INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

March 28, 2014

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Chairman Murphy:

I appreciate the opportunity to testify before your Subcommittee on "Counterfeit Drugs: Fighting Illegal Supply Chains."

The following question was asked in follow-up to the hearing, and my response is included as well as referenced materials.

The Honorable Michael C Burgess

1. **During the hearing when we discussed the reflection of cost in internet activity with the purchase of other brands that remained on patent and were therefore more expensive, you offered to provide the Committee with the findings of various studies that show which type of categories were being purchased more and what kinds of factors and root causes were leading to that. Please provide those findings to the Committee.**

I thank Congressman Burgess for his question and hope this response provides useful information on the nature of online pharmaceutical activity in the United States.

The Institute of Medicine report does not discuss the relationship between the price of patented drugs and internet sales. A 2006 study published by the Frasier Institute, however, estimated that 60% of the top-selling cross-border drugs bought online by Americans from Canada between 2004 and 2005 were brand-name products. The other 40% were generic drugs. The study also reported that more than half of Canadian internet pharmacy sales were for top-selling brand-name prescription drugs consumed primarily by seniors. This study (Skinner, 2006) was not referenced by the IOM committee, but a copy is attached.

It is difficult to comment on the proportions of types of drugs purchased online. Most online drug sellers are illegal which makes it difficult to track and precisely measure their activity. It is clear, however, that patients attempt to purchase all types of drugs online. People often think of patients as turning to online pharmacies for lifestyle drugs, such as Viagra. Americans are also purchasing drugs for more serious medical conditions, including asthma, arthritis, cholesterol, diabetes, Parkinson's disease, and cancer. While somewhat dated, Fox (2004) reported that three-quarters of those who purchased prescription drugs online, purchased a drug for a chronic medical condition. One quarter purchased them for other purposes, such as weight loss or sexual performance. A study by researchers at the University of California San Diego, which analyzed the web traffic of a major fake online pharmacy, found that Americans purchase non-lifestyle drugs a third of the time (Kanich, et al, 2011). The IOM committee did not reference these studies, but both are attached.

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The report does discuss the factors which encourage patients to purchase drugs over the internet. Many American shoppers believe that internet pharmacies sell cheaper drugs. This is particularly attractive to the elderly or uninsured patients who might not otherwise be able to afford their medicines. Patients are also motivated by convenience, access, addiction, or a desire to self-prescribe without a physician's advice. Studies demonstrating these motivations, all referenced in the IOM report, are attached (Baert and De Spiegeleer, 2010; Crawford, 2003; Levaggi et al., 2012).

The studies referenced above and attached include:

- Baert, B., and B. De Spiegeleer. 2010. Quality analytics of internet pharmaceuticals. *Analytical and Bioanalytical Chemistry* 398(1):125-136

- Crawford, S. Y. 2003. Internet pharmacy: Issues of access, quality, costs, and regulation. *Journal of Medical Systems* 27(1):57-65.

- Fox, Susannah. 2004. *Prescription drugs online*. Pew Internet & American Life Project. Washington, DC. http://web.pewinternet.org/~/media//Files/Reports/2004/PIP_Prescription_Drugs_Online.pdf.pdf

- Kanich, C., N. Weavery, D. McCoy, T. Halvorson, C. Kreibichy, K. Levchenko, V. Paxson, G. M. Voelker, and S. Savage. 2011. *Show me the money: Characterizing spam-advertised revenue*. Paper presented at Proceedings of the 20th USENIX conference on Security, San Francisco, CA.

- Levaggi, R., C. Marcantoni, L. Filippucci, and U. Gelatti. 2012. Not a good buy: Value for money of prescription drugs sold on the internet. *Health policy (Amsterdam, Netherlands)* 106(3): 241-245.

- Skinner, Brett. 2006. *Price Controls, Patents, and Cross-Border Internet Pharmacies Risks to Canada's Drug Supply and International Trading Relations*. The Fraser Institute. Vancouver, Canada.

I hope this information will be helpful to Congressman Burgess and the Committee.

Sincerely,

Prashant Yadav
Member, IOM Committee on Understanding the Global Public Health Implications of Counterfeit, Falsified and Substandard Drugs (February 2012-February 2013)

cc: Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachments

Anal Bioanal Chem (2010) 398:125–136
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REVIEW

Quality analytics of internet pharmaceuticals

B. Baert · B. De Spiegeleer

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Abstract Trading pharmaceutical products through the Internet poses several challenges related to legal responsibilities, good distribution practices, information content and patient use, financial implications, but also regarding product quality. One of the major concerns is the well-known phenomenon of counterfeited and/or substandard drugs commercialized through rogue Internet sites. Therefore, controlling and assuring the quality of those products has become an important and challenging task for the authorities. This review gives an overview of the different quality attributes that can be evaluated to have a complete understanding of the quality of the finished pharmaceutical product traded through the Internet, as well as the current analytical techniques that serve this objective. Aspects considered are labelling and packaging, physicochemical quality attributes, identification and assay of active substances and/or excipients, impurity profiling, biopharmaceutical testing and data interpretation.

Keywords Internet · Quality · Pharmaceuticals · Counterfeit · Substandard

Introduction

The Internet is one of the most widely used technological innovations in the past 20 years and its use by the public to obtain medical information and services continues to grow [1]. It is increasingly used to provide information to and facilitate interaction among product suppliers, patients, practitioners, health decision makers, insurance organizations, consumers and researchers [2]. Between 1999 and 2004, there was a tenfold increase in pharmaceuticals commercially available through the Internet [1]. Moreover, Web-based direct-to-consumer marketing practices gained much interest [3], resulting in rapidly growing online sales of all kinds of pharmaceuticals. Bostwick and Lineberry [4] identified four patient populations that turn to the Internet to buy drugs, each with divergent needs and desires. Cost savings motivate the first group and therefore they are called ‘bargain hunters’. The second group, ‘fixed-income elderly’ and disabled poor, have both chronic medical conditions and restricted financial means. They often take multiple medications simultaneously, but as the latest and greatest brand-name medications are too expensive, drugs obtained from the Internet offer a way to stretch limited funds. ‘Lifestyle libertines’ prefer to acquire their lifestyle products (such as hair tonics, obesity remedies or virility pills) privately to avoid embarrassment or having to discuss their issues with a medical practitioner. The last group consists of ‘drug addicts’, who want nothing to do with medical practitioners if they can get their products some other way. There is also a variation among online drug sellers. According to Liang and Mackey [5], four major types exist: (1) traditional, established chain pharmacies with a Web presence; (2) independent community pharmacies with a Web presence; (3) stand-alone, exclusively online pharmacy sites; and (4) rogue or illegal sites. The exact number of Internet drug sale sites is difficult to determine exactly owing to the fact that illegitimate or rogue Internet drug sellers often have several URLs for one company, and may only be transiently listed on select search engines. Nevertheless, some data are available: according to the US National Association of Boards of

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Pharmacy, there are between 3,000 and 4,000 questionable pharmacies on the Internet, compared with a few hundred in 1997 [6].

As outlined above, patronage of online drug-selling stores can be considered as part of a cost-containment strategy. However, many of the drugs ordered online are not cheaper at the online site [7]. Beyond the perception of lower price, the Internet improves access to medications through one-stop shopping, 24 h a day, 7 days a week. It eliminates the need for travel and time away from work or daily activities. Another important factor that attracts consumers to online pharmacies is the privacy and confidentiality in the acquisition and consumption of pharmaceuticals, thereby minimizing the social discomfort associated with the use of certain medications. Furthermore, a patient can easily obtain medications that are not available or approved in his/her own country.

In most countries, pharmaceutical retailing is governed by regulations concerning ownership, staffing, medicines, prescriptions and prices [8]. This national legislation determines who is allowed to practise pharmacy, the conditions under which a pharmacy may operate, and sets out rules for prescription, importation, sales, distribution and promotion of drugs. In almost all countries, prescription medicines and restricted medicines can only be sold or dispensed at a pharmacy by a registered and qualified pharmacist upon presentation of a prescription. Over-the-counter and non-prescription medicines are sold by a variety of drug sellers, and may be sold by pharmacy assistants and staff with little or no formal training.

Specific guidance concerning Internet pharmacy services is available in most countries. In general, the guidance documents state that safety and welfare of patients is the prime concern of the pharmacist and the pharmacist must adhere to this principle [9]. Compared with other methods of distribution, the Internet is weakly regulated with respect to the purchase of medicines [10]. Controls and safeguards relating to Internet-based commercial operations are imposed by national and international legislation, but in most cases consumers are not automatically prohibited from buying illegal and/or counterfeit medicines. Because of the anonymity and poorly regulated nature of the Internet, there is a low risk of perpetrators being caught and their operations being shut down. A great difference between the market for pharmaceuticals in developed countries and this market in developing countries is regulatory capacity. In most low- and middle-income countries, regulatory oversight is constrained by governments which lack the enforcement staff, budgets or efficient regulatory and judicial frameworks that exists in developed countries. Therefore, rogue Internet pharmacies often operate from these countries, making it more difficult to close down illegal sites and prosecute those behind the business. Nevertheless, most countries have been and/or are in the process of adapting their regulations to the Internet, and are allowing marketing and sales under restricted and regulated conditions. In practice, this generally comes down to registration of the Web site, marketing and selling of “non-critical” pharmaceuticals (e.g. non-prescription) only and pharmacist responsibility [11–13]. Moreover, the general public is actively informed of the risks related to the Internet purchase, as well as of the close-down and prosecution of non-conforming Web sites [12, 13].

In spite of all the benefits, there are a multitude of potential dangers associated with the purchase of pharmaceuticals through the Internet. These dangers include the supply of drugs without a valid prescription, lack of professional oversight, poor or lack of medication instructions, failure to provide adequate independent information to patients on possible adverse reactions and drug interactions, inability of consumers to be reimbursed by health insurance programmes, lack of confidentiality of personal medical data, fraud and the illegal action of obtaining or possessing some pharmaceuticals, causing violation of the law. Moreover, patient safety could be at risk because of questionable quality of the counterfeit or substandard drugs. Corrupt and disreputable individuals have entered this market, eager to sell at high profit tainted, fake and poor-quality drugs. These sales are often not only an illicit means of profit, but are also a foundation for additional criminal activity. The definition of ‘counterfeit drug’ by the World Health Organization is as follows: “A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging” [14]. The following type of fake drugs are encountered [15]: (1) drugs that do not contain active substances marked on the packing (i.e. placebo); (2) drugs that contain active substances that are not marked on the packing; (3) drugs that actually contain the marked substance, but these drugs are produced by another manufacturer.

All kinds of medicines have been counterfeited, ranging from medicines for the treatment of life-threatening conditions to inexpensive versions of painkillers and antihistamines. Although counterfeiting is greatest in regions where regulatory and enforcement systems for medicines are weakest, it is a worldwide problem (Table 1). In over 50% of cases, medicines purchased over the Internet from illegal sites that conceal their physical address were found to be counterfeit [16]. Veronin et al. [17] determined whether generic simvastatin tablets and capsules obtained via the Internet from international markets are equivalent to the US innovator product regarding major

Table 1 Examples of counterfeit medicines (WHO fact sheet number 275, January 2010)

Counterfeit medicine	Country, year	Report
Antidiabetic traditional medicine	China, 2009	Contained 6 times the normal dose of glibenclamide. 2 people died, 9 people were hospitalized
Metakelfin®	Tanzania, 2009	Discovered in 40 pharmacies: lacked sufficient API
Viagra® and Cialis®	Thailand, 2008	Smuggled into Thailand from an unknown source in an unknown country
Xenical®	USA, 2007	Contained no API and sold via Internet sites operated outside the USA
Zyprexa®	UK, 2007	Detected in legal supply chain: lacked sufficient API
Lipitor®	UK, 2006	Detected in legal supply chain: lacked sufficient API

API active pharmaceutical ingredient

aspects of pharmaceutical quality. Several samples analysed were not comparable to the US product in one or more quality attributes and significant variability was found among the foreign-made tablets themselves. Five samples failed to meet the United States Pharmacopeia (USP) standards for dissolution and two samples failed to meet the standards for content uniformity. Among all samples, variability was observed in hardness, weight and physical characterization. The lack of specific regulations concerning Internet marketing and the lack of systematic control of the pharmaceutical market, both legal and illegal, increases the health risk for the population [18, 19]. Therefore, the need for fast, easy, reliable and inexpensive analytical methods for drug screening is essential. These methods should enable the detection of pharmaceuticals and their classification as counterfeit with high selectivity and specificity. A large number of analytical techniques are used to achieve this goal (Table 2).

Labelling and packaging

The ability to investigate the quality of pharmaceuticals obtained through the Internet is a critical component of monitoring this type of drug supply by regulatory authorities. Although it seems trivial, the verification of the legal classification state of the products sold through the Internet is the first question when considering the quality of these products, as different product classes have different legal status and quality requirements. Moreover, there is a continuously growing overlapping grey zone, making demarcation between the different product classes increasingly difficult. Next to pharmaceuticals, there are nutrients or food supplements, cosmetics and cosmeceuticals, nutricosmeceuticals, biocides and plant protection products, medical devices and other chemicals. Depending upon regional and/or national legislation, a product is thus classified according to the applicable definitions. However, in general, the legal definitions agree that a pharmaceutical contains a pharmacologically active substance executing an effect (even without claiming so), or it is presented as having this effect (even in the absence of an active substance). There is a wealth of lists with compounds and claims for compounds that are considered as pharmaceuticals. The form alone is not proof of the compound being a pharmaceutical, e.g. a gel can be registered as a medical device or a tablet can be a regular food supplement. Once a product is defined as a pharmaceutical, then an important quality aspect is the information content of the labelling on the packaging and leaflet, which should minimally comply with the regulations. The packaging should also comply with good manufacturing practice regulations, e.g. traceability and regulatory compliance of the packaging is to be assured and relatively easily verifiable. Moreover, physicochemical and chemical investigations of the primary and secondary packaging can also be performed if counterfeiting is suspected; for example ink, carton/paper, glue, plastic, etc. can be examined to determine the possible origins. Last, trace analysis of the inevitable contamination on the outer surface [20] can give a fingerprint signature of the manufacturing site and/or its logistics chain.

