools like the NABP “recommended” and “not recommended” lists and by using common sense when examining packaging and pills. Future studies should assess drugs from unapproved websites in a linear fashion - orders should be staggered over several months to ensure provenance of each drug received. With few identifiable marks on packages received from these websites one cannot be sure of the source if multiple orders are made within a few weeks.

Introduction

Spending for prescription drugs in the United States hit \$216.7 billion in 2006, more than triple the \$40.3 billion spent in 1990 [1]. While the lion's share is still spent in large chain stores like CVS Caremark or RiteAid, consumers on a quest for cheaper drugs or drugs off-prescription are embracing alternative distribution channels—and are increasingly buying over the Internet [2, 3].

In 2009, 30 percent of prescription drug users reported buying drugs online or through the mail in the previous 12 months, a 9 percent increase over the number who said so in 2008, according to the Deloitte Center for Health Solutions [4]. Reluctant to acknowledge purchasing so-called “lifestyle” drugs like painkillers or those used to treat erectile dysfunction or depression—among the most popular drugs sold over the Internet—consumers may underreport their online purchasing behavior. U.S. fraud prevention and brand protection firm Mark Monitor estimates the total size of the online market at \$12 billion [5].

Website pharmacies are diverse. They include licit companies accredited by the National Association of Boards of Pharmacy (NABP) as well as outfits based in undisclosed international locations, willing to illegally divert and distribute drugs without a prescription. The NABP is an independent association of all State Boards of Pharmacies which accredits websites that sell only drugs approved by the U.S. Food and Drug Administration (FDA), comply with recognized quality assurance policy, and provide meaningful consultation between patients and pharmacists.

Website pharmacies not accredited by the NABP, however, may be willing to sell drugs after consumers complete a brief medical questionnaire, allegedly reviewed by a physician at the website pharmacy (while some NABP-approved websites ask patients questions, an original prescription from an outside physician is always required). In other instances, medical questions will not be asked. In 1999, University of Pennsylvania researchers identified 86 websites—based in the U.S. and internationally—that offered to deliver the erectile dysfunction drug sildenafil citrate (Viagra[®]) directly to consumers without a prescription [6]. The Ohio State Board of Pharmacy has warned pharmacists about Internet-based pharmacies that urge them to fill orders without prescriptions. According to the Board's newsletter, solicitations are often targeted at independent pharmacies, “probably knowing that many of them are suffering financially due to the initial problems with Medicare Part D, Medicaid reimbursement cuts, insurance cuts, etc” [7].

Until recently, much of the academic literature focused on understanding which drugs—brand and generic—Americans could buy over the Internet, under what conditions—on or off-prescription—and at what prices. The quality of drugs available on the Internet was a secondary consideration, if it was considered at all [8]. With incidents of poor drug quality widely reported in the media, and with policymakers considering legislation that would allow Americans to buy drugs directly from Canada, researchers have begun to shift their focus. A 2007 study found that tablets of the cholesterol-lowering drug

simvastatin obtained from Canadian generic manufacturers over the Internet contained a comparable amount of active ingredient to the brand-name drug, although it cautioned that other tests were needed to determine the safety and effectiveness of the drug [9]. A 2008 study of simvastatin that used more tests—high-performance liquid chromatography (HPLC), disintegration, dissolution, weight variation, hardness, and assessment of physical characteristics—identified several international samples that were not comparable to the brand-name drug in one or more aspects of quality assurance testing and warned that “Internet drug products should not be considered interchangeable with their respective U.S. innovator product” [10].

While many analysts have explored institutional answers to the problem of counterfeit and substandard drugs—improving laws, increasing criminal penalties for counterfeiters, and making enforcement stronger and more consistent—few analysts have explored what is arguably the most significant driver of the problem: consumer demand. The conventional belief has long been that “the most obvious determinant of whether counterfeit drugs are purchased is price” [11]. But exclusive focus on price ignores other potentially powerful determinants including product appearance, prestige associated with use, perceived quality, and a consumer’s general attitude toward counterfeiting, often influenced by the culture in which he or she lives [12, 13]. It also assumes, without evidence, that counterfeits will always be less expensive than original products, and fails to consider the growing body of evidence that suggests many consumers may choose counterfeits to avoid prescription requirements [3].

Purchasing drugs over the Internet can offer significant benefits, including, as the FDA acknowledges, a “convenient, private, way to obtain needed medications, sometimes at more affordable prices.” The elderly, infirm, or geographically isolated may be able to obtain prescriptions more quickly and easily. But drugs purchased from unverified website pharmacies without a valid prescription can be dangerous. In February 2001, 18-year-old Ryan Haight died from an overdose of Vicodin[®] that he had purchased over the Internet without a doctor’s examination. (In 2008, Congress passed the Ryan Haight Online Pharmacy Consumer Protection Act, which prohibited the dispensing of controlled substance medications over the Internet without a valid prescription.) In July 2007, Canadian investigators uncovered email records that linked the death of fifty-eight-year-old Canadian Marcia Bergeron to counterfeit antidepressants and acetaminophen that she had purchased from several unlicensed website pharmacies. The drugs contained dangerously high levels of aluminum, phosphorus, titanium, tin, strontium, arsenic, and other metals.