Westenberger et al. [21] investigated the quality of selected drug products (fluoxetine hydrochloride, laevothyroxine sodium, metformin hydrochloride, phentoin sodium and warfarin sodium) purchased through the Internet from foreign sources. It was found that sample packaging was a significant problem with virtually all of the 20 Internet samples studied. Only one of the products had a final packaging that was similar to that of the US Food and Drug Administration (FDA)-approved reference product. Of the 19 remaining Internet samples, many had either no or minimal labelling information for proper usage or testing of these drugs. Moreover, seven of the 20 samples investigated arrived in questionable containers. Some samples were even shipped loosely in an unlabelled plastic bag. These findings illustrate the absolute need for this first inspection step in assessing the quality of a product bought through the Internet. However, owing to increasingly sophisticated counterfeiting techniques, the detection of substandard drugs by simple visual package inspection alone has become gradually more difficult. An

Table 2 Overview of analytical methods used to assess different quality attributes of Internet (and/or counterfeit and/or substandard) pharmaceuticals

Pharmaceutical	Analytical method	Quality attribute	Reference
Fluoxetine hydrochloride, laevothyroxine sodium, metformin hydrochloride, phentoin sodium, warfarin sodium	Physical characterization	Physicochemical properties	[21]
	Dissolution	Biopharmaceutical behaviour	
	HPLC	Assay, impurities	
	NIR	Qualitative assessment of uniformity	
	NIR imaging	Density of API and excipients	
	Thermogravimetric analysis	Chemical composition	
	Chemometry	Grouping	
Antimalarials	Dissolution	Biopharmaceutical behaviour	[29]
	HPLC	Assay, impurities	
Captagon	Physical characterization	Physicochemical properties	[48]
	IR/UV spectra	Identification	
	TLC	Identification	
Antimalarials	Refractometry	Refractive index	[23]
	Colorimetry	Assay	
Antimalarials	Disintegration tests	Break-up of tablet	[62]
	Visual inspection	Physicochemical properties	
	Qualitative colour reaction	Assay	
	Semiquantitative TLC	Chemical composition	
Testosterone	Dissolution	Biopharmaceutical behaviour	[30]
	Release profiles (Franz cell)	Biopharmaceutical behaviour	
	HPLC, ESI-MS	Assay, impurities	
Artesunate	Fast Red dye test	Assay, chemical composition (chalk)	[31]
	HPLC, MS	Assay, chemical composition	
	X-ray diffraction	Mineral composition	
	Pollen analysis	Geographical origin	
Simvastatin	Disintegration tests	Break-up of tablet	[32]
	Dissolution tests	Biopharmaceutical behaviour	
	HPLC	Assay	
Tuberculosis drugs	TLC	Chemical composition, assay	[67]
Tuberculosis drugs	TLC	Chemical composition, assay	[26]
Oseltamivir	HPLC-UV detection	Assay	[27]
Oseltamivir	HPLC	Assay	[28]
Betamethasone	HPLC	Assay, chemical composition	[33]
	ESI-MS	Identification	
Captagon	GC-MS	Chemical composition	[34]
Halfan (antimalarial)	MS/MS, LC-MS	Identification	[37]
Allyl phenylamine, phenylamine, ethylpyridine, propranolol, amlodipine, oxazoline-5-carboxyl ester	TLC	Chemical composition	[46]
	EASI-MS	Structural information	
Mesembrine	Capillary zone electrophoresis	Chemical composition, assay	[36]
Artesunate	2D DOSY ^{1}H NMR	Chemical composition	[40]
	DART MS	Chemical composition	
	DESI MS	Chemical composition	
Sildenafil	X-ray powder diffraction	Qualitative composition analysis	[18]
Tadalafil	^{1}H NMR	Identification	[54]
	2D DOSY ^{1}H NMR	Fingerprinting	
	Raman spectroscopy	Fingerprinting	
Sildenafil	2D DOSY ^{1}H NMR	Chemical composition	[59]
	3D DOSY COSY ^{1}H NMR	Structural information	

Table 2 (continued)

Pharmaceutical	Analytical method	Quality attribute	Reference
Acetaminophen, artesunate, halofantrine hydrochloride, multivitamin tablets, dibenzosuberone, cholesterol, angiotensin I, lactose	DEMI (combination DESI and DART)	chemical composition, identification	[45]
Lamivudine (Heptodin)	NIR NIR-CI PCA, *k*-clustering	Chemical composition Spatial distribution API Clustering, quantification of main components	[49]
Vitamin tablets	NIR (qualitative, quantitative)	Chemical composition (qualitative and quantitative)	[50]
Bisoprolol hemifumerate	NIR-CI Statistical variance analysis	Chemical composition, spatial uniformity Clustering	[57]
Different drugs	FT-IR ATR	Chemical composition, spatial distribution	[38]
Antimalarials	FT-IR ATR DESI-MS	Chemical composition, spatial distribution Identification	[52]
Different drugs	NIR diffuse reflectance Multivariate analysis	Chemical composition Clustering	[15]
Simvastatin	NIR-CI	Blend uniformity	[17]
Artesunate	FT-Raman spectroscopy DESI, DART	Chemical composition Identification	[39]
Sildenafil	Raman spectroscopy PCA, hierarchical cluster analysis	Chemical composition (qualitative) Clustering	[55]
Antimalarials	Raman spectroscopy Multivariate analysis	Chemical composition (qualitative) Clustering	[53]
Codeine, diazepam, morphine, benzodiazepines	IMS	Identification	[47]

HPLC high-performance liquid chromatography, *NIR* near-IR, *TLC* thin-layer chromatography, *ESI* electrospray ionization, *MS* mass spectrometry, *GC* gas chromatography, *LC* liquid chromatography, *EASI* easy desorption sonic spray ionization, *DOSY* diffusion-ordered spectroscopy, *NMR* nuclear magnetic resonance, *DART* direct analysis in real time, *DESI* desorption electrospray ionization, *COSY* correlation spectroscopy, *DEMI* desorption electrospray/metastable-induced ionization, *CI* chemical imaging, *PCA* principal component analysis, *FT* Fourier transform, *ATR* attenuated total reflection, *IMS* ion mobility spectrometry

interesting aspect that has received a great deal of attention recently is 'serialization'. Serialization refers to the assignment and placement of unique markings on a primary package [22]. These unique codes are placed on each package at the packaging stage and are uploaded to an event repository database that can be accessed by various parties, including pharmacists, law enforcement officials and even consumers, after the product has been shipped and sold. This will provide the ability to track and trace products from the point of packaging to the end user.

Physicochemical quality attributes

In a second step, the physicochemical properties of the pharmaceutical product obtained via the Internet can be assessed. These include visual aspects of the drug product (e.g. the printing, embossing or engraving, scores of tablets), the physical dimensions of the sampled drug product (such as weight, length, width, thickness, geometric shape, external markings of a tablet), odour, colour (direct and/or indirect measurement modes, both internal and external), hardness and friability, surface roughness analysis, disintegration time, density, viscosity, refractive index, crystal morphology, pH and solubility. The equipment needed to measure most of these properties (e.g. balance, refractometer, hydrometer, microscope) is relatively inexpensive and, with appropriate training, high-level technical experience is not required. For example, it has been shown that a simple refractometer can be used to monitor tampering with controlled substances by measuring the refractive index of a drug solution [23]. More advanced techniques involve surface texture analysis using image processing of untreated and/or treated drugs, e.g. tablet surface as well as the surface of the broken tablet.

Identification and assay of active substance and/or excipients

Further characterization of the pharmaceutical product under investigation can be done by chemical analysis. The presence of the label-claimed active ingredient is a first quality requirement. Identification methods described in pharmacopoeias as well as in the common technical document and drug master files are meant for confirmation only, and are certainly not meant for exhaustive proof of the structure. A chromatographic retention characteristic, combined with a UV-vis spectrum, mostly fulfils this confirmatory requirement. So, these mostly restricted methods fit their intended purpose of confirming the identification null hypothesis that the analyte is the active pharmaceutical ingredient (API) mentioned on the label (versus the analyte not being the API mentioned on the label). However, it has been shown that such simple identification systems may lead to false positives: a so-called obestatin peptide was correctly identified by high-performance liquid chromatography (HPLC) with simple UV detection, but appeared to be a totally unrelated milk-derived peptide by mass-spectrometric analysis [24]. The possibility of false identification is expressed by the reliability, or the probability of a correct result. High reliability is related to low type I or α errors (i.e. falsely rejecting the null hypothesis, false alarm or false non-compliance) and type II or β errors (i.e. falsely accepting the null hypothesis, false alarm or false compliance). It is clear that the univariate (e.g. chromatographic retention time) or the better performing multivariate (e.g. whole spectrum [25]) identification data for Internet pharmaceuticals should minimize type II errors, even if this increases the type I errors, at least at the initial quality verification.

Contrary to the regulatory controlled medicines, where it is expected that the correct API is used with an assay value within the 90–110% label claim or stricter, this is by no means guaranteed for rogue Internet pharmaceuticals. The identification and quantization of the API in a preparation can be assessed by commonly used basic tests applicable to field testing such as colorimetric tests and thin-layer chromatography (TLC). Colorimetric techniques make use of colour changes produced by selective chemical reactions. The colour changes are usually rapid and easily discernible. Quantitative measurements of active ingredient concentration as a function of colour absorbance can be made using a simple spectrophotometer [23]. TLC is a selective, sensitive and inexpensive technique. A sample of dissolved drug is placed on a thin layer, mostly of silica, attached to a plate of glass or plastic, and its end is dipped into a solvent mixture, which, through capillary action, causes migration of the solvent through the silica layer. The relative affinity of different drugs for the silica surface and the solvent mixture results in chemical separation of the sample components, which are then detected by transformation into coloured spots via chemical reactions or with a UV lamp. TLC techniques, or the rapid high performance variant (high-performance TLC), are available for most common pharmaceuticals. Kenyon et al. [26] performed a TLC analysis of 13 fixed-dose-combination tuberculosis drugs to determine the actual drug content in these preparations. Four samples were found to be substandard. With UV as the gold standard, the statistical sensitivity of the TLC method used for rifampicin was 100%, whereas the statistical specificity was 90%. More sophisticated chemical analysis methods are also applied. HPLC [21, 27–33] and gas chromatography (GC) [34, 35], coupled with use of optical or electrochemical detectors, are the traditional methods for quality control of drug substances and products. HPLC is used for non-volatile chemicals such as adulterants and organic residues, whereas GC is particularly useful in the analysis of volatile constituents. Both techniques can be used to assess the identity, content (i.e. assay) and impurity profiling of the API. Onwujekwe et al. [29] measured the amount of API in a number of antimalarials using HPLC and found that 37% of the products tested did not meet the USP specifications for the amount of active ingredients, with the suspected drugs either lacking the APIs or containing suboptimal quantities of the APIs. Both HPLC and GC can also be used to elucidate the chemical composition of the suspect sample. A plot of absorbance versus chromatographic retention time generated by HPLC or GC is an example of a one-dimensional fingerprint. Identification is most commonly accomplished by matching the retention time. An extra dimension can be supplied by diode-array detection, thereby allowing comparison of the UV-vis spectrum of the unknowns with the UV-vis spectra of candidates stored in a database. Multidimensional chemical fingerprints can be achieved by coupling different orthogonal chromatographic separations (e.g. two-dimensional GC × GC or HPLC × GC). Another separation technique used for the detection of counterfeit drugs is capillary zone electrophoresis, where compounds are separated on the basis of their size-to-charge ratio in the interior of a small capillary filled with an electrolyte. Patnala and Kanfer [36] analysed commercialized (including Internet-obtained) tablets of *Sceletium*, a plant that has been reported to contain psychoactive alkaloids, using this analytical technique. Their method allowed the identification of five alkaloids and the quantization of mesembrin, the most important alkaloid present in this dosage form.

Identification power can be enhanced by sending the eluted stream of chromatographically or electrophoretically separated compounds into a mass spectrometry (MS) detector [30, 31, 33–35, 37]. MS can also be used as a stand-alone technique, i.e. without coupling it with a separation technique. The MS principle consists of ionizing chemical compounds to generate charged molecules or molecule fragments and measurement of their mass-to-charge ratios. Techniques for ionization have been key to determining what types of samples can be analysed by MS. Electron ionization and chemical ionization are used for gases and vapours. Electron ionization, where very high energy electrons (approximately 70 eV) bombard the gas-phase sample and form the cation radical, is the most common form of ionization. In chemical ionization sources, ionization occurs owing to collisions of ionized gases with the target analyte. The reagent gas (e.g. methane, isobutane or ammonia) is present in the ion source at a very low pressure (1 Torr). Atmospheric pressure chemical ionization is an ionization method analogous to chemical ionization. The significant difference is that atmospheric pressure chemical ionization occurs at atmospheric pressure and has its primary applications in the areas of ionization of low-mass pharmaceutical compounds.

Two techniques often used with liquid and solid biological samples are electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI). In ESI, a sample solution is sprayed from a capillary into a strong electric field in the presence of a flow of nitrogen to assist desolvation. The ESI source operates at atmospheric pressure. The droplets formed evaporate in a region maintained in a vacuum, causing the charge to increase on the droplets. The multiply charged ions then enter the analyser. The most obvious feature of an ESI mass spectrum is that the ions carry multiple charges, which reduces their mass-to-charge ratio compared with a singly charged species. This allows mass spectra to be obtained for large molecules. MALDI provides for the non-destructive vaporization and ionization of both large and small biomolecules. In MALDI analysis, the analyte is first cocrystallized with a large molar excess of a matrix compound, usually a UV-absorbing weak organic acid, after which laser radiation of this analyte-matrix mixture results in the vaporization of the matrix, which carries the analyte with it. A major drawback of the ionization techniques mentioned above is their requirement for sample preparation.

Desorption ESI (DESI) [38–40] and direct analysis in real time (DART) [39–42] are surface ionization techniques for ambient MS and both allow high-throughput pharmaceutical analysis with no sample preparation. In DESI, a continuous pneumatically assisted electrospray jet is directed onto the sample, resulting in a thin solvent film where surface molecules are extracted. The solvent flow from the spray dynamically dislodges the surface film, resulting in the generation of analyte-containing secondary droplets, sampled downstream by the inlet of the mass spectrometer. Ionization occurs following ion evaporation and charge residue mechanisms as in ESI. DESI is particularly powerful for analysing thermally labile, non-volatile, polar molecules in a mass range up to 66 kDa [43]. In DART, an ion source which produces a heated stream of protonated reactant ions is used. This stream is directed towards the sample under investigation, desorbing chemical species from the sample, simultaneously ionizing them by a mechanism involving gas-phase proton transfer. These ions are generated in the open air between the ion source and the mass spectrometer, and are sampled by the inlet of the mass spectrometer. DART has been shown to be best suited for the analysis of molecules with a broad range of polarities in a mass range of up to 800 Da [44]. The features of both DESI-type and DART-type ionization can be combined into an ambient multimode ionization technique, desorption electrospray/metastable-induced ionization, enabling the simultaneous and direct detection of molecules within a broader range of polarities and molecular weights without loss of throughput or spatial resolution [45]. Another innovative ionization technique is the so-called easy desorption sonic spray ionization (EASI). EASI uses the gentlest sonic spray ionization to create charged droplets, which are formed owing to the sonic spray that causes a statistical imbalance in the distribution of charges. EASI has been applied with success for forensic counterfeit screening and quality control [46].

Ion mobility spectrometry can also be used to determine the authenticity of a pharmaceutical product by identifying its components and their relative proportions. The term 'ion mobility spectrometry' refers to a method that characterizes chemical substances via their gas-phase ion mobility. In an ion mobility spectrometer, samples are introduced via one of the different modes, such as thermal desorption. Subsequently, the compounds are ionized at atmospheric pressure by an internal ionization source, such as ^{63}Ni, and an electric field drives the ions through a drift tube, where collisions occur between the ions and neutral buffer gas molecules (usually purified air). The characteristic speed at which an ion moves under the influence of an electric field, i.e. its ion mobility, is a distinct thumbprint that identifies the original substance. Owing to its speed and relatively inexpensive nature as well as convenience (portable hand-held field use possibilities), this technique has great potential for pharmaceutical quality control of Internet samples [47].

Spectroscopic techniques are also used for the analysis of suspected counterfeit medicines. Near-IR (NIR) spectroscopy [15, 21, 48–52] and Raman spectroscopy [39, 53–55] are non-destructive analytical techniques with little or no sample preparation required. NIR spectroscopy can be used for the determination of physical properties such as tablet hardness [56], but can also provide detailed information on the chemical composition. Quantitative data about the API can be obtained. However, in many cases dosage forms contain not only active substances, but also excipients, which permits the traceability of Internet samples. NIR spectra thus not only provide information about the API, but at the same time they provide information about the complete chemical composition and/or processing of the pharmaceutical preparation. This enables detection of counterfeit drugs even with the proper active substance being present. NIR chemical imaging is a powerful coupled extension, as it combines chemical information obtained through spectroscopy with the ability to provide spatial information on the distribution of the components in a drug product. NIR chemical imaging has been successfully applied for drug identification and quantification [17, 21, 49, 57] and for estimation of homogeneity [17]. Raman spectroscopy has been used for drug identification of APIs as well as excipients, determination of solid-state properties (e.g. polymorphism), imaging of tablets and assays. Its non-destructive character (tablets can even be analysed through the packaging) and high speed of analysis make this method well suited for investigating Internet drugs, where the limit of detection is not a main issue.

X-ray diffraction analysis provides information not only about the crystallographic structure, but also about the other ingredients. The atomic planes of a crystal cause an incident beam of X-rays (with wavelength approximating the magnitude of the interatomic distance) to interfere with one another as they leave the crystal. Results obtained for counterfeit Viagra® tablets [18] show that this relatively simple technique can be adapted to a method suitable for pharmaceutical market screening control purposes. Its advantage is that no or minimal sample preparation is required. Such a method could easily discriminate fake and original Viagra® samples, even by visual examination of diffraction patterns, which can be done by employees who are relatively inexperienced in this technique.

As most finished pharmaceutical products (FPPs) can be considered as complex mixtures, nuclear magnetic resonance (NMR) spectroscopy is an excellent analytical tool for studying such formulations. Although NMR spectroscopy has traditionally been limited by sensitivity compared with other analytical techniques, the development of new acquisition and data processing tools has overcome this problem [58]. Diffusion-ordered spectroscopy (DOSY) NMR provides precise analysis of a complex mixture without any prior separation of the different compounds. DOSY NMR relies on the differences in translational diffusion as a means to separate components in a solution mixture. The diffusion coefficient generally decreases with increasing molecular weight. It is a two-dimensional NMR experiment: one dimension accounts for conventional chemical shifts and the other for diffusion coefficients. Trefi et al. [54] showed that two-dimensional DOSY NMR spectra clearly show similarities and differences in the composition of Internet-obtained pharmaceutical formulations of tadalafil (Cialis®), thus giving a precise and global signature of the manufacturer. The data indicated that the quality of the Cialis® imitations manufactured in India and Syria was correct, whereas the Chinese formulation was adulterated with APIs. DOSY experiments are non-destructive, do not need complicated set-ups and the method can easily be standardized and automated. When a non-conforming formulation is detected, classic methods such as ^{1}H NMR spectroscopy and MS are necessary for an unambiguous structural determination [54]. The evolution towards three-dimensional DOSY correlation spectroscopy will make such additional testing superfluous, as this technique provides both virtual separation and structural information [59].

Impurity profiling

The detailed chemical analysis of pharmaceuticals by modern analytical techniques assigns to every drug sample a characteristic chemical signature of major, minor and trace components. An impurity can be defined as any component of the finished drug product that is not the drug substance or an excipient of the product. Impurities can be classified as related or unrelated to the active drug substance. Unrelated substances can originate from the manufacturing process of the API or FPP (e.g. reagents, ligands, catalysts residual metals and solvents and filter aids such as charcoal) or from the environment (e.g. heavy metals, pollen, polyaromatic hydrocarbons). Drug-related substances are organic and include starting materials, by-products, intermediates and degradation products. Careful examination of the impurity profiles offers a valuable means of comparing and grouping different products, even with respect to the geographical region where they were produced. In a recent study, Sengaloudeth et al. [31] investigated four poor-quality artesunate samples by X-ray diffractometry and isotope ratio MS to determine the mineral composition and by microscopy for pollen and invertebrate remains. Calcite was detected in three samples and starch in one sample. The stable isotope analysis of the calcite suggested a high-temperature or volcanic origin. Although not sufficient for proof, the results for the pollen analysis are consistent with a source of the fake artesunate in southern China.

One of the challenging major differences between the 'brick and mortar' supply chain and Internet trading is the practical application and implementation (or its lack thereof) of good distribution practices. This is an inherent and fundamental part of the overall quality chain of pharmaceuticals from manufacturing to the patient. Traceability and integrity, encompassing the assurance of correct storage conditions, are the key principles of good distribution practices. A formally approved FPP has undergone extensive stability testing to justify the stated shelf life under the defined conditions. The stability conclusions are evidently only valid for the specific drug product with its own manufacturing processes of API, excipients and FPP. Changes in an ingredient supplier or FPP manufacturing process can alter the stability profile. Therefore, the stability profile, i.e. the quantitative kinetics as well as qualitative degradation pathway, is also a quality and origin marker for the drug product.

We have examined five antimalarial fixed-combination drug products, consisting of a powder for oral suspension containing β-artemether. A short-term comparative stability study was performed, where the products were stored at 50 °C and 70% relative humidity for 3 months, with monthly analysis of β-artemether and related degradants by HPLC-UV detection and ESI/ion trap MS. Assuming first-order kinetics and disregarding differences in β-artemether assay at the start of the stability study, we give the half-life of β-artemether in these seemingly similar formulations in Table 3. Moreover, although the major degradation product formed overall was the diketoaldehyde derivative 2-[4-methyl-2-oxo-3-(3-oxobutyl)cyclohexyl]propanal, this hardly increased for Artemef, which, in contrast, showed an increase of an as-yet unidentified degradant. These results stress the point that for uncontrolled pharmaceutical products distributed through rogue Internet sites there may be claims of similar shelf lives, whereas in reality they may differ quite considerably. Moreover, whereas short and limited excursions from the storage conditions mentioned on the label are investigated and assured for regular medicines, this may not be the case for uncontrolled medicines. Given, in addition, that the Internet distribution chain may contain longer and more profound excursions from the maximally claimed storage conditions, it may not be possible to disregard the impact on the resultant quality, especially if degradants significantly exceed the qualification thresholds.

Biopharmaceutical quality attributes

Biopharmaceutical characterization tests aimed at assuring an adequate pharmacokinetic profile of the product under investigation are often neglected, but are of critical importance for assessing the quality of pharmaceuticals obtained through the Internet. Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality and purity, as well as content uniformity and disintegration and dissolution rates [60]. Although a preparation could have the correct amount of active ingredient and a correct excipient formulation, different aspects together can affect the product's dissolution behaviour, resulting in decreased or increased bioavailability of the product. Variable clinical response to the same dosage form of a drug product supplied by different manufacturers has been reported [61]. Therefore, biopharmaceutical characterization techniques are required to ascertain the quality of Internet-obtained drug products.

Table 3 Half-life of β-artemether at 50 °C in selected antimalarials

Product	$t_{1/2}$ (months)
Lufanter	1.10
Lum-artem	0.70
Artemef	9.52
Lomart	0.96
Co-artesiane	5.61

A first test that can be performed is the disintegration test. The disintegration test is used to determine whether tablets, capsules, suppositories or pessaries soften or disintegrate within the prescribed time when placed in a liquid medium under prescribed experimental conditions. Tipke et al. [62] evaluated the disintegration characteristics of 77 antimalarial drug samples obtained from both the licensed and the illicit market. In total, four samples, corresponding to approximately 5%, failed the disintegration test. Not surprisingly, all samples that failed the disintegration test were obtained from the illicit market. Most likely, this was the result of poor storage conditions. Another factor that can prevent proper disintegration is related to the formulation of the drug itself as deliberately counterfeit drugs might contain substances such as flour and baking powder.

The key biopharmaceutical characterization is the dissolution test or a related test. This test is not only a powerful and valuable tool to guide formulation development, monitor the manufacturing process and in some cases predict in vivo performance, but it can also be used to assess product quality. Dissolution tests also provide a useful and comprehensive, functional and overall quality attribute, encompassing particle size distribution, crystal form, production parameters, etc. Evidently, Internet-obtained pharmaceuticals should comply with the expected specifications. For the test to be useful in quality control of Internet pharmaceuticals, it should be simple, reliable and reproducible. Ideally, it should be able to discriminate between different degrees of in vivo product performance [63]. The value of the test is significantly enhanced when product performance is evaluated as a function of time, i.e. when the dissolution profile is determined rather than there being a single-point determination. Since dissolution testing plays a different role when it is used as a quality-control test from when it is used as a surrogate for bioequivalence, different dissolution protocols are required [64]. An over-discriminatory test might be suitable for quality-control purposes to detect even small product deviations. However, such a test is not desirable for the prediction of the in vivo performance of the product, where dissolution testing should be a sensitive and reliable predictor of bioavailability. For example, most antimalarial drugs pass the basic tests for pharmaceutical dosage forms such as the uniformity of weight for tablets and the content test, but do not comply because of incorrect in vitro product dissolution [65]. Onwujekwe et al. [29] analysed antimalarial drug samples (including artesunate, dihydroartemisinin, sulphadoxine-pyrimethamine, quinine and chloroquine) that were obtained from public and private health-care providers in southeast Nigeria. The quality of these drugs was assessed by laboratory analysis of the dissolution profile using published pharmacopoeial monographs. In total, 60 of the 225 samples (37%) did not meet the USP tolerance limits for the dissolution test. Detailed analysis showed that 78% of the non-conforming samples were obtained from private pharmacy shops, questioning their reliability regarding product quality. Westenberger et al. [21] investigated the dissolution behaviour of selected drug products purchased through the Internet from foreign sources. Most of the samples passed the dissolution test, with two exceptions: laevothyroxine sodium tablets and extended phenytoin sodium capsules. Owing to incomplete labelling, it was not clear which specific product with its related dissolution profile was present, leading to inferior quality.

The dissolution test or the drug-release test is also employed to evaluate other non-oral special dosage forms such as topicals, transdermals and implants. The drug-release test for these products is also of value in assuring drug product quality. Nevertheless, the value and application of such in vitro release systems are not as widely accepted as for oral dosage forms, e.g. owing to the use of several different pieces of equipment, designs and operational protocols. In an earlier study, we investigated the release profile of different testosterone gels, obtained from a pharmacist or through the Internet, using Franz diffusion cell experiments [30]. This test has emerged as the most popular design for testing the in vitro release of topical semisolid dosage forms [66]. Differences in biopharmaceutical behaviour were demonstrated, questioning the interchangeability of these topically applied preparations. Moreover, apart from chemical quality differences as observed between the Internet- and pharmacy-obtained preparations, microscopic investigations showed a different particle morphology.

Data interpretation

For cost-efficiency reasons, a tierced system is favoured, starting with the simplest and most inexpensive methods (Fig. 1). At every stage, bioinformatics and/or chemometric support is recommended. At the inspection of the labelling and packaging, an updated database encompassing the legal classification of and visual information on the product would increase the quality of the decision. As more sophisticated and coupled analytical methods are used to determine the (physico-)chemical aspects of the product under investigation, it becomes more difficult to interpret

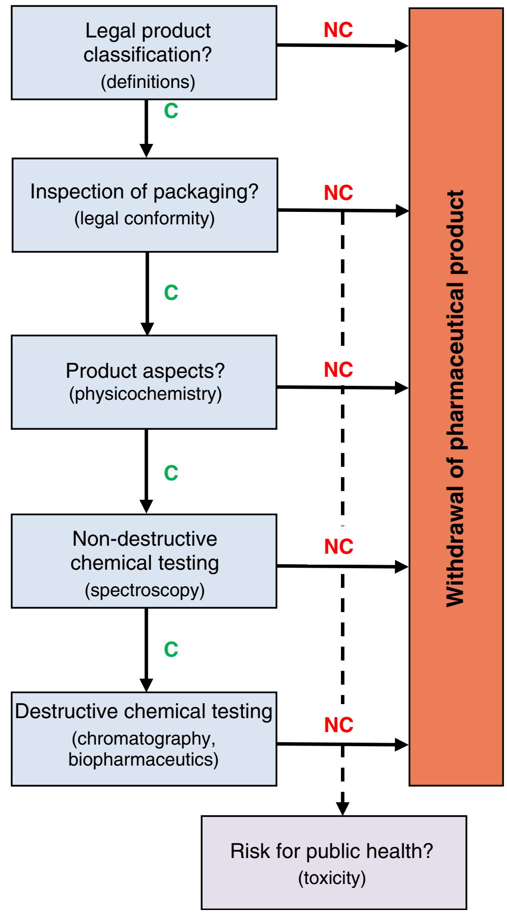

Fig. 1 Tierced flow chart for quality evaluation of Internet pharmaceuticals. *NC* non-conformity

the raw data as such which are presented as a multivariate matrix. Although the measurements themselves can be rapid and simple, they often carry information in a hidden way: to extract the desired information, adequate data processing is necessary. Data obtained from such instruments are typically highly correlated and corrupted with noise. Therefore, chemometric techniques, such as principal component analysis (PCA) [49, 53, 55], multivariate data analysis [15, 53, 57] and clustering methods [49, 55], can assist in extracting the useful information.

Westenberger et al. [21] compared the uniformity of warfarin sodium tablets obtained through the Internet with that of FDA-approved samples by recording their NIR spectra. Chemometric analyses of the second derivatives yielded principle component plots showing an increased variability of the Internet product. Moreover, both groups were sufficiently dissimilar to allow them to be separately clustered. This illustrates that it is not always necessary to compare the concentrations of APIs or determine the exact chemical composition to demonstrate that an Internet sample is counterfeit. All that is needed is to check whether a given sample is identical to the genuine drug or not [15].