According to a 2004 Wall Street Journal/Harris Interactive poll, most Americans (61 percent) think online drug purchasing can be dangerous, but nearly one-in-four (23 percent) say they “aren’t sure” whether drugs purchased online are more or less dangerous than drugs purchased through traditional pharmacies [14]. Even though federal law technically prohibits the importation of drugs from overseas except under special circumstances, 4% of prescription drug users in the United States said in 2009 that they bought from a foreign source, and 20% of all consumers said they would likely buy from a source outside the United States if they could save 50% or more in price [4].

The authors aimed to assess the quality of prescription drugs that could be purchased over the Internet, and under what conditions. In order to compare the quality of drugs procured from websites subject to different levels of regulatory supervision, the authors intended to stratify the sample into four groups: “approved,” “legally compliant,” “not recommended,” and “highly not recommended” (See Appendix).

Methods

The authors identified drugs most likely to be purchased by American consumers in several drug classes (nonsteroidal anti-inflammatory drugs, proton pump inhibitors, synthetic lipid-lowering agents, selective serotonin reuptake inhibitors, and oral therapy for erectile dysfunction) by cross-tabulating consumer self-reports [14] with industry data, including lists of the most-popular online drug searches from licit website pharmacies and IMS’s list of the top 10 products “most often prescribed” in the United States in 2007. The five drugs selected for purchase were (in order of selection priority):

Lipitor[®] 10mg (atorvastatin calcium) a synthetic lipid-lowering agent to reduce cholesterol, manufactured by Pfizer Inc.

Viagra[®] 100mg (sildenafil citrate) an oral therapy for erectile dysfunction, manufactured by Pfizer Inc.

Celebrex[®] 200mg (celecoxib) a nonsteroidal anti-inflammatory drug for treatment of arthritis, manufactured by Pfizer Inc.

Nexium[®] 40mg (esomeprazole magnesium) a proton pump inhibitor for treatment of Gastroesophageal Reflux Disease, manufactured by AstraZeneca Pharmaceuticals LP

Zoloft[®] 100mg (sertraline HCl) a selective serotonin reuptake inhibitor for treatment of depression, manufactured by Pfizer Inc.

The dosages chosen were the most popular among identified websites and after consultation with Joseph Moody, MD, the physician advising this study. Once the most popular dosages were identified, reference standards were established for the chosen Raman spectrometer.

With the approval of his state health board, Dr. Moody provided prescriptions for the drugs. The prescriptions were for the established dosages but in varying quantities. The aim was to choose enough samples of each drug from each website pharmacy to be clinically relevant; it was important that the sample not be biased by making website managers suspicious of ordering intent. It was also important that enough samples were procured for a reasonable quality assessment, whilst not choosing too many in an attempt to keep costs down and allow sampling from as many websites as possible. A uniform homogeneous database of samples from website pharmacies was not possible since many websites only sell in prohibitively large (and expensive) quantities, do not sell all five brand-name versions of the drugs, or do not sell the drugs in the required dosages. While only Zoloft is no longer under patent in the United States, websites sourcing drugs from overseas may try to supply generic or copy versions of the other drugs, which may be legally produced for domestic consumption in other parts of the world (although illegal if sold in the United States). During the procurement process, the authors always instructed

website pharmacies to provide brand-name drugs, and did not procure from websites where only generic versions were available.

The authors contacted Citibank to establish a bank account for the lead author with accompanying debit card to make all purchases. Citibank's fraud early warning unit was informed of the study, and the lead author was contacted on several occasions throughout the study to query payments. Citibank refused to allow the completion of transactions to some website pharmacies, presumably because the pharmacies were known or suspected criminal entities. Some website pharmacies refused MasterCard as a method of payment. Given that fewer websites than originally envisaged could be purchased from, the lead author procured drugs using different payment methods, primarily using a separate personal Visa card.

The authors used a handheld Raman spectrometer to create a detailed spectral "fingerprint" for each reference standard, which was then compared against spectral readings from drugs procured over the Internet. To create the reference standards, genuine samples provided via prescription by a national pharmacy chain (West Lafayette, IN, USA) were analyzed using the Raman spectrometer and cross-checked against a second lot from a separate pharmacy to verify consistency and determine method robustness. In cases where it appeared slight lot-to-lot variation was present (as in the case for Lipitor coating thickness), a reference spectrum from both lots was included in the Raman spectroscopic method. In all cases, the two lots of drugs matched well and it was deemed that they were representative samples of authentic products.

Drugs were ordered in January, February, and March 2009 from website pharmacies identified using Google and Yahoo! search criteria and the NABP list of approved and not recommended websites (See Appendix), as well as examination of spam emails sent to the authors and those caught in the spam filters of their organizations. Attempts to purchase from some websites were unsuccessful. Some website pharmacies returned prescriptions; some websites would not accept payment; and in some cases, the ordered drugs were never received. While every reasonable effort was made to procure drugs from each website, this was not always possible as described above. The lead author attempted to procure drugs from websites experiencing problems three times before moving on to the next website.

For each purchase, the authors recorded the following variables: name of drug purchased, dosage, formulation (this was added later once the authors began receiving different formulations for Nexium and Zoloft), quantity, price (listed price, shipping cost, consultation fee if applicable, miscellaneous charges and total price with tax), name of website pharmacy, listed geographic location of website, type of prescription requirement (mail-in prescription, fax or email prescription, no prescription requirement with extensive medical questionnaire, or no requirements at all), any disclaimers or warnings, and general usability of the website.