Table 4 Analytical results of assay (API), impurity profiling (*I1–I7*) and residual solvent (*I8*) analysis of eight antibiotic samples (*S1–S8*)

	API	I1	I2	I3	I4	I5	I6	I7	I8
	A1	A2	A3	A4	A5	A6	A7	A8	A9
S1	87.03	5.709	2.220	0.785	0.444	0.489	3.322	0	134
S2	93.22	5.460	0.393	0.579	0.101	0.249	0	0	4,274
S3	89.16	5.079	1.361	0.983	0.613	0.722	1.659	0.421	137
S4	88.94	6.946	1.294	0.933	0.439	0.618	0.831	0	197
S5	94.04	4.227	0.404	0.598	0.167	0.559	0	0	3,808
S6	86.86	5.650	1.583	1.795	0.537	2.389	0.641	0	429
S7	89.41	6.250	0.783	1.531	0.430	1.038	0.556	0	109
S8	90.44	5.360	0.604	1.322	0.540	0.550	0.412	0.774	90

API, assay in percent; I1–I7, related substances in percent; I8, residual solvent in parts per million

These investigations can help the authorities to track and close down counterfeiting operations [49]. Moreover, a chemometric approach offers the advantage that it can be used to develop an automated interpretation system. De Veij et al. [55] showed that it is possible to design an automated approach to distinguish between genuine and counterfeit Viagra® tablets with Raman spectroscopy by using PCA and hierarchical clustering. This feature makes it possible for non-specialist users (e.g. at customs) to use this analytical technique.

A recent investigation by our group evaluating different samples of an antibiotic confirmed the usefulness of this multivariate approach. Different qualities are available on the international market, e.g. all claiming conformance of the API with the European Pharmacopoeia (Ph. Eur.) standard, which is a purified form obtained by recrystallization in an organic solvent. Eight samples were evaluated for the API content and impurity profiling by HPLC and for residual solvent by GC. The analytical results obtained are given in Table 4. This data set contains different variables and can be simplified by variable reduction, thereby facilitating the interpretation of the data. PCA showed two major clusters, where samples 2 and 5 were clustered together (see the score plot in Fig. 2). The loading plot (Fig. 2) shows that the assay and residual solvent values are most influential in explaining the score plot cluster. Further independently obtained information indeed confirmed that sample 5 was a FPP containing Ph. Eur. quality API. So, only two samples out of eight contained Ph. Eur. quality API.

Conclusions

Purchasing of pharmaceuticals through the Internet is a rapidly growing phenomenon and will continue. Apart from legal Internet trading, many counterfeited or substandard pharmaceuticals are distributed in that way. This often underrecognized problem can contribute to morbidity, mortality, drug resistance and loss of confidence in health-care systems. Therefore, the ability to investigate the quality of these products is a critical component of monitoring this type of drug supply by drug regulatory authorities. Of course, the choice of the analytical method to tackle this issue is a balance between the available resources (including time spent) and the information required to make a decision.

We propose a tierced approach in assessing the different quality attributes related to the overall quality of Internet-obtained pharmaceuticals. In a first step, the product classification is compared with the regional and/or national legislation. Secondly, the labelling and packaging should be carefully examined for legal conformity. If more detailed chemical information is required, determination of the physicochemical properties of the pharmaceutical product should be a starting point, followed by non-destructive

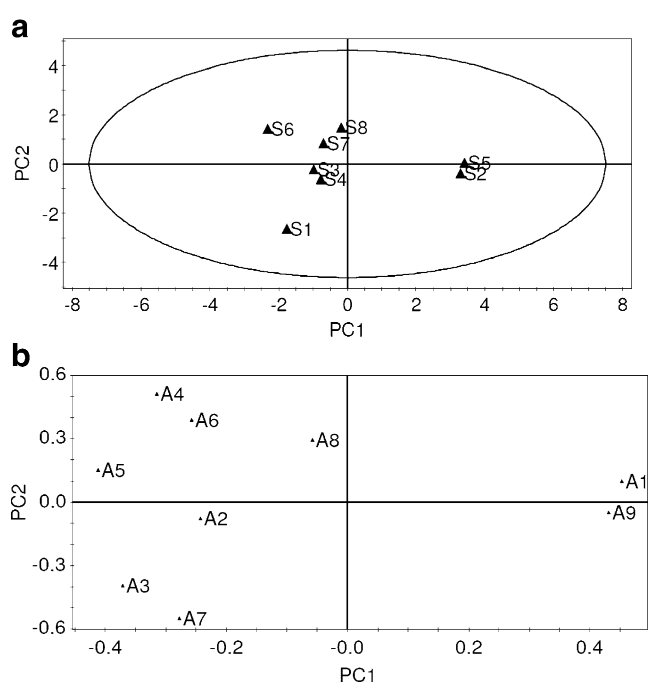

Fig. 2 Scoring (*top*) and loading (*bottom*) plots for the eight samples (*S1–S8*) and nine quality attributes (*A1–A9*). *PC* principal component

chemical testing. In the last stage, destructive analytical techniques, often in a remote laboratory, will be applied. Whenever non-conformity is found, the risk for public health is to be evaluated, e.g. by toxicity testing. Evidently, pharmaceutical products that do not comply should be withdrawn from the market and their origin traced back for legal action.

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Internet Pharmacy: Issues of Access, Quality, Costs, and Regulation

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Internet pharmacy has been the focus of heightened interest over the past 3 years since the first major Web site was introduced in the United States. This paper addresses issues pertaining to Internet pharmacies that sell prescriptions and other products to consumers at the retail level. The Internet pharmacy industry has shifted rapidly in the short time span. This paper begins with a summary of historical considerations and the shifting organization of Internet pharmacy. The advantages and disadvantages of online pharmacy practice are listed. Issues of access, quality, and cost are described. The challenges in regulation at the state and federal levels are presented. Advice to consumers is offered regarding the use of Internet pharmacy sites for purchasing prescription drug products.

KEY WORDS: prescription drugs; Internet; pharmacies; United States; quality; regulation.

BACKGROUND

Internet pharmacy is also known as online pharmacy, cyberpharmacy, e-pharmacy, and virtual pharmacy/drugstores. The introduction of Soma.com marked the arrival of a major pharmacy presence on the Internet in January 1999.(1) Many online pharmacy sites followed soon after, with drugstore.com and PlanetRx.com being the most notable. These three sites were widely regarded as among the most credible and reputable in the industry. Most Internet pharmacy sites were initially stand-alone, full-service online pharmacies. The industry has shifted quickly, with traditional pharmacy chains aggressively acquiring all or part of the Internet start-ups or establishing their own divisions for online prescription and nonprescription sales.

Wall Street awarded billion-dollar valuations to companies like drugstore.com at the beginning of 1999, even though the companies had meager revenues and projected years of losses.(2) The initial public offering (IPO) price for drugstore.com was $16, and the stock reached a high of over $70 per share in its first year. In 1999, Rite Aid acquired 40% of drugstore.com. The stock price for drugstore.com

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hovered around $1 per share, or less, for most of year 2001; as of January 2002, shares were selling around $3 each. Shares of PlanetRx.com jumped 62% on its first day of trading on the Nasdaq stock market in 1999 and settled at about $26 per share;[3] PlanetRx.com no longer exists as an online pharmacy. CVS is one of the nation's largest pharmacy chains. CVS bought Soma.com, which is now CVS.com. The initial euphoria about Internet drugstores is diminishing despite the fact that the numbers of sites continues to grow. A well-known annual pharmaceutical industry report predicted that online pharmacy sales will reach more than $20 billion by year 2004, compared with almost $2 billion in sales in 1999.[4] Such growth projections, however, are highly speculative.

The pharmacy Internet industry continues to grow as the result of consumer interest in more competitive prices and greater convenience.[1] Estimates of the number of Internet pharmacy sites range between 500 and 600.[5,6] The proliferation of online pharmacies has generated considerable controversy, largely due to the variability of sites and professional concerns. Significant variation exists with respect to the quality and level of service provided by Internet pharmacies. There are four major types of online pharmacies that sell prescriptions and other products to consumers on the retail level: (1) traditional chain pharmacies with a web presence; (2) independent community pharmacies with a web presence; (3) stand-alone, exclusive pharmacy sites; and (4) "rogue" pharmacy sites.[5,7] Other types of Internet pharmacies are beyond the scope of this paper because average consumers cannot access the sites to purchase prescription medications. This includes hospital pharmacy Web sites, sites that sell only nonprescription products, veterinary pharmacy sites, and Internet pharmacy sites that are associated with pharmacy benefit management companies and require prior approval of a third-party.

Traditional community pharmacies are also referred to as bricks-and-mortar pharmacies. The number of stand-alone, full-service pharmacies continues to decrease due to closures and acquisitions by traditional retail chains and others. The combination of bricks-and-mortar pharmacies with online pharmacy extensions or divisions is increasingly referred to and "clicks-and-mortar."[1] Such arrangements are generally viewed as advantageous for patients who can obtain medications for acute needs from their neighborhood pharmacy while utilizing Internet pharmacies for refills and medications needed on a chronic basis.[1] The types of products and services sold and/or by Internet pharmacies include prescription drugs, nonprescription drugs and herbal products, health and beauty aids, drug information, physician consultation fees, consumer health information, and others.[7]

Not all World Wide Web sites provide quality services and products. Unscrupulous Internet pharmacy sites have been known to sell unapproved or counterfeit drugs, expired or illegally diverted drugs, and adulterated drugs.[8] There have been reports of online pharmacies failing to send the medications after purchase and payment. These well-publicized illegal practices, however, have also occurred in the nonelectronic marketplace. Many Web sites have been established hastily to sell popular drugs for conditions that are potentially embarrassing, such as erectile dysfunction, male pattern baldness, and obesity. Some of these sites do not even require a valid prescription.[1] Other notorious sites might advertise the sale of Schedule II controlled substances, which are drugs with legitimate medical indications but have a great potential for abuse, misuse, and diversion (e.g., oxycodone, codeine). As the result of the increased terrorist attacks in the United States in Fall 2001, a plethora of sites have sprung up promoting the sale of ciprofloxacin to treat anthrax.(9) On November 1, 2001, the Federal Trade Commission issued an alert about online offers to treat biological threats which advised consumers to: (1) talk with a health professional first; (2) be aware that some Web sites sell ineffective drugs; and (3) know who they are buying from.(10)

The American Medical Association (AMA) issued explicit guidelines for Internet medicine,(11) which should apply to online pharmacy sites where the physicians prescribe based on "form medicine," e.g., physician consultation and prescribing based on the review of a patient's self-reported questionnaire submission.(1) AMA guidelines state that physician/patient encounters online should not be subjected to a lower level of protection than traditional office encounters. Further, AMA states that physicians who prescribe online fall below minimum standards of medical care when they fail to: (1) obtain a patient's medical history; (2) conduct a physical examination prior to confirming a specific medical problem or diagnosis; (3) discuss potential side effects; (4) disclose alternative treatment options; or (5) arrange for adequate follow-up care.(11) Many Internet pharmacies actively recruit physicians who are unemployed, semiretired, or trying to supplement declining practice incomes. Physicians are typically paid \$5000 to \$10,000 per month part-time for reviewing questionnaires and approving prescriptions. Those who work full time may earn much more based on a percentage of the \$50 to \$80 fees typically charged by online pharmacies for the brief consultations.(11)

To assure patient safety and minimize liability, many online pharmacy sites automatically reject a prescription drug order if the potential buyer's questionnaire suggests a clearly inappropriate medical use (e.g., Viagra [sildenafil] for the treatment of a dermatological problem). Even when the prescription is rejected, buyers can circumvent barriers by revising and resubmitting their orders. The process is more haphazard for other sites. For example, on certain sites, a person of normal weight would not be denied the purchase of drugs for severe weight loss, or a patient with a complaint of asthma would receive the requested Celebrex (celecoxib), which is indicated for arthritis, not asthma.(11) Most online pharmacies do not make an effort to confirm the accuracy of the questionnaire. Physicians who prescribe outside of the established norms of practice, and pharmacists who practice below the accepted standards of care, are subject to charges of unprofessional conduct or more severe sanctions by their respective state boards.(12)

ADVANTAGES AND DISADVANTAGES

The advantages and disadvantages of Internet pharmacies are shown in Table I.(1,6,13,14) These issues are discussed in subsequent sections.

Access

Generally, Internet pharmacies may enable greater access to pharmaceutical products and drug information. Online pharmacies are available 24 h a day, 7 days

Table I. Advantages and Disadvantages of Internet Pharmacies

Advantages of online pharmacies	Disadvantages of online pharmacies
Available 24 h a day, 7 days a week	Limited participation by third-party payers
Lessened perceptions of intimidation when obtaining embarrassing or sensitive drugs	Pharmacists not always immediately available online to answer important questions patients may have
Some sites allow patients to check medication profiles online	Concerns about issues of privacy of information
Price comparisons easy with searchable databases	Concerns about security of financial information transmitted
Medications delivered directly to patient's home via standard or special mail	Questions about the integrity of drugs shipped
Convenience	Questions about the quality of drug information provided
Medication availability to patients with physical or other disabilities that hinder retail patronage	May bypass the pharmacist/patient and physician/patient relationship
	Difficult to ascertain whether licensed practitioners are dispensing drugs or providing consultations

a week for patients to order their prescriptions or other products.(1) Although traditional chain drugstores have been increasing the number of 24-h pharmacies in certain neighborhoods, such locations represent a small percentage of the total number of traditional retail drugstores. Similarly, patients can submit questions to pharmacist online at any time of the day although it may require at least 1 day for a response (there may be no response from less reputable pharmacy sites). Patients may be more likely to obtain drugs over the Internet because they perceive less intimidation when they e-mail an embarrassing or sensitive personal question rather than having to speak directly to a pharmacist in a busy community pharmacy. Patients have a sense of "assumed anonymity" because the Internet site seems more private in this respect.(1)

Conversely, access may be restricted by the fact that limited insurance coverage is available on Internet pharmacy sites. Also, some people (e.g., poor, less educated, and the elderly to some extent) may not be able to readily access Internet pharmacy sites.

Quality

Peterson surveyed 33 Internet pharmacies in the United States and found that patients were required to provide their own prescriptions at 88% of sites, and 75% of these sites verified prescription integrity through mail or fax.(5) Further, more than half of the online pharmacy sites posted privacy policies. In terms of complexity, chain pharmacy online extensions required completion of an average of 10.2 pages to order drugs, versus 2.4–4 pages for other site types (independent pharmacies with a web presence, mail-order pharmacies extending their service online, and stand-alone online pharmacies). The study found that drug information was written at the eighth grade level for 36% of the sites. In a review of more credible Internet pharmacies, one study found that the quality of drug information was variable, but generally more comprehensive than was provided by community pharmacy drugstores.(6)

The National Association of Boards of Pharmacy (NABP) has developed a program to certify the quality of online pharmacies—the Verified Internet Pharmacy Practice Site (VIPPS™) program.[4,13,15] VIPPS criteria were developed through a coalition that included representatives from state and federal regulatory associations, professional associations, and consumer advocacy groups. To meet VIPPS certification standards, the pharmacy must comply with the licensing regulations of the state where located, as well as the states to which they dispense medications.[4] In addition, certified pharmacies must comply with VIPPS criteria regarding patient privacy, authentication and security of prescription orders, adherence to a recognized policy for quality assurance, and a provision of a meaningful consultation between patients and pharmacists. Only 12 pharmacies currently have the VIPPS seal of approval (as of November 2001); in the past, the number has reached 16 certified pharmacies. This represents a minuscule percentage of the hundreds of online pharmacies.

Consumers and health professionals who use or provide service to Internet pharmacies should consider the following quality aspects of Web sites. Any sites believed to be illegal should be reported to the FDA.[16]

Structure

Potential users of pharmacy Internet sites should look for the VIPPS seal of approval as a start. Regardless of whether the site is certified by NABP, other credentials should be reviewed. This would include disclosure of state and federal pharmacy licenses, state licensure of pharmacists, and prescriber identities (name, address, phone number, and medical licensure status). The location of the Internet pharmacy should be posted. Consumers should consider the site's name (some names strongly suggest dubious sites) and aesthetic appearance. Internet pharmacy sites that claim amazing results and quick cure-alls should be avoided;[14] such claims may suggest rogue sites.

Process

An explicit process should be described online regarding steps taken to verify legitimacy of the prescription. This would include processes to establish whether a valid professional relationship exists between the patient and the prescribing physician. The consumer should have access to a licensed pharmacist and be able to ask questions and receive answers and credible drug information. There should be consideration of how cumbersome (or lax) the steps are to order and obtain a prescription.[5] The methods of payment requested should also be considered, specifically whether the site demands cash or a credit card transaction (rather than insurance plan options). Consumers should attempt to establish the security of the site before providing personal and confidential information.

Outcomes

Once the medications are received, if they are received, consumers should reflect upon their satisfaction with the mode of service delivery. The quality of pharmaceuticals procured through Web sites is variable and somewhat unknown.[17] There are questions about the integrity of prescription drugs that are shipped in the mail and whether extreme differences in temperature adversely affect the product quality.[1] After medication consumption, consumers should be sensitive to whether they experience symptom improvement, adverse effects, or no effects.

Costs

In 1999, Bloom and Iannacone examined 46 Web sites to determine the availability and median costs of prescription medications and payments for physician visits.[17] The study compared the costs and processes for two drugs—sildenafil (Viagra, main indication erectile dysfunction) and finasteride (Propecia, indicated primarily for male pattern baldness). The study reported that the two medicines cost 10% higher on the Internet, compared with prescription drug costs in a sample of five community pharmacies in the Philadelphia area. The costs of the drugs online ranged vastly in comparison with community pharmacy prices. For sildenafil, the median price per tablet ranged from $4.50 to $28.50 (plus shipping costs) online, compared with $4.30 to $6.45 at community pharmacies; the cost range for finasteride was $1.55 to $5.20 (plus shipping costs) online and $1.55 to $1.95 for community pharmacies. The fee for the sites that offered form-medicine consultation (review of online questionnaire) ranged from $20 to $90, with a median price of $70. This fee was almost 17% higher than the payments by Medicare or local managed care organizations for a primary care physician visit in the Philadelphia area (median $60).

A different study collected data on pharmacy product costs from three chain Internet pharmacies and compared costs with their associated retail chain drugstore counterparts.[6] The authors compared costs of medications used to treat Parkinson's disease because patients with this disease are often disabled and have difficulty driving, and the medications are generally taken on a long-term basis and require extensive monitoring. The study found the cost of purchasing medications online for Parkinson's disease ranged from 7 to 58% less for brand name, and 31 to 76% less for generic medications, in comparison with the same associated community pharmacy.

In the spirit of marketplace competition, costs of prescription drugs are generally lower on Internet sites if the online pharmacies are reputable. Rogue sites seem to charge more for the lifestyle and other drugs they promote. Consumers may experience more out-of-pocket expenses with online pharmacies because third-party payers have been slow to contract with Web site providers although this situation is changing.[1] More studies are needed to firmly establish the cost-effectiveness of Internet pharmacies in comparison with traditional pharmacies.

Outcomes

A thematic content analysis was performed on 1078 consumer comments culled from nine prominent Web pharmacy sites to determine attributes of service quality that lead to patient satisfaction and dissatisfaction.[18] The study identified 19 quality dimensions, which were grouped into three categories: product cost/availability, customer service, and online information systems. Among the attributes indicating satisfaction, the most frequently mentioned were: perceived cost (37.6%), responsiveness (13.7%), credibility (8%), product variety/availability (6.8%), convenience

(6.6%), and ease of use (6.1%). These six attributes accounted for 79% of all mentions under the theme of satisfaction. When analyzing comments that voiced dissatisfaction, the most frequent involved the following dimensions: responsiveness (20%), reliability (12%), credibility (9%), ease of use (9%), and perceived cost (8%). The five attributes accounted for 58% of the mentions under dissatisfaction.

Patient outcomes from ingestion or administration of medications obtained through the Internet would be symptom improvement, no change, or deterioration. Legitimate prescriptions can cause adverse events. The rogue practices of some Internet pharmacy providers (e.g., inappropriate form medicine, unapproved drug products and drugs of questionable integrity) could lead to patient harm.[8] The FDA has received just a few reports of adverse events related to Internet drug sales, but the incidents point out the dangers of buying pharmaceuticals online without a prescription or based just upon a questionnaire history. The empirical literature is void with respect to documented outcomes of adverse events related to Internet pharmacy practice.

Regulation

The lack of effective regulation is one of the biggest problems of Internet pharmacy practice. Legitimate practice of Internet pharmacy involves complying with federal and state laws. This includes obeying the laws of the state in which the dispensing facility is located and the laws of the state in which the prescription drug is being shipped. These issues cross the traditional regulatory boundaries and blur federal and state jurisdictional lines; such regulatory issues have not been settled. Of special concern to regulators are the ability of unscrupulous sites to shut down and reopen quickly under a different name and Internet address, and offshore or foreign prescribing sites that do not meet U.S. standards.[13] Important questions have been raised about the quality of pharmaceutical products and information dispensed online.[19] Better regulation is needed without unduly restricting access.

FDA is working with state boards of pharmacy to curtail and shut down online pharmacies that offer popular prescription drug products without a prescription or without an initial face-to-face visit and examination by a licensed physician. The agency has taken more than 250 enforcement actions and penalties against Internet pharmacy sites, ranging from warnings to court injunctions.[11,19] The FTC has urged the U.S. Congress to require Internet pharmacy sites to disclose the identities of their prescribing physicians (name, address, phone numbers) as well as the states where the prescribers are licensed to practice.[11] The Drug Enforcement Administration has issued a guidance that explains when controlled substances can legally be purchased through Internet pharmacy sites.[16] The U.S. Customs service is also involved in Internet pharmacy because it is illegal to ship pharmaceuticals into the United States that are undeclared or are non-FDA approved; the ability of Customs to thoroughly screen the millions of packages entering the United States is severely restricted.[19]

The majority of states explicitly allow physicians to send electronic prescriptions to both in-state and out-of state pharmacies. These laws were written to protect physicians who were prescribing for their own patients, but Internet pharmacy is considered to be different. Guidelines established by the Federation of State

Medical Boards state that physicians who prescribe pharmaceuticals based solely on the provision of an electronic medical questionnaire clearly fail to meet an acceptable standard of medical care (unless there is an existing relationship between the physician [and/or his physician associates] and patient, the order is a simple refill for an existing prescription, or an emergent situation is present).(11)

Existing legal safeguards for the protection of health information privacy provided through the Internet are lacking in the United States.(20) Security is a feature of technology which is designed to protect data from accidental or unauthorized disclosure, destruction, or modification.(21) Private information that may transmitted during an e-pharmacy transaction include: name, address, e-mail address, birth date, phone number, gender, allergies, medical conditions, current medications, and financial information.(6) Techniques such as passwords, encryption, firewalls, and cookies improve the chances for confidentiality, but it is difficult to guarantee security of private information through the Internet. Some Internet pharmacy sites do not offer any security features when requesting personal and financial information from purchasers. Policies regarding Internet pharmacy should focus on improving the privacy of consumer information and the secure transmission of financial information.(5)

ADVICE TO CONSUMERS

Credible Internet sites can provide benefits to consumers who desire to purchase pharmaceuticals through the Internet. The FDA recommends that consumers do not buy from sites that offer to sell a prescription drug without an initial physician visit and examination, without a prescription, or to sell drugs that are not approved by the FDA.(14) It is important for a patient to talk with his or her health professional before using medications for the first time. Consumers should avoid sites that do not identify the person who you are dealing with and do not provide contact information for a U.S. address and phone number. Consumers should be wary of purchasing from foreign Web sites (which are especially difficult to regulate in the United States) and sites that advertise lifestyle drugs, controlled substances, or other drugs popularized by media attention. In addition, consumers should avoid sites that advertise cure-alls.

CONCLUSIONS

It is unlikely that Internet pharmacies will replace traditional retail community pharmacies, but they could be a useful supplement. Internet pharmacies provide varying levels of service. Credible Internet sites can offer some patient benefits through expanded and easier access to prescription drugs and other products. Public awareness campaigns would help consumers in evaluating pharmacy Web site credibility. Pharmacists, physicians, and other health professionals should help educate consumers on the pros and cons of Internet pharmacy. Consumers are advised to talk with a trusted and knowledgeable health professional before obtaining and using medications dispensed by Internet pharmacies.

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PEW/INTERNET

PEW INTERNET & AMERICAN LIFE PROJECT

Prescription Drugs Online

One in four Americans have looked online for drug information, but few have ventured into the online drug marketplace

Embargoed until 4pm Eastern on 10 October 2004

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Summary of Findings

Sixty-four percent of American households are regular consumers of prescription drugs.

Forty-five percent of American adults, or about 91 million people, take prescription drugs on a regular basis. Forty-one percent of American adults live with someone who regularly takes prescription drugs. In total, 64% of American households have a regular connection to the prescription drug marketplace.

One in four American adults has searched online for information about prescription drugs.

Twenty-six percent of American adults have researched prescription drugs online – 21% have personally done so and 5% have had it done for them by someone else. Those groups most likely to have personally searched for drug information include: internet users with high-speed connections at work and at home; internet users who have been online for six or more years; Americans with a college degree; and Americans in the Baby Boom generation. Americans living with a disability or chronic illness are no more likely than other Americans to search for prescription drug information online.

Most Americans do not fully trust the online prescription drug marketplace.

Sixty-two percent of Americans think purchasing prescription drugs online is less safe than purchasing them at a local pharmacy. Twenty percent of Americans think such online purchases are as safe as local purchases. Eighteen percent of Americans responded that they did not know or that it depends on the situation.

A fraction of Americans has ever bought prescription drugs online.

Only 4% of Americans have ever purchased prescription drugs on the internet. Three percent of Americans placed the order themselves and 1% had someone else do it. Our survey of 2,200 American adults yielded just 93 people who had purchased prescription drugs online, so this small sample of buyers is subject to a much larger sampling error than applies to the total sample of respondents. Americans living in higher-income households ($50,000+ annually) and internet users with six or more years of online experience are more likely to have made such a purchase.

Rx purchasers – Americans who answer yes to the following question: "Have you ever purchased prescription drugs on the internet, whether you placed the order yourself or someone else did it for you?"

Convenience is the top reason for online prescription-drug purchasing.

The small number of Americans who have ordered prescription drugs online are likely to cite convenience and cost savings as the main reasons why they decided to take the leap. Privacy is the least likely factor of the choices offered in the survey.

The typical online transaction includes a doctor's prescription, a U.S.-based pharmacy, and satisfied customers.

When asked about the last time they purchased prescription drugs online, the vast majority of Rx purchasers say the site required a prescription and nearly all Rx purchasers say they had a prescription from their doctor. The vast majority of Rx purchasers visited a site that was based in the United States; a few visited a site based in another country and a few do not know where the site is based.

In addition:

- Three-quarters of Rx purchasers say the last time they purchased prescription drugs online, they bought a drug for a chronic medical condition such as high blood pressure or arthritis.
- One quarter of Rx purchasers say their last purchase at an online pharmacy was for some other purpose, such as weight loss or sexual performance.
- Most Rx purchasers were satisfied with their last contact with an online pharmacy and plan to order prescription drugs online in the future.

Few respond to email advertisements, but drug spam continues to pile up.

A tiny percentage of Rx purchasers say their last trip to an online pharmacy was in response to an email advertisement. Many more internet users have received unsolicited email advertising drugs, however.

- 63% of internet users say they have received an unsolicited email advertising a sexual health medication like Viagra.

- 55% of internet users say they have received an unsolicited email advertising a prescription drug.
- 40% of internet users say they have received an unsolicited email advertising an over-the-counter drug.

Ignorance and mistrust of the online prescription drug market may be dispelled by further research and good experiences.

There are indications that Americans could change their minds about the safety of online prescription drug purchases. Those who research a product online often become customers. Convenience is the number one reason why banking became the fastest-growing activity between 2000 and 2002 – and it is the main reason why current Rx purchasers made the switch from off-line to online ordering. Most Rx purchasers are satisfied customers and plan to continue buying prescription drugs online.

Prescription Drugs Online: Summary of Findings at a Glance
Sixty-four percent of American households are regular consumers of prescription drugs.
One in four American adults has searched online for information about prescription drugs.
Most Americans do not fully trust the online prescription drug marketplace.
A fraction of Americans has ever bought prescription drugs online.
Convenience is the top reason for online prescription-drug purchasing.
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Few respond to email advertisements, but drug spam continues to pile up.
Ignorance and mistrust of the online prescription drug market may be dispelled by further research and good experiences.
Source: Fox, Susannah. *Prescription Drugs Online.* Washington, DC: Pew Internet & American Life Project, October 10, 2004.

Contents

Acknowledgements

About the Pew Internet & American Life Project: The Pew Internet Project is a nonprofit, non-partisan think tank that explores the impact of the internet on children, families, communities, the work place, schools, health care and civic/political life. The Project aims to be an authoritative source for timely information on the internet's growth and societal impact. The project is part of the Pew Research Center and support for the project is provided by The Pew Charitable Trusts. The project's Web site: www.pewinternet.org

About Princeton Survey Research Associates: PSRA conducted the survey that is covered in this report. It is an independent research company specializing in social and policy work. The firm designs, conducts, and analyzes surveys worldwide. Its expertise also includes qualitative research and content analysis. With offices in Princeton, New Jersey, and Washington, D.C., PSRA serves the needs of clients around the nation and the world. The firm can be reached at 911 Commons Way, Princeton, NJ 08540, by telephone at 609-924-9204, by fax at 609-924-7499, or by email at ResearchNJ@PSRA.com

Part 1.

Prescription drug information searches

The prescription drug market is enormous.

Forty-five percent of American adults take prescription drugs on a regular basis, 27% occasionally take prescription drugs, and an additional 27% say they never take prescription drugs. In addition, 41% of American adults live with someone who takes prescription drugs on a regular basis. When the two groups of regular users are combined, 64% of American households can be described as "Rx households."

Rx households – American households with at least one regular prescription drug user.