Upon receipt of the drug packages, details such as return address, postmark, and appearance of the package were recorded. Suspect mail packages and drugs failing

spectrometry testing were photographed. Four of the drug packages received could not be linked directly to a website because multiple purchases were ‘active’ at the same time, and the packaging was not identifiable. The purchases were not made in a linear fashion – ordering from one website and not ordering from the next until the first was received.

The authors assessed drug quality using Raman spectrometry. Numerous studies have demonstrated that Raman spectrometry is a quick, reliable and cost-effective way for non-specialists to differentiate between genuine and counterfeit drugs [15-17]. To ascertain the nature, and not just the spectra, of all compounds in a given drug, including degradation products as well as active ingredients, high-performance liquid chromatography (HPLC), considered the current gold standard analytical method in drug analysis, would be required. HPLC requires sophisticated sample preparation that is expensive and time consuming and requires trained chemists for analysis and interpretation of results. Given that the aim of this study was to identify a finished product (rather than its individual components), comparison with a known HPLC standard was unnecessary. The authors used a handheld Raman spectrometer, the TruScan by Ahura Scientific (Wilmington, MA), on loan for the duration of the study. One necessity, and potential limitation, of spectrometers is that they require exact reference standards, obtained by scanning each separate brand with the same formulation for calibration. This means that a drug substituted for the branded version would record likely as a failure (since the excipients could be different, yielding different spectra, between two equally effective drugs). For this reason, generic substitutes were not sought from websites for this study.

Four samples from each drug from each website pharmacy were tested; additional samples were tested when there were failures, with the more positive results being recorded. Five websites only sent three tablets of Viagra each, all of which were tested.

In order to compare prices of drugs with the same formulations, purchased in the same quantities, the authors identified prices posted on the website or quoted by a pharmacy representative over the phone in early May 2009. (Drugs were not purchased again.) If the formulation was not available in the same quantity, the authors selected the closest quantity available. Prices were calculated as “stand-alone” orders; that is, shipping expenses were not amortized across the entire five-drug order. The authors also identified prices of the five drugs sold at physical-location pharmacies in the Washington, D.C. area. Six pharmacies were selected as the closest within a 0.5 mile radius of the lead author's home address using Google Maps. No more than one of each chain pharmacy was selected. In addition, the authors included a nearby Wal-Mart store after one pharmacy volunteered that the “customer loyalty” program at their store was designed to compete with Wal-Mart’s “low prices.” One pharmacist refused to provide price information. When the author reminded the pharmacist that this was required by law, the pharmacist told them they were too busy that day, but they should call back tomorrow; when the author called the next day, the pharmacist said that they had to see the prescription before they quoted a price.

Results

The authors received drugs from 26 website pharmacies, among them five “approved,” six “legally compliant,” five “not recommended,” six “highly not recommended,” and four that were “not recommended” or “highly not recommended” but could not be identified by name because packaging did not match any of the pre-orders. A total of 88 drug orders were received, including 15 Celebrex, 17 Lipitor, 16 Nexium, 24 Viagra, 15 Zoloft and one unknown from an unidentifiable website. Of these, samples from 70 drug orders were tested using Raman spectrometry. Nexium tablets from nine websites and Zoloft capsules from two websites could not be assessed because the authors’ spectrometry protocol was established with reference standards for Nexium capsules and Zoloft tablets (the typical drug formulations sold in the United States). Additionally, one order of “sertraline HCl” tablets and three orders of “Daxid” tablets were received in place of Zoloft and could not be assessed since reference standards were not available. Lastly, blue tablets shaped like Viagra, which were not labeled “Viagra” and not labeled as being manufactured by Pfizer, were received from two unidentifiable websites; they were not assessed since their identity could not be confirmed (these two are included in the 24 Viagra drug orders received above). An unknown drug accompanied one of the suspected Viagra orders and was not assessed since its identity could not be confirmed.

Samples were tested from January to April 2009. 3% (2/70) of tested samples failed Raman spectrometry: 0% of Celebrex (0/15), 0% of Lipitor (0/17), 0% of Nexium (0/7), 9% of Viagra (2/22), and 0% of Zoloft (0/9) (See Table 1).

While a pass identifies a good quality drug, a “failure,” as assessed by the authors, does not mean that a given drug is necessarily of low quality. The spectrometer recorded a “failure” if a sampled drug was spectroscopically inconsistent with the reference standard; under this metric, both copy versions and FDA-approved, bioequivalent generics of the chosen drugs may fail, because while they must contain the same quantities of active ingredient, they often contain different binding agents (excipients) in different concentrations. The spectrum created by the spectrometer is for the total sample formulation, not only the active ingredient.

Only brand-name drugs were ordered in this study; however, some website pharmacies failed to comply with instructions and sent copy versions in place of the brand-name drug. The authors did not attempt to verify the authenticity or quality of these substitutes since reference standards were not available. Previous attempts to obtain samples from various companies led the authors to believe that samples could not be procured from all companies in a timely manner, potentially biasing results. It is possible that drug substitution may have occurred unbeknownst to the authors, i.e. the drugs were not labeled as such, and as a result they may have failed testing due to different excipients as explained above.

Of the website pharmacies accredited by NABP, only one provided a drug which failed testing; in this case, the bottle was labeled “Sertraline HCl 100mg.” Since the authors could not test this suspected Zoloft generic against a generic Zoloft reference standard,

the sample was considered “not in testable form” and was not included in the study results.

Two NABP-accredited website pharmacies sent Lipitor tablets that initially failed spectrometry testing. Upon examining the tablets more closely, it was determined that they failed because of the sensitivity of the spectrometer to variations in coating thickness. When the tablets were cleaved and retested against a reference standard of a cleaved Lipitor tablet, the samples passed, and were recorded as passes.

Two NABP-accredited website pharmacies sent Nexium capsules that initially failed spectrometry testing. Upon further examination, it was determined that the capsules were of good quality; the samples failed because of the sensitivity of the spectrometer to the gelatin capsules themselves. The authors observed that genuine Nexium had capsules that varied in thickness and color shades. Once the capsules were opened and the contents retested against a reference standard established from Nexium capsule contents, the samples passed, and were recorded as passes.

Six “legally compliant,” “not recommended,” or “highly not recommended” website pharmacies sent Nexium tablets, allegedly produced for AstraZeneca in Turkey (4 orders), Canada (1 order), and Sweden (1 order) instead of capsules. Nexium tablets are not approved for sale in the United States, but are common in Europe and much of the rest of the world. Since tablets have different excipients and different coatings than capsules, their spectra are slightly different. As a result, samples from each of the Nexium tablet orders failed when tested against the Nexium capsule reference standard. Since the authors could not test the samples against a Nexium tablet reference standard, they were considered “not in testable form” and were not included in the study results. The authors did however compare the Raman spectra of the Nexium tablets against the spectra of the Nexium capsules to look for the presence of active ingredient, which should be in all of the tablets. All of these Nexium tablets appeared to contain the active ingredient. Additional follow-up of samples from two of the Nexium tablet orders with AstraZeneca’s Global Quality Operations identified the tablets and their batch numbers as consistent with genuine product packaged for AstraZeneca in Turkey.

Additionally, three orders of tablets labeled “Neksium” instead of Nexium, allegedly manufactured by a company for AstraZeneca India in Bangalore, were received from “legally compliant” or “not recommended” website pharmacies. The tested samples had spectra unlike the Nexium capsules or Nexium tablets, and did not appear to contain the main Nexium active ingredient, esomeprazole. A high level of fluorescence was associated with the individual spectra of these tablets which precluded the automated analysis. Since the authors could not test the samples against a Neksium reference standard, they were considered “not in testable form” and were not included in the study results. The packaging indicated that Neksium is “For Sale in India and Nepal Only.” One website pharmacy attempted to cover up this text by placing a sticker “To be dispensed against doctor’s prescription only” on top of it. The authors informed AstraZeneca about this potentially counterfeited drug and, as a result, AstraZeneca launched an internal investigation. After careful consideration of samples from two of the

Nexium orders, a report was returned to the authors indicating the tablets and their batch numbers were consistent with product manufactured and packaged for AstraZeneca India by a third party contractor.

Three “legally compliant” or “not recommended” website pharmacies sent “Daxid” tablets in place of Zoloft tablets. Since the authors could not test the samples against a Daxid reference standard, they were considered “not in testable form” and were not included in the study results; however, samples from all three orders did pass spectrometry testing when tested against the Zoloft reference standard. The packaging indicated that Daxid is “For Sale in India Only” and is manufactured by Pfizer Limited in India. All website pharmacies attempted to cover up this text by placing either a blank sticker or one that read “To be dispensed against doctor's prescription only” on top of it.

Samples from the two suspected Viagra orders were tested against the Viagra reference standard and all failed. However, since their provenance and identity could not be confirmed, the samples were considered “not in testable form” and were not included in the study results.

Of the 26 website pharmacies sampled, and of those drugs which could be tested against established reference standards, 0% (0/24) of drugs from “approved” websites failed, 0% (0/21) of drugs from “legally compliant” websites failed, 0% (0/11) of drugs from “not recommended” websites failed, 8% (1/12) of drugs from “highly not recommended” websites failed, and 50% (1/2) of drugs from websites that were either “not recommended” or “highly not recommended” but could not be identified by name failed (See Table 1). All drugs purchased from the “approved” and “legally compliant” website pharmacies were accounted for, whereas the latter classifications had websites which may not have delivered drugs, or had delivered drugs in unidentifiable packaging and were not identifiable in other ways.

“Highly not recommended” website pharmacies tended to offer fewer types of drugs than the other website classifications. Of these six websites, only three delivered any of the five drugs other than Viagra. In two cases, Viagra and Nexium were initially ordered, but only Viagra was delivered. In the first instance, Nexium was crossed out on the package receipt but the author’s account was charged for the missing drug, in the second, the author’s account was charged for the Viagra but not the Nexium.

The authors assessed the country of manufacture, where possible. Many websites, particularly NABP-approved websites, like most US retail pharmacies, sent drugs packaged in orange, cylindrical “pill pots,” which often did not list a country of manufacture. Of the 88 drug orders received, 37.5% (33) came from outside of North America and 20.5% (18) from within North America (Canada 6, United States 12). The remaining 42% (37) were of unknown origin or could not be assessed.

Drugs were manufactured in Italy (2 samples), Germany (1 sample), Australia (1 sample), Australia/New Zealand (11 samples; both countries were listed on the same package; a phone call to the pharmacy could not clarify where these drugs were

manufactured), India (5 samples), Sweden (1 sample), Turkey (13 samples), Canada (6 samples) and the United States (12 samples). For one of the drug orders, half of the packages received listed Italy as the country of manufacture and the other half listed Germany. Of the remaining 37 drug orders, it is likely that many were manufactured in the U.S., given their source (NABP-approved websites), appearance, and formulations. Some of the drugs with an unknown country of manufacture, however, likely came from elsewhere: drugs that were probably copy versions of Viagra arrived with postmarks from India, for example.