According to IMS Health, a company that tracks the pharmaceutical market, over 3 billion prescriptions are filled in the U.S. each year, totaling sales of over $200 billion. Chain drug stores garner the most sales of prescription drugs (36.2%), followed by independent drug stores (14.4%), and mail services (13.8%).[1]

Over the last five years, the Pew Internet & American Life Project has tracked significant increases in the number of Americans seeking health information online.[2] Thus, we felt it was important to study the situation with online medicine purchases because of the significant interest that grew around the subject after recent changes in federal policy.

In the spring of 2004, the federal government announced changes to the Medicare system, including the publication of prescription drug prices online. In addition, there has been a recent effort to legalize the importation of prescription drugs from Canada, where prices are significantly lower. In August, Illinois joined Minnesota, Wisconsin, and New Hampshire in launching online directories of recommended Canadian pharmacies.[3] The U.S. House of Representatives passed a bill in July that would allow for prescription drug imports from Canada and other countries.[4]

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But there is strong opposition from the pharmaceutical industry, and the U.S. Food and Drug Administration, both of which claim that they cannot guarantee the safety of imported drugs. However, a June 2004 study conducted by the General Accounting Office found that Canadian online pharmacies were just as likely as U.S.-based sites to adhere to safety standards.[5]

We undertook this study in order to measure Americans' current interest in online prescription drug research and purchasing.

One in four American adults has searched online for information about prescription drugs.

Twenty-six percent of American adults have researched prescription drugs online – 21% have personally done so and 5% have had it done for them by someone else. Those groups most likely to have personally searched for drug information include: internet users with high-speed connections at work and at home; internet users who have been online for six or more years; Americans with a college degree; and Americans in the Baby Boom generation.

Internet use

Not surprisingly, internet users are more likely than non-users to have personally researched prescription drugs online. Thirty percent of internet users have done so. Four percent of non-internet users have personally researched prescription drugs online. (Another 4% of internet users and 7% of non-users have had someone else perform such a search on their behalf.)

Connection speed

Broadband users are among the most likely Americans to have searched for prescription drug information online. Forty-one percent of internet users with fast connections at both home and work have personally looked for prescription drug information online. Twenty-nine percent of dial-up users have done so.

Years of experience online

The longer someone has had access to the internet, the more likely he or she is to have searched for information about prescription drugs. Thirty-eight percent of internet users with six or more years of experience have personally looked for prescription drug information online, compared to 28% of those who have been online for four to five years. Just 13% of internet users with one to three years of experience have done this type

[5] "Internet Pharmacies: Some Pose Safety Risks for Consumers" (United States General Accounting Office: June 17, 2004) Available at: http://www.gao.gov/new.items/d04820.pdf

of research online. Thirteen percent of newcomers (those with less than one year of online experience) have searched for prescription drug information.

Education

College graduates are more likely to have internet access and, once online, are more likely to have done health searches. Therefore it is not surprising that 32% of college graduates have personally gone online to search for prescription drug information, compared to 23% of American adults who attended college, but did not graduate. Just 15% of high school graduates have personally done this type of search online.

Age

Younger baby boomers – those born between 1955 and 1964 – are the most likely to have personally searched online for prescription drug information. Some 28% of these 40-49 year-olds have done so. Twenty-four percent of older baby boomers (50-58 year-olds) have done so. Twenty-three percent of the Gen X generation (28-39 year-olds) have searched for prescription drug information, compared to 17% of Gen Y (18-27 year-olds). Eighteen percent of 59-68 year-olds have personally searched for this type of information, compared to just 8% of internet users age 69 and older.

Household use of prescription drugs

Members of an Rx household are more likely to have searched for drug information online than Americans who are not part of a household so dependent on prescription drugs. Twenty-four percent of members of an Rx household have personally done this type of research online, compared to 15% of Americans who do not live in a household where prescription drugs are taken on a regular basis.

Race

Twenty-four percent of whites have personally done this type of research online, compared to 12% of blacks. Fourteen percent of English-speaking Hispanic or Latino Americans have personally gone online to look for information about prescription drugs.

Health insurance

According to the latest Census Bureau estimates, 15.6% of Americans lack health insurance.[6] In our survey of U.S. adults, 13% say they lack health insurance.

Americans with health insurance are more likely to take prescription drugs on a regular basis than those who lack insurance, but we do not know whether it is because insured

[6] "Income, Poverty, and Health Insurance Coverage in the United States." (Census Bureau: August 26, 2004) Available at: http://www.census.gov/prod/2004pubs/p60-226.pdf

Americans are more likely to have the need or simply the means to do so. Forty-nine percent of Americans who have health insurance take prescription drugs on a regular basis, 26% do so occasionally, and 24% never do. Twenty percent of Americans who do not have health insurance take prescription drugs on a regular basis, 35% do so occasionally, and 45% never do. Americans with health insurance are also more likely than the uninsured to have visited a doctor or medical clinic in the past year. Eighty-one percent of insured Americans did so, compared to 57% of uninsured Americans.

American adults covered by some form of health insurance, including Medicare or Medicaid, are more likely to have personally searched for prescription drug information online. Twenty-two percent of insured Americans have done so, compared to 14% of Americans who do not have any type of health insurance coverage.

It is important to note that 34% of uninsured American adults are between 18 and 27 years old – the most likely age group to report "excellent" health and the least likely age group to have searched online for prescription drug information. By comparison, 14% of Americans with some form of health insurance are 18-27 years old.

Health status has little to do with a person's likelihood to have personally researched prescription drug information.

Overall health

Americans in excellent health are only slightly more likely than those in poor health to have personally searched online for prescription drug information – 21% of those in the best of health and 17% of those who describe their health as "fair" or "poor" have done so. However, people in poor health are more likely to have been the subject of a search – 11% have had a prescription drug information search done on their behalf. By comparison, 5% of those in excellent health have been the subject of such a search.

Disability status

Americans living with a disability are just as likely as other Americans to have personally searched for prescription drug information online – 19% and 21% respectively. Eleven percent of Americans living with a disability have had someone else look on the internet for prescription drug information, compared to 5% of Americans who are not living with a disability. It is important to note that only 38% of Americans living with a disability go online, compared to 69% of other Americans. This may explain why more Americans living with a disability have been the subjects of a search for information – they are more likely to need someone else to go on the internet for them.

Internet user – defined as those answering "yes" to the following question: "Do you ever go online to access the internet or the World Wide Web or to send and receive email?"

Part 2.

The prescription drug marketplace

Most Americans do not fully trust the online prescription drug marketplace.

Sixty-two percent of Americans think purchasing prescription drugs online is less safe than purchasing them at a local pharmacy. Twenty percent of Americans think such online purchases are as safe as local purchases. Eighteen percent of Americans responded that they did not know or that it depends on the situation.

Sixty-eight percent of Americans agree with the following statement: "Some argue that allowing people to purchase prescription drugs online makes it too easy to obtain drugs illegally, without a prescription." Seventy-one percent of Americans agree with a second statement: "Others argue that people should not be allowed to purchase prescription drugs online because not all pharmacies are licensed in the United States, and there's no way to guarantee the safety of drugs that come from other countries."

A handful of states encourage their residents to purchase lower-cost prescription drugs from Canada, despite opposition from the pharmaceutical industry and the FDA.

> "Show me the dead Canadians." – Minnesota Gov. Tim Pawlenty (R) in response to the federal government's safety concerns about the importation of drugs from Canada[7]

Few health plans require mail order or online purchasing.

Of the 86% of Americans who are covered by a health plan, 5% report that they are required to order certain prescription drugs by mail or online. Eighty-nine percent of insured Americans are allowed to order all of their prescription drugs at a local pharmacy, if they wish. Six percent of insured Americans do not know if there is such a requirement associated with their health plan.

[7] "Pawlenty pitches prescription plan to Congress" (Stateline.org: November 20, 2003) Available at: http://www.stateline.org/stateline/?pa=story&sa=showStoryInfo&print=1&id=335987

IMS Health estimates that 13.8% of prescriptions are fulfilled by mail. Most are filled by chain drugstores (36.2%), independent drug stores (14.4%), or non-federal hospitals (10.5%).[8]

A fraction of Americans has ever bought prescription drugs online.

According to our survey, just 4% of Americans have ever purchased prescription drugs on the internet. Three percent of Americans placed the order themselves and 1% had someone else do it. Not surprisingly, internet users are more likely to have bought prescription drugs online but a small number of non-internet users have done so. Americans living in higher-income households ($50,000+ annually) are more likely than those living in lower-income households to have done so. Internet users with six or more years of online experience are also more likely to be "Rx purchasers."

Rx purchasers – Americans who answer yes to the following question: "Have you ever purchased prescription drugs on the internet, whether you placed the order yourself or someone else did it for you?"

Americans who perceive buying drugs online as safe are more likely to have actually made a purchase. Americans who are on prescription medication, or live with someone who is, are more likely to have bought prescription drugs online. Americans who have gone on the internet to look for information about prescription drugs are more likely to have made such a purchase online.

Convenience is the top reason for online prescription-drug purchasing.

The small number of Americans who have ordered prescription drugs online are likely to cite convenience, time savings, and cost savings as the main reasons why they decided to take the leap. Privacy is the least likely factor of the four offered in the survey.

The typical online purchase includes a doctor's prescription and U.S.-based pharmacy.

When asked about the last time they purchased prescription drugs online, vast majority of Rx purchasers say the site required a prescription and near majority of Rx purchasers say they had a prescription from their doctor. The vast majority of Rx purchasers visited a site that was based in the United States; a few visited a site based in another country and a few do not know where the site is based.

[8] IMS Health, "U.S. Purchase Activity by Channel, June 2004." Available at: http://www.imshealth.com/media

Three in four online drug purchases are for a chronic medical condition.

Three-quarters of Rx purchasers say the last time they purchased prescription drugs online, they bought a drug for a chronic medical condition such as high blood pressure or arthritis. One quarter of Rx purchasers say their last purchase at an online pharmacy was for some other purpose, such as weight loss or sexual performance.

Most are satisfied customers, few report bad experiences.

Most Rx purchasers were satisfied with their last contact with an online pharmacy and plan to order prescription drugs online in the future. The quality of the drugs purchased online garnered the most positive feedback – the vast majority of Rx purchasers said they were "very satisfied" with the quality. A large majority of Rx purchasers were "very satisfied" with the customer service they received and about half were "very satisfied" with the price they paid.

Nine in ten Rx purchasers plan to go online to fill a prescription in the future. However, a small group of Rx purchasers reported a bad experience ordering prescription drugs online. Most had to do with shipping problems – packages lost in the mail or routed to the wrong address.

Part 3.

Drug advertising via email

Few respond to email advertisements, but drug spam continues to pile up.

A tiny percentage of Rx purchasers say their last trip to an online pharmacy was in response to an email advertisement. Many more internet users have received unsolicited email advertising drugs, however.

In October 2003, the Pew Internet Project reported that longtime internet users, those who have been online at least 6 years, are significantly more likely to have heard or read about spam than anyone else. These veteran users are also more likely than less-experienced internet users to say that spam is a big problem. Despite sophisticated efforts to avoid it, longtime internet users get just as much spam as everyone else, possibly because their email address may have been circulating for many years before they learned how to protect it.[9] In this study, we find that men and the most veteran internet users are the most likely to report receiving drug spam. Statistical analysis shows that these traits – being a man and being a longtime internet user – are independent predictors of receiving drug spam. That is, holding all variables constant, men are more likely than women to report a heavy volume of drug spam. Longtime internet users – whether they are men, women, young, middle-aged, etc. – are also more likely than other internet users to receive drug spam.

Sexual health medication spam

Sixty-three percent of internet users say they have received an unsolicited email advertising a sexual health medication such as Viagra. Seventy-one percent of male internet users say they have received such an ad, compared to 56% of female internet users. Seventy-two percent of internet users with six or more years of experience online say they have received sexual health drug spam, compared to 59% of those who have been online 4-5 years, 53% of those who have been online 2-3 years, and 30% of those who got online within the past year.

[9] "Spam: How It Is Hurting Email and Degrading Life on the Internet." (Pew Internet Project: October 22, 2003) Available at: http://www.pewinternet.org/PPF/r/102/report_display.asp

Prescription drug spam

Fifty-five percent of internet users say they have received an unsolicited email advertising a prescription drug. Sixty percent of male internet users say they have received prescription drug spam, compared to 50% of female internet users. Sixty-five percent of internet users with six or more years of experience online say they have received prescription drug spam, compared to 47% of those who have been online 4-5 years, 44% of those who have been online 2-3 years, and 20% of those who got online within the past year.

Over-the-counter drug spam

Forty percent of internet users say they have received an unsolicited email advertising an over-the-counter drug. Forty-nine percent of male internet users say they have received over-the-counter drug spam, compared to 32% of female internet users. Forty-seven percent of internet users with six or more years of experience online say they have received over-the-counter drug spam, compared to 36% of those who have been online 4-5 years, 32% of those who have been online 2-3 years, and 19% of those who got online within the past year.

Part 4.

Implications for the future

Ignorance and mistrust of the online prescription drug market may be dispelled by further research and good experiences.

Only 4% of Americans have purchased prescription drugs online. A majority of Americans profess fear and mistrust of the online pharmaceutical market. However, there are indications that Americans could change their minds about the safety of online prescription drug purchases, especially as the debate heats up nationwide.

Window shoppers may become buyers

The online travel industry saw a 90% growth rate between 2000 and 2002.[10] Internet users who have done travel-related research online are more likely to have made a travel purchase on the internet than those who have not done such a search. If an increasing number of Americans goes online to research prescription drugs, online pharmacies may see an accompanying increase in customers.

Convenience is a strong selling point online

Convenience is the number one reason why banking became the fastest-growing online activity between 2000 and 2002, when the industry saw a 164% growth rate. The same trend may hold true for online pharmacies since 84% of Rx purchasers say that convenience was important to their decision to buy online for the first time.

Satisfied customers say they will return

Nine out of ten Americans who have purchased prescription drugs online say they plan to do so again. Those who were dissatisfied with their purchase are unlikely to cite reasons related to fears about drug safety. As more municipalities and states encourage online prescription drug purchases, it seems likely that the universe of potential satisfied customers will grow.[11]

[10] "Online Banking" (Pew Internet Project: November 17, 2002) Available at: http://www.pewinternet.org/PPF/r/77/report_display.asp
[11] "Montgomery Passes Drug Import Plan" (Washington Post: September 22, 2004) Available at: http://www.washingtonpost.com/wp-dyn/articles/A39932-2004Sep21.html

Methodology

The results in this report are based on data from telephone interviews conducted by Princeton Survey Research Associates from May 15 to June 17, 2004, among a sample of 2,200 adults, 18 and older. For results based on the total sample, one can say with 95% confidence that the error attributable to sampling is plus or minus 2 percentage points. For results based internet users (n=1,399), the margin of sampling error is plus or minus 3 percentage points. In addition to sampling error, question wording and practical difficulties in conducting telephone surveys may introduce some error or bias into the findings of opinion polls.

The sample for this survey is a random digit sample of telephone numbers selected from telephone exchanges in the continental United States. The random digit aspect of the sample is used to avoid "listing" bias and provides representation of both listed and unlisted numbers (including not-yet-listed numbers). The design of the sample achieves this representation by random generation of the last two digits of telephone numbers selected on the basis of their area code, telephone exchange, and bank number.