Half of the samples with packaging that said they were manufactured in Canada (3 of 6), all of the samples from India (5 of 5), the single sample from Sweden (1 sample), 4 of the 13 samples from Turkey, and 1 of 12 samples from the United States were not in testable form. Of the drugs that were in testable form, only one that listed a country of manufacture (in this case, Viagra tablets that were allegedly manufactured in the United States) failed spectrometry testing.

Table 1: Spectrometry testing results by drug type and website pharmacy classification

	Website classification	Number received	Number in testable form	Percent that failed testing
Lipitor	NABP approved ⁱ	5	5	0%
	Legally compliant ⁱⁱ	6	6	0%
	Not recommended ⁱⁱⁱ	4	4	0%
	Highly not recommended ^{iv}	2	2	0%
	Combined Total	17	17	0%
Viagra	NABP approved	5	5	0%
	Legally compliant	5	5	0%
	Not recommended	5	5	0%
	Highly not recommended	5	5	20% (1/5)
	Unidentifiable	4	2	50% (1/2)
	Combined Total	24	22	9% (2/22)
Celebrex	NABP approved	5	5	0%
	Legally compliant	6	6	0%
	Not recommended	2	2	0%
	Highly not recommended	2	2	0%
	Combined Total	15	15	0%
Nexium	NABP approved	5	5	0%
	Legally compliant	6	1	0%
	Not recommended	2	0	
	Highly not recommended	3	1	0%
	Combined Total	16	7	0%
Zoloft	NABP approved	5	4	0%
	Legally compliant	5	3	0%
	Not recommended	3	0	
	Highly not recommended	2	2	0%
	Combined Total	15	9	0%

	Website classification	Number received	Number in testable form	Percent that failed testing
Unknown	Unidentifiable	1	0	
TOTAL	NABP approved	25	24	0%
	Legally compliant	28	21	0%
	Not recommended	16	11	0%
	Highly not recommended	14	12	8% (1/12)
	Unidentifiable	5	2	50% (1/2)
	Combined Total	88	70	3% (2/70)

- i. “Approved”: have been accredited by the U.S. NABP.
- ii. “Legally compliant”: have not been accredited by NABP, but nor are they listed on NABP’s “not recommended” list. PharmacyChecker, an independent group not affiliated with any given pharmacy, indicates that they are in compliance with the laws in the country in which they are registered.
- iii. “Not recommended”: approved by PharmacyChecker, but “not recommended” by NABP.
- iv. “Highly not recommended”: “not recommended” by NABP and unlisted or “not approved” by PharmacyChecker.

Problems of Provenance & Packaging

Many drugs, including some that did not fail spectrometry testing, had worrying irregularities in provenance or packaging. One website pharmacy claimed to be based in Ontario, Canada, but the receipts included in the packages stated that the drugs had been shipped from Australia and India, as well as the United States. The return addresses on the packages indicated that they had passed through Vanuatu, Germany, or Santa Ana, California. Four of the five drugs (with the exception of Nexsium) purchased from this website pharmacy passed spectrometry testing.

In many cases, drugs were shipped from a different location than was indicated on the website. Some claimed to be U.S. or Canada-based and advertised prices in dollars on their website, yet charged in Chinese or Indian currency. One website pharmacy described itself as an “off-shore company based in Cyprus,” but listed a contact address in British Columbia. The authors were not able to determine where exactly the funds were deducted from for the transaction. In reviewing statements from the bank account used in this study, the initial transfer was sent to Panama, not a known location for the company. Viagra ordered from this website arrived wrapped in aluminum foil, with a postmark from Shanghai. Labeled as “Pfizer Inc. USA” Viagra, all four tablets tested failed Raman spectrometry. The shipping envelope and drug packaging was similar to a reported port security seizure one of the authors had seen at a public presentation by a Pfizer security expert.

Some website pharmacies shipped international versions of brand-name drugs. One website pharmacy provided Zolofit capsules that were bright orange in a bottle labeled as “Pfizer Canada.” Another website, based in Vanuatu, shipped Celebrex, Lipitor, and Zolofit marked “Pfizer Australia” – all of which passed Raman spectrometry testing. Another website pharmacy claimed to be based in British Columbia, Canada, but the drug orders arrived with postmarks from the Deutsche Post, a Swiss Post Declaration and Customs Authorities Form, and a Zurich Airport Label. The drugs received were allegedly manufactured by three separate drug companies. Another website pharmacy

sent an order of loose tablets in a plastic bag with packaging and information inserts that could not be connected with any of the initial purchase websites. In this case, the drug order arrived with a return address for Vienna, Austria. The tablets were blue in color, shaped like Viagra and stamped with “Pfizer” - all tested samples failed Raman spectrometry.

The Purchasing Experience

Other website pharmacies could not supply all the drugs they claimed to offer. One website claimed to have “sold out” of Lipitor when the authors attempted to procure it. Some websites were portals to many other websites, many of which crashed after the lead author submitted the medical questionnaire that accompanies many websites. When this happened, drugs could not be procured.