New sample was released daily and was kept in the field for at least five days. This ensures that complete call procedures were followed for the entire sample. Additionally, the sample was released in replicates to make sure that the telephone numbers called are distributed appropriately across regions of the country. At least 10 attempts were made to complete an interview at every household in the sample. The calls were staggered over times of day and days of the week to maximize the chances of making contact with a potential respondent. Interview refusals were re-contacted at least once in order to try again to complete an interview. All interviews completed on any given day were considered to be the final sample for that day. The final response rate to this survey was 30.9%.

Non-response in telephone interviews produces some known biases in survey-derived estimates because participation tends to vary for different subgroups of the population, and these subgroups are likely to vary also on questions of substantive interest. In order to compensate for these known biases, the sample data are weighted in analysis. The demographic weighting parameters are derived from a special analysis of the Census Bureau's March 2003 Annual Social and Economic Supplement Survey. This analysis produces population parameters for the demographic characteristics of adults age 18 or older, living in households that contain a telephone. These parameters are then compared with the sample characteristics to construct sample weights. The weights are derived using an iterative technique that simultaneously balances the distribution of all weighting parameters.

Show Me the Money: Characterizing Spam-advertised Revenue

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Abstract

Modern spam is ultimately driven by product sales: goods purchased by customers online. However, while this model is easy to state in the abstract, our understanding of the concrete business environment—how many orders, of what kind, from which customers, for how much—is poor at best. This situation is unsurprising since such sellers typically operate under questionable legal footing, with "ground truth" data rarely available to the public. However, absent quantifiable empirical data, "guesstimates" operate unchecked and can distort both policy making and our choice of appropriate interventions. In this paper, we describe two inference techniques for peering inside the business operations of spam-advertised enterprises: purchase pair and basket inference. Using these, we provide informed estimates on order volumes, product sales distribution, customer makeup and total revenues for a range of spam-advertised programs.

1 Introduction

A large number of Internet scams are "advertising-based"; that is, their goal is to convince potential customers to purchase a product or service, typically via some broad-based advertising medium.[1] In turn, this activity mobilizes and helps fund a broad array of technical capabilities, including botnet-based distribution, fast flux name service, and bulletproof hosting. However, while these same technical aspects enjoy a great deal of attention from the security community, there is considerably less information quantifying the underlying economic engine that drives this ecosystem. Absent grounded empirical data, it is challenging to reconcile revenue "estimates" that can range from $2M/day for one spam botnet [1], to analyses suggesting that spammers make little money at all [6]. This situation has the potential to distort policy and investment decisions that are otherwise driven by intuition rather than evidence.

In this paper we make two contributions to improving this state of affairs using measurement-based methods to estimate:

- *Order volume.* We describe a general technique—purchase pair—for estimating the number of orders received (and hence revenue) via on-line store order numbering. We use this approach to establish rough, but well-founded, monthly order volume estimates for many of the leading "affiliate programs" selling counterfeit pharmaceuticals and software.
- *Purchasing behavior.* We show how we can use third-party image hosting data to infer the contents of customer "baskets" and hence characterize purchasing behavior. We apply this technique to a leading spamvertized pharmaceutical program and identify both the nature of these purchases and their relation to the geographic distribution of the customer base.

In each case, our real contribution is less in the particular techniques—which an adversary could easily defeat should they seek to do so—but rather in the data that we used them to gather. In particular, we document that seven leading counterfeit pharmacies together have a total monthly order volume in excess of 82,000, while three counterfeit software stores process over 37,000 orders in the same time.

On the demand side, as expected, we find that most pharmaceuticals selected for purchase are in the "male-enhancement" category (primarily Viagra and other ED medications comprising 60 distinct items). However, such drugs constitute only 62% of the total, and we document that this demand distribution has quite a long tail; user shopping carts contain 289 distinct products, including surprising categories such as anti-cancer medications

[1] Unauthorized Internet advertising includes email spam, black hat search-engine optimization [26], blog spam [21], Twitter spam [4], forum spam, and comment spam. Hereafter we refer to these myriad advertising vectors simply as spam.

(Arimidex and Gleevec), anti-schizophrenia drugs (Seroquel), and asthma medications (Advair and Ventolin). We also discover significant differences in the purchasing habits of U.S. and non-U.S. customers.

Combining these measurements, we synthesize overall revenue estimates for each program, which can be well in excess of $1M per month for a single enterprise. To the best of our knowledge, ours is the first empirical data set of its kind, as well as the first to provide insight into the market size of the spam-advertised goods market and corresponding customer purchasing behavior.

We structure the remainder of this paper as follows. In § 2 we motivate the need for such research, explain the limitations of existing data, and provide background about how the spam-advertised business model works today. We discuss our *purchase pair* technique in § 3, validating our technique for internal consistency and then presenting order volume estimates across seven of the top pharmaceutical affiliate programs and three counterfeit software programs. We then explore the customer dynamics for one particular pharmaceutical program, EvaPharmacy, in § 4. We explain how to use image log data to identify customer purchases and then document how, where and when the EvaPharmacy customer base places its orders. We summarize our findings in § 5, devising estimates of revenue and comparing them with external validation. We conclude with a discussion about the implications of our findings in § 6.

2 Background

The security community is at once awash in the technical detail of new threats—the precise nature of a new vulnerability or the systematic analysis of a new botnet's command and control protocol—yet somewhat deficient in analyzing the economic processes that underlie these activities. In fairness, it is difficult to produce such analyses; there are innate operational complexities in acquiring such economic data and inherent uncertainties when reasoning about underground activities whose true scope is rarely visible directly.

However, absent a rigorous treatment, the resulting information vacuum is all too easily filled with opinion, which in turn can morph into "fact" over time. Though pervasive, this problem seemingly reached its zenith in the 2005 claim by US Treasury Department consultant Valerie McNiven that cybercrime revenue exceeded that of the drug trade (over $100 billion at the time) [11]. This claim was frequently repeated by members of the security industry, growing in size each year, ultimately reaching its peak in 2009 with written Congressional testimony by AT&T's chief security officer stating that cybercrime reaped "more than $1 trillion annually in illicit profits" [23]—a figure well in excess of the entire software industry and almost twice the GDP of Germany. Nay-sayers are similarly limited in their empirical evidence. Perhaps best known in this group are Herley and Florencio, who argue that a variety of cybercrimes are generally unprofitable. However, lacking empirical data, they are forced to use an economic meta-analysis to make their case [5, 6, 7].

Unfortunately, the answer to such questions matters. Without an "evidence basis", policy and investment decisions are easily distorted along influence lines, either over-reacting to small problems or under-appreciating the scope of grave ones.

2.1 Estimating spam revenue and demand

In this paper we examine only a small subset of such activity: spam-advertised counterfeit pharmacies and, to a lesser extent, counterfeit software stores. However, even here public estimates can vary widely. In 2005, one consultancy estimated that Russian spammers earned roughly US$2–3M per year [18]. However, in a 2008 interview, one IBM representative claimed that a single spamming botnet was earning close to $2M *per day* [1]. Our previous work studied the same botnet empirically, leading to an estimate of daily revenue of up to $9,500, extrapolating to $3.5M *per year* [10]. Most recently, a report by the Russian Association of Electronic Communication (RAEC) estimated that Russian spammers earned 3.7 billion rubles (roughly $125 million) in 2009 [12].

The demand side of this equation is even less well understood, relying almost entirely on opt-in phone or email polls. In 2004, the Business Software Alliance sponsored a Forrester Research poll to examine this question, finding that out of 6,000 respondents (spread evenly across the US, Canada, Germany, France, the UK and Brazil) 27% had purchased spam-advertised software and 13% had purchased spam-advertised pharmaceuticals [3]. If such data were taken at face value, the US market size for spam-advertised pharmaceuticals would exceed 30 million customers. Similar studies, one by Marshal in 2008 and the other sponsored by the Messaging Anti-Abuse Working Group (MAAWG) in 2009, estimate that 29% and 12%, respectively, of Internet users had purchased goods or services advertised in spam email [8, 19].

In our previous work on empirically quantifying revenue for such activities, our measurements were only able to capture a few percent of orders for sites advertised by a single botnet serving a single affiliate program, GlavMed [10]. Here, we aim to significantly extend our understanding, with our results covering *total order volume* for five of the six top pharmacy affiliate programs, and three of the top five counterfeit software affiliate programs. Moreover, to the best of our knowledge our analysis of EvaPharmacy is the first measurement-based examination of customer purchasing behavior, the demand component of the counterfeit pharmacy ecosystem.

2.2 How spam-advertised sites work

To provide context for the analysis in this paper, we first describe how modern spam is monetized and the ecosystem that supports it.

Today, spam of all kinds represents an outsourced marketing operation in service to an underlying sales activity. At the core are "affiliate programs" that provide retail content (e.g., storefront templates and site code) as well as back-end services (e.g., payment processing, fulfillment and customer support) to a set of client affiliates. Affiliates in turn are paid on a commission basis (typically 30–50% in the pharmaceutical market) for each sale they bring in via whatever advertising vector they are able to harness effectively. This dynamic is well described in Samosseiko's "Partnerka" paper [22] and also in our recent work studying the spam value chain [16].

Thus, while an affiliate has a responsibility to attract customers and host their shopping experience (which includes maintaining the contents of their "shopping cart"), once a customer decides to "check out" the affiliate hands the process over to the operators of the affiliate program.[2] Consequently, we would expect to find the order processing service shared across *all* affiliates of a particular program, regardless of the means used to attract customers. Indeed, as discussed below, our measurements of purchases from different members of the same affiliate confirm that the order numbers associated with the purchases come from a common pool. This finding is critical for our study because it means that side-effects in the order processing phase reflect the actions of *all sales activity* for an entire program, rather than just the sales of a single member.

On the back end, order processing consists of several steps: authorization, settlement, fulfillment, and customer service. Authorization is the process by which the merchant confirms, through the appropriate payment card association (e.g., Visa, MasterCard, American Express, Japan Credit Bureau, etc.), that the customer has sufficient funds. For the most common payment cards (Visa/MC), this process consists of contacting the customer's issuing bank, ensuring that the card is valid and the customer possesses sufficient funds, and placing a lien on the current credit balance. Once the good or service is ready for delivery, the merchant can then execute a settlement transaction that actualizes this lien, transferring money to the merchant's bank. Finally, fulfillment comprises packaging and delivery (e.g., shipping drugs directly from a foreign supplier or providing a Web site and password for downloading software). For our study, however, the key leverage lies in *customer service*. To support customer service, payment sites generate individual order numbers to share with the customer. In the next section, we describe how we can use the details of this process to infer the overall transaction rate, and ultimately revenue, of an entire affiliate program.

3 Order volume

Underlying our *purchase pair* measurement approach is a model of how affiliate programs handle transactions, and, in particular, how they assign order numbers.

3.1 Basic idea

Upon placing an order, most affiliate programs provide a confirmation page that includes an "order number" (typically numeric, or at least having a clear numeric component) that uniquely specifies the customer's transaction. For purchases where an order number does not appear on the confirmation page, the seller can provide one in a confirmation email (the common case), or make one available via login to the seller's Web site. The order number allows the customer to specify the particular purchase in any subsequent emails, when using customer support Web sites, or when contacting online support via email, IM or live Web chat. For the purchases we made, we found that the seller generally provides the order number *before* the authorization step (indeed, even before merchant-side fraud checks such as Address Verification Service), although purely local checks such as Luhn digit validation are frequently performed first. Accordingly, we can consider the creation of an order number only as evidence that a customer *attempted* an order, not that it successfully concluded. Thus, the estimates we form in this work reflect an *upper bound* on the transaction rate, including transactions declined during authorization or settlement.[3]

The most important property for such order numbers is their *uniqueness*; that each customer order is assigned a singular number that is distinguished over time without the possibility of aliasing. While there are a vast number of ways such uniqueness could be implemented (e.g., a pseudo-random permutation function), the easiest approach by far is to simply increment a global variable for each new order. Indeed, the serendipitous observation that motivated our study was that multiple purchases made from the same affiliate program produced

[2]This transfer typically takes the form of a redirection to a payment gateway site (with the affiliate's identity encoded in the request), although some sites also support a proxy mode so the customer can appear to remain at the same Web site.

[3]In 2008, Visa documented that card-not-present transactions such as e-commerce had an issuer decline rate of 14% system-wide [25]. In addition, it seems likely that some orders are declined at the merchant's processor due to purely local fraud checks (such as per-card or per-address velocity checks or disparities between IP address geolocation versus shipping address).

order numbers that appeared to *monotonically increase* over time. Observing the monotonic nature of this sequence, we hypothesized that order number allocation is implemented by serializing access to a single global variable that is incremented each time an order is made; we call this the *sequential update hypothesis*. To assess this hypothesis, we examined source code for over a dozen common e-commerce platforms (e.g., Magento, X-cart, Ubercart, and Zen-cart [17, 24, 27, 28]), finding ubiquitous use of such a counter, typically using an SQL auto-update field, but sometimes embodied explicitly in code.

Given use of such a global sequential counter, the *difference* between the numbers associated with orders placed at two points in time reflects the total number of orders placed during the intervening time period. Thus, from any *pair* of purchases we can extract a measurement of the total transaction volume for the interval of time between them, even though we cannot directly witness those intervening transactions. Figure 1 illustrates the methodology using a concrete example. This observation is similar in flavor to the analysis used in blind/idle port scanning (there the sequential increment of the IP identification field allows inference of the presence of intervening transmissions) [2]. It then appears plausible that this same purchase-pair approach might work across a broad range of spam-advertised programs, a possibility that we explore more thoroughly next.

3.2 Data collection

To evaluate this approach requires that we first identify which sites advertise which affiliate programs, and then place repeated purchases from each. We describe how we gathered each of these data sets in this section.

Program data

In prior work, we developed a URL crawler to follow the embedded links contained in real-time feeds of email spam (provided by a broad range of third-party anti-spam partners) [16]. The crawler traverses any redirection pages and then fetches and renders the resulting page in a live browser. We further developed a set of "page classifiers" that identify the type of good being advertised by analyzing the site content, and, in most cases, the particular affiliate program being promoted. We developed specific classifiers for over 20 of the top pharmaceutical programs (comprising virtually all sites advertised in pharmaceutical spam), along with the four most aggressively spam-advertised counterfeit software programs.

After placing multiple test orders with nine of these pharmaceutical programs, we identified seven with strictly incrementing order numbers.[4] Five of these (Rx–Promotion, Pharmacy Express (aka Mailien), GlavMed, Online Pharmacy and EvaPharmacy) together constituted two-thirds of all sites advertised in the roughly 350 million distinct pharmaceutical spam URLs we observed over three months in late 2010. We found the sixth, 33drugs (aka DrugRevenue), and seventh, 4RX, less prevalent in email spam URLs, but they appear to be well advertised via search engine optimization (SEO) techniques [15]. We did a similar analysis of counterfeit software programs, finding three (Royal Software, EuroSoft, and SoftSales) with the appropriate order-number signature. While counterfeit software is less prevalent in total spam volume, these three programs constitute over 97% of such sites advertised to our spam collection apparatus during the same 3-month period. For the remainder of this paper we focus exclusively on these ten programs, although it appears plausible that the same technique will prove applicable to many smaller programs, and also to programs in other such markets (e.g., gambling, fake antivirus, adult).