Many website pharmacies offered prescription drugs without requiring an original prescription. All of the NABP-approved and “legally compliant” websites, except one, either demanded original prescriptions or (for two websites) accepted faxed prescriptions but followed-up with the prescribing physician to establish provenance. These website pharmacies appeared to focus on building a long-term relationship with the consumer. Indeed, seven of the 16 websites described by NABP as “recommended” would not even sell prescription drugs to an individual unless he or she was connected with a medical insurer.

Nearly all of the “not recommended” and “highly not recommended” website pharmacies claiming to require prescriptions accepted faxed or emailed copies without contacting the prescribing physician to confirm. One website openly advertised the provision of drugs off prescription. Other website pharmacies offered to supply drugs after the consumer filled out an online evaluative questionnaire, which varied in length and complexity. Most of the “not recommended” and “highly not recommended” website questionnaires were very basic, although a few took at least 10 minutes to complete and asked questions relevant to the conditions and contraindications associated with the drugs. For example, questions about heart conditions were asked when Viagra was ordered, whether Gastroesophageal Reflux Disease had been diagnosed by a physician when Nexium was ordered, and whether cholesterol levels had been measured when Lipitor was ordered. One “highly not recommended” website pharmacy called to check that the consumer (the lead author in this study) was an adult. Another website contacted the lead author after he accidentally (and incorrectly) filled out that his recent EKG was abnormal; the website representative said “our doctor wanted to check whether this result was accurate, because if so we cannot prescribe Viagra to you.”

“Cheap” Drug Websites: Buyer Beware?

There was wide price variation among the procured drugs. Among purchased drugs, which had some variation in formulation and quantity, Viagra was, on average and within each website classification, the most expensive drug, and also the drug with the greatest range in price. Prices per tablet for Viagra ranged from \$13.12 to \$41.00 per tablet, including shipping expenses and other expenses (one website charged a processing fee and another website charged for a pill splitter) amortized across the entire order (average

price of \$19.45). This compared to ranges between \$1.14 and \$19.40 per tablet/capsule for Nexium (average price of \$4.86), \$0.91 to \$7.07 for Lipitor (average price of \$2.39), \$1 to \$4.63 for Zoloft (average price of \$2.55), and \$1.24 to \$4.27 for Celebrex (average price of \$2.46) (See Table 2).

Table 2: Average price per tablet/capsule (minimum-maximum) of drugs as purchased, of varying formulations and quantities

Website Classification (Number of websites*)	Celebrex	Lipitor	Nexium	Viagra	Zoloft
NABP approved (5)	\$3.79 (3.27-4.27)	\$3.77 (2.76-7.07)	\$8.28 (4.17-19.40)	\$15.20 (13.37-17.00)	\$3.39 (1.60-4.54)
Legally complian (6)	\$1.99 (1.24-3.93)	\$1.77 (0.91-2.94)	\$2.86 (1.14-5.62)	\$14.35 (13.25-15.43)	\$2.18 (1.21-3.61)
Not recommended (5)	\$1.70 (1.63-1.76)	\$1.82 (1.39-2.55)	\$2.85 (2.23-3.46)	\$20.81 (13.12-41.00)	\$1.35 (1.00-2.02)
Highly not recommended (6)	\$1.96 (1.66-2.25)	\$1.94 (1.76-2.12)	\$4.49 (2.37-6.47)	\$27.44 (17.25-40.65)	\$3.14 (1.65-4.63)

*Not all drugs were ordered from all websites, either because they were not available or the lead author experienced difficulties while ordering.

For all drugs except one (Viagra), average prices at NABP-approved websites were slightly more expensive than drugs offered at website pharmacies from the other three classifications, although the difference was only significant for Celebrex (p-value= 0.0002). Viagra offered from non-NABP-approved website pharmacies, was on average more expensive than Viagra from NABP-approved websites (p-value= 0.046). Viagra 100mg procured from NABP-approved websites ranged from \$13.37 per tablet to \$17 per tablet (mean= \$15.20), while at non-NABP approved website pharmacies, it ranged from \$13.12 to \$41 per tablet (mean=\$20.87).

In general, larger orders tended to have lower per-tablet/per-capsule prices, and were more prevalent among website pharmacies that had not been approved by NABP. In order to determine whether the difference in price observed was due to order size, the authors assessed the prices offered for all of the drugs in consistent formulations (insofar as was possible; not all websites offered drugs in the same, consistent quantities) (See Table 3). In this case, orders were considered “stand-alone” and shipping prices were not amortized across the entire order. Again, prices for all of the drugs with the exception of Viagra were slightly more expensive at NABP-approved websites than at other websites; the difference was significant for all other drugs - Celebrex (p-value= 0.000005), Lipitor (p-value= 0.000002), Nexium (p-value= 0.01), and Zoloft (p-value= 0.0006). For all of the drugs except Viagra, prices were most expensive at physical-location pharmacies (See Table 3).

Table 3: Average price per tablet/capsule (minimum-maximum) of drugs with as consistent formulations and quantities as possible (not purchased)

Website Classification (number of websites*)	Celebrex 200mgX90	Lipitor 10mgX90	Nexium 40mgX28	Viagra 100mgX4**	Zoloft 100mgX100
NABP approved (5)	\$3.86 (3.54-4.06)	\$2.85 (2.71-2.98)	\$5.61 (5.07-6.20)	\$16.56 (13.94-20.55)	\$3.64 (3.12-4.32)
Legally compliant (6)	\$1.92 (1.33-3.84)	\$1.71 (1.00-2.89)	\$3.12 (1.43-5.62)	\$15.44 (12.38-17.49)	\$2.10 (1.05-3.53)
Not recommended (5)	\$1.78 (1.72-1.84)	\$1.57 (1.09-1.88)	\$3.12 (2.50-3.75)	\$20.62 (15.00-36.00)	\$1.46 (1.08-2.21)
Highly not recommended (6)	\$1.63 (1.58-1.69)	\$1.69 (1.61-1.76)	\$5.56 (2.71-7.03)	\$24.44 (17.25-33.65)	\$2.70 (1.60-3.79)
	Celebrex 200mgX30	Lipitor 10mgX30	Nexium 40mgX30	Viagra 100mgX4	Zoloft 100mgX30
Physical-location pharmacy*** (5)	\$4.50 (4.00-5.07)	\$3.44 (3.00-3.87)	\$6.26 (5.40-6.83)	\$17.75 (15.58-20.35)	\$4.36 (4.03-5.03)

* Not all websites offered drugs in the same, consistent quantities.

** There was greater variation in the quantities for Viagra than for the other drugs. Quantities ranged from 3 tablets to 10 tablets.

*** “Physical-location pharmacy”: Pharmacies were selected as the closest within a 0.5 mile radius of the lead author's home address (using Google Maps). No more than one of each chain pharmacy was selected. In addition, the authors included a nearby Wal-Mart store. One pharmacist refused to provide price information.

While a larger sample size is needed to make broad conclusions, these findings suggest that drugs procured from so-called “cheap” website pharmacies may not *always* be less expensive than more reputable websites, or at least in the case of Viagra, even less expensive than physical-location pharmacies. Several of the “not recommended” and “highly not recommended” website pharmacies required that consumers purchase drugs in large quantities, or only permitted consumers to purchase one kind of drug at a time (each time adding processing and shipping fees), which increased the overall price even more. Consumers may be motivated to buy from these websites regardless of price for reasons of privacy or to avoid needing a prescription, or because of ignorance.

If sellers of diverted drugs have relatively low transit and transaction costs, they can profit handsomely. Nexium procured from one website for \$83 (\$2.96/tablet) included a label on the box that indicated it could be sold for no more than INR 6.73/tablet in India (approximately \$0.14/tablet depending on the exchange rate), a mark-up of more than 2000%. For an additional twenty drugs whose packages included list prices from countries other than the United States, mark-ups ranged from -36% to more than 1400% (See Table 4).

Table 4: Diverted drug mark-ups: Price per tablet/capsule

Drug Received	Price US\$	Other Price	% Mark-Up (difference price/other)
Celebrex 90X200mg	\$1.22	EU 1.43 (= \$1.91)	-36%
Lipitor 90X10mg	\$0.89	TRY 1,07 (= \$0.67)	33%
Lipitor 30X10mg	\$1.67	TRY 1,07 (= \$0.67)	149%
Lipitor 30X10mg	\$1.83	TRY 1,08 (= \$0.67)	173%
Lipitor 90X10mg	\$1.22	TRY 1,08 (= \$0.67)	82%
Lipitor 90X10mg	\$1.37	TRY 1,08 (= \$0.67)	104%
Nexium 28X40mg	\$1.07	INR 6.81 (= \$0.14)	664%
Nexium 28X40mg	\$2.68	TRY 2,27 (= \$1.45)	85%
Nexium 28X40mg	\$3.39	TRY 2,27 (= \$1.45)	134%
Nexium 28X40mg	\$2.96	INR 6.73 (= \$0.14)	2014%
Nexium 28X40mg	\$2.14	INR 6.81 (= \$0.14)	1429%
Nexium 28X40mg	\$2.37	TRY 2,26 (= \$1.45)	63%
Nexium 28X40mg	\$2.47	TRY 2,26 (= \$1.45)	70%
Viagra 4X100mg	\$15.25	TRY 17,73 (= \$11.10)	37%
Viagra 4X100mg	\$12.50	TRY 18,6 (= \$11.89)	5%
Viagra 8X100mg	\$14.50	TRY 17,73 (= \$11.34)	28%
Zoloft 112X100mg	\$1.92	EU 1.61 (= \$2.16)	-11%
Zoloft 100X100mg	\$1.45	INR 9.08 (= \$0.18)	706%
Zoloft 100X100mg	\$0.98	INR 8.67 (= \$0.18)	444%

Discussion

Few drugs that could be tested against reference standards, failed; there was, however, some drug substitution, which limited the number of samples that could be assessed. Even assuming all substitutes were bioequivalent generics, risks remain for unwary purchasers of drugs over the Internet. Substandard Viagra, almost certainly counterfeit, was procured with packaging that indicated the samples originated in China. There have been reports that many fake pharmaceuticals originate in China and India [18].

The study findings underscore the difficulty for monitoring organizations like the NABP and PharmacyChecker to keep their “recommended” and “not recommended” website lists up-to-date. Google, Yahoo! and Microsoft *require* all advertisers and their affiliates who sell prescription drugs to be approved by PharmacyChecker. One website pharmacy appeared to have changed classification during the course of the study: when drugs were purchased from the website, it was within the “legally compliant” classification, listed as approved by PharmacyChecker.com, and was not listed on NABP’s “not recommended” list. It later appeared on NABP’s “not recommended” list. (In this study, the website was listed as “legally compliant” to reflect classification at the time of selection.) All of the drugs from this website passed spectrometry testing or were not in testable form (Nexium).

“Fly-by-night” website pharmacies can shut down and simply re-open under a new name. For website pharmacies based in foreign countries, the FDA and Drug Enforcement

Agency have little recourse for action except to appeal to national authorities in these countries. Encouragingly, evidence suggests that some foreign governments are taking action, as the Chinese government did when it publicly blacklisted 25 websites for selling and/or advertising counterfeit and substandard products in March 2009.

Problems in provenance and packaging observed by the authors are consistent with earlier findings. Research by Cyveillance, an online risk monitoring and management firm, for example, found that only 214 websites out of 11,000 that were designed to appear as Canadian pharmacy websites were actually based in Canada. Many were registered to individuals in countries like Australia, the Czech Republic, El Salvador, Germany, Mexico, and Vietnam [7].

The variety of price mark-ups—and some mark-downs—illustrate the inner-workings of an illicit, global “parallel” trade in pharmaceuticals (although wholesalers are permitted to sell pharmaceuticals across borders in the European Union, such practice is illegal in the United States). The presence of a mark-down at first appears puzzling: why would a seller offer a pharmaceutical for \$1.22 over the Internet when he or she theoretically could sell it for \$1.91 in the European Union? It is possible that the market in the European Union may have been “flooded” with the product, thereby depressing prices. The product may have been stolen; by peddling it overseas, the seller faced less chance of detection; in a market characterized by government-imposed profit caps, heavy taxes, and other disincentives to sell the product to the highest bidder, wholesalers and/or pharmacies might well be eager to sell the product overseas.

The ease with which the authors were able to procure drugs from non-NABP-approved websites without a prescription or by using photocopies or faxed versions of prescriptions suggests that there is ample opportunity for prescription drug abuse. The lead author was able to procure several drugs from 26 website pharmacies under the same consumer name within just a few months. For the websites that required prescriptions, the lead author was able to use the same prescriptions more than five times because of the lack of insistence on original versions (many website pharmacies allow consumers to fax prescriptions without contacting the prescribing physician). Not one website pharmacy checked why the lead author, a resident of Washington D.C., was using a physician in Indiana for his prescriptions (he has no obvious ties to Indiana and has never visited the state).

Regulatory agencies or associations such as the NABP might consider establishing an information-sharing system among registered pharmacies that would allow pharmacists to quickly identify whether a prescription for a given drug has already been dispensed to a given individual. Such information systems already exist for physicians to track prescriptions of controlled substances in some states, but are not widely used [19].

Of course, one of the reasons consumers buy over the Internet is convenience, and often they know exactly what drugs they require. There may be frustration in dealing with increased drug delivery bureaucracy. The authors suggest that the situation established by the better known websites may be the way forward. A consumer establishes a profile with a website pharmacy, sends in an original prescription for each drug, and from then

on everything can be done by email and phone, with the pharmacist dealing directly with the prescribing physician for drug refills. This provides the pharmacist and physician assurance that the patient is not abusing drugs and it is also convenient for the patient.

Not all consumers—particularly those wishing to bypass the requirement for a doctor's prescription, however—will favor such an option.

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APPENDIX

How website pharmacies were selected

The authors selected website pharmacies in two ways (1) by using the NABP “recommended” and “not recommended” lists and (2) by using the two most heavily used search engines, Google and Yahoo!, to identify websites where each of the five brand name drugs could be purchased without a prescription, or where a prescription could be obtained via a questionnaire. For each drug, search terms included “[name of drug],” “cheap,” and “prescription” and “[brand name of drug].” The perspective was of a consumer looking for the cheapest drug available off-prescription.

Website pharmacies were classified into four broad groups:

1. **“Approved” (5 websites):** these pharmacies have been accredited by the NABP under their Verified Internet Pharmacy Practice Sites program, which is recognized by the U.S. FDA. From the original list of 15 websites provided by NABP (list accessed in December 2008), drugs were purchased from five of them. The other ten websites only sold drugs through insurance companies/membership organizations, required a prescription drug benefit card, or would not accept the author’s credit card after repeated attempts. All five drugs tested in this study were available from each website.
2. **“Legally Compliant” (6 websites):** these pharmacies have not been accredited by NABP, but nor are they listed on NABP’s “not recommended” list. PharmacyChecker, an independent group not affiliated with any given pharmacy, indicates these websites are “approved” and in compliance with the laws in countries in which they are registered. Google, Yahoo! and Microsoft *require* all advertisers and their affiliates who sell prescription drugs to be approved by PharmacyChecker. From the original list of eight websites that the authors attempted to order from, drugs were only ordered from six. Two websites that the authors attempted to order from would not accept prescriptions. All five drugs were available from four of the six websites.
3. **“Not Recommended” (5 websites):** these pharmacies are listed as “approved” by PharmacyChecker, but are listed on NABP’s “not recommended” list. Drugs were procured from five websites. All five drugs were only available from one of the websites. The authors attempted to purchase drugs from many other websites but encountered problems. Some only accepted Visa; others returned mailed-in or faxed prescriptions without explanation.
4. **“Highly Not Recommended” (6 websites):** these pharmacies are listed on NABP’s “not recommended” list and are unlisted or listed as “not approved” by PharmacyChecker. Drugs were procured from six websites, none of which could provide all five drugs tested in this study. Some websites that were initially

selected crashed when the lead author tried to order drugs; some only accepted Visa; others never delivered ordered (and paid for) drugs.