Order data

We collected order data in two manners: actively via our own purchases and opportunistically, based on the purchases of others. First and foremost are our own purchases, which we conducted in two phases. The first phase arose during a previous study, during which we executed a small number of test purchases from numerous affiliate programs in January and November of 2010 using retail Visa gift cards. Of these, 46 targeted the ten programs under study in this paper. The second phase (comprising the bulk of our active measurements) reflects a regimen of purchases made over three weeks in January and February 2011 focused specifically on the ten programs we identified above.

When placing these orders, we used multiple distinct URLs leading to each program (as identified by our page classifiers). The goal of this procedure was to maximize the likelihood of using distinct affiliates to place purchases in order to provide an opportunity to determine whether different affiliates of a given program make use of different order-processing services.

Successfully placing orders had its own set of operational challenges [9]. Except where noted, we performed all of our purchases using prepaid Visa credit cards provided to us in partnership with a specialty issuer, and funded to cover the full amount of each transaction. We used a distinct card for each purchase and went to considerable lengths to emulate real customers. We used valid names and associated residential shipping addresses, placed orders from a range of geographically

[4] Of the two programs that we did not select, ZedCash used several different strictly increasing order number subspaces that would complicate our analysis and decrease accuracy, while World Pharmacy order numbers appeared to be the concatenation of a small value with the current Unix timestamp, which would thwart our analysis altogether.

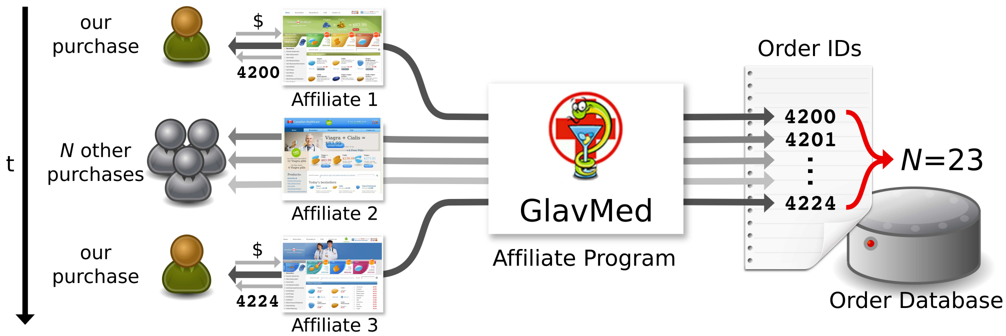

Figure 1: How the purchase pair technique works. In this hypothetical situation, two measurement purchases are made that bracket some number of intervening purchases made by real customers. Because order number allocation is implemented by a serialized sequential increment, the difference in the order numbers between measurement purchases, $N = 23$, corresponds to the total number of orders processed by the affiliate program in the intervening time.

proximate IP addresses, and provided a unique email address for each order. We used five contact phone numbers for order confirmation, three from Google Voice and two via prepaid cell phones, with all inbound calls routed to the prepaid cell phones. In a few instances we found it necessary to place orders from IP addresses closely geolocated to the vicinity of the billing address for a given card, as the fraud check process for one affiliate program (EuroSoft) was sensitive to this feature. Another program (Royal Software) would only accept one order per IP address, requiring IP address diversity as well.

In total we placed 156 such orders. We scheduled them both periodically over a three-week period as well as in patterns designed to help elucidate more detail about transaction volume and to test for internal consistency, as discussed below.

Finally, in addition to the raw data from our own purchase records, we were able to capture several purchase order numbers via forum scraping. This opportunity arose because affiliate programs typically sponsor online forums that establish a community among their affiliates and provide a channel for distributing operational information (e.g., changes in software or name servers), sharing experiences (e.g., which registrars will tolerate domains used to host pharmaceutical stores), and to raise complaints or questions. One forum in particular, for the GlavMed program, included an extended "complaint" thread in which individual affiliates complained about orders that had not yet cleared payment processing (important to them since affiliates are only paid for each settled transaction that they deliver). These affiliates chose to document their complaints by listing the order number they were waiting for, which we determined was in precisely the same format and numeric range as the order numbers presented to purchasers. By mining this forum we obtained 122 numbers for past orders, including orders dating back to 2008.

Affiliate Program	Phase 1 (1/10 – 11/10)	Phase 2 (1/11 – 2/11)
Rx–Promotion	7	27
Pharmacy Express	3	9
GlavMed	12	14
Online Pharmacy	5	16
EvaPharmacy	7	16
33drugs	4	16
4RX	1	13
EuroSoft	3	25
Royal Software	2	9
SoftSales	2	11

Table 1: Active orders placed to sites of each affiliate program in the two different time phases of our study. In addition, we opportunistically gathered 122 orders for GlavMed covering the period between 2/08 and 1/11.

Note that this data contains an innate time bias since the date of complaint inevitably came a while later than the time of purchase (unlike our own purchases). For this reason, we identify opportunistically gathered points distinctly when analyzing the data. We will see below that the bias proves to be relatively minor.

We summarize the total data set in Table 1. It includes order numbers from 202 active purchases and 122 opportunistically gathered data points.

3.3 Consistency

While our initial observations of monotonicity are quite suggestive, we need to consider other possible explanations and confounding factors as well. Here we evaluate the data for *internal consistency*—the degree to which the data appears best explained by the *sequential update hypothesis* rather than other plausible explanations. At the end of the paper we also consider the issue of *external consistency* using "ground truth" revenue data for one program.

Sequential update

The fundamental premise underlying our purchase-pair technique is that order numbers increment sequentially for each attempted order. The monotone sequences that we observe accord with this hypothesis, but could arise from other mechanisms. Alternate interpretations include that updates are monotone but not sequential (e.g., incrementing the order number by a small, varying number for each order) or that order numbers are derived from timestamps (i.e., that each order number is just a normalized representation of the time of purchase, and does not reflect the number of distinct purchase attempts).

To test these hypotheses, we executed back-to-back orders (i.e., within 5–10 seconds of one another) for each of the programs under study. We performed this measurement at least twice for all programs (excepting EvaPharmacy, which temporarily stopped operation during our study). For eight of the programs, every measurement pair produced a sequential increment. The GlavMed program also produced sequential increments, but we observed one measurement for which the order number incremented by two, likely simply due to an intervening order out of our control. Finally, we observed no sequential updates for Rx–Promotion even with repeated back-to-back purchase attempts. However, upon further examination of 35 purchases, we noticed that order numbers for this program are always odd; for whatever reason, the Rx–Promotion order processing system increments the order number *by two* for each order attempt. Adjusting for this deviation, our experiments find that on finer time scales, every affiliate program behaves consistently with the sequential update hypothesis.

We need however to consider an alternate hypothesis for this same behavior: that order numbers reflect normalized representations of timestamps, with each order implicitly serialized by the time at which it is received. This "clock" model does not appear plausible for fine-grained time scales. Our purchases made several seconds apart received sequential order numbers, which would require use of a clock that advances at a somewhat peculiar rate—slowly enough to risk separate orders receiving the same number and violating the uniqueness property.

A possible refinement to the clock model would be for a program to periodically allocate a block of order numbers to be used for the next T seconds (e.g., for $T = 3{,}600$), and after that time period elapses, advancing to the next available block. The use of such a hybrid approach would enable us to analyze purchasing activity over fine-grained time scales. But it would also tend towards misleading over-inflation of such activity on larger time scales, since we would be comparing values generated across gaps.

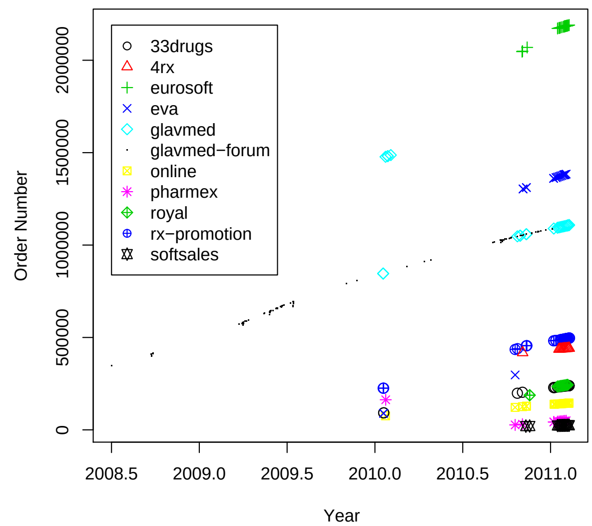

Figure 2: Order numbers (y-axis) associated with each affiliate program versus the time of attempted purchase (x-axis).

We test for whether the order numbers in our data fit with a clock model as follows. First, we consider the large-scale behavior of order numbers as seen across the different affiliate programs. Figure 2 plots for each program the order number associated with a purchase attempt made at a given time. We plot each of the 10 affiliate programs with a separate symbol (and varying shades, though we reuse a few for programs whose numbers are far apart). In addition, we plot with black points the order numbers revealed in the GlavMed discussion forum.

Three basic points stand out from the plot. First, all of the programs use order numbers distinct from the others. (We verified that neither of those closest together, 33drugs and Royal Software, nor Pharmacy Express and SoftSales, overlap.) Thus, it is not the case that separate affiliate programs share unified order processing.

Second, the programs nearly always exhibit monotonicity even across large time scales, ruling out the possibility that some programs occasionally reset their counters. (We discuss the outliers that manifest in the plot below.)

Third, the GlavMed forum data is consistent with our own active purchases from GlavMed. In addition, the data for both has a clear downward concavity starting in 2009—inconsistent with use of clock-driven batches, but consistent with the sequential update hypothesis. Assuming that the data indeed reflects purchase activity, the downward concavity also indicates that the program has been losing customers, a finding consistent with mainstream news stories [13].

We lack such extensive data for the other programs, but can still assess their possible agreement with use

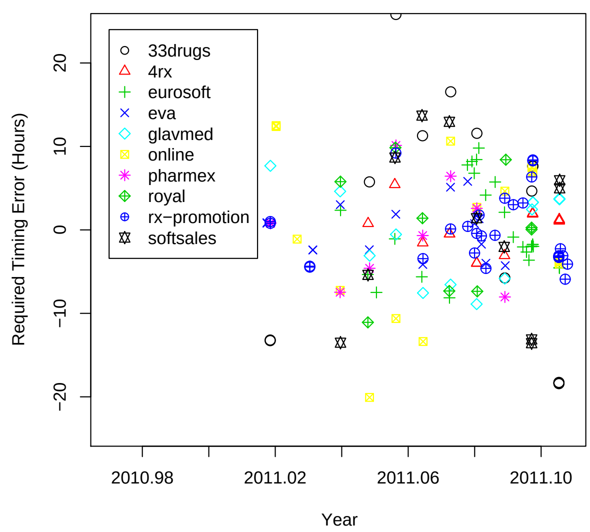

Figure 3: The amount of error—either in our measurement process, or due to batching of order numbers—required for each measurement in 2011 to be consistent with the Null Hypothesis that order numbers are derived from a clock that advances at some steady rate. Note that the y-axis is truncated at ± 24 hrs, though additional points lie outside this range.

of clock-driven batches, as follows. For each program, we consider the purchases made in 2011. We construct a least-squares linear fit between the order numbers of the purchases and the time at which we made them. If the order numbers come from clock-driven batches (the Null Hypothesis), then we would expect that all of the points associated with our purchases to fall near the fitted line. Accordingly, for each point we compute how far we would have to move it along the x-axis so that it would coincide with the line for its program. If the Null Hypothesis is true, then this deviation in time reflects the *error* that must have arisen during our purchase measurement: either due to poor accuracy in our own time-keeping, or because of the granularity of the batches used by the program for generating order numbers.

Figure 3 plots this residual error for each affiliate program. For example, in the lower right we see a point for a 33drugs purchase made in early February 2011. If the Null Hypothesis holds, then the purchaser's order number reflects a value that should have appeared 18 hours earlier than when we observed it. That is, either we introduced an error of about 18 hours in recording the time of that purchase; or the program uses a batch-size of 18+ hours; or the Null Hypothesis fails to hold.

For all ten of the affiliate programs, we find many purchases that require timing errors of many hours to maintain consistency with the Null Hypothesis. (Note that we restrict the y-axis to the range ± 24 hr for legibility, although we find numerous points falling outside that range as well.) In addition, we do not discern any temporal patterns in the required errors, such as would be the case if the least-squares fit was perturbed by an outlier. Finally, if we extend the analysis out to November 2010 (not shown), we find that the required error *grows*, sometimes to 100s of hours, indicating that the discrepancy does not result from a large batch size such as $T = 1$ day.

Given this evidence, we reject the Null Hypothesis that the order numbers derive from a clock-driven mechanism. We do however find the data consistent with the sequential update hypothesis, and so proceed from this point on the presumption that indeed the order numbers grow sequentially with each new purchase attempt.

Payment independence

We placed most of our orders using cards underwritten by Visa. We selected Visa because it is the dominant payment method used by these affiliate programs (few accept MasterCard, and fewer still process American Express). However, it is conceivable that programs allocate distinct order number ranges for each distinct type of payment. If so, then our Visa-based orders would only witness a subset of the order numbers, leading us to underestimate the total volume of purchase transactions. To test this question, we acquired several prepaid MasterCard cards and placed orders at those programs that accept MasterCard (doing so excludes Rx–Promotion, GlavMed, 4RX and Online Pharmacy). In each case, we found that Visa purchases made directly before and after a MasterCard purchase produced order numbers that precisely bracketed the MasterCard order numbers as well.

Outliers

Out of the 324 samples in our dataset, we found a small number of outliers (six) that we discuss here. Almost all come from the GlavMed program. The outliers fall into two categories: two singleton outliers completely outside the normal order number range for the program, and one group of four internally consistent order numbers that were slightly outside the expected range, violating monotonicity. We discuss these in more detail here, as well as their possible explanations.

The first singleton outlier was a purchase placed at a Web site that is clearly based on the SE2 engine built by GlavMed. However, the returned order number was close to 16000 when co-temporal orders from all other GlavMed sites returned orders closer to 1080000. The site differs in a number of key features, including a unique template not distributed in the standard package made available to GlavMed affiliates, a different support phone number, different product pricing, and purchases processed via a different acquiring bank than used by all other GlavMed purchases. Taken together, we believe this reflects a site that is simply using the SE2 engine, but is not in fact associated with the GlavMed operation.[5]

The second outlier occurred in a very early (January 2010) purchase from a Pharmacy Express affiliate, which returned an order number much higher than any seen in later purchases. We have no clear explanation for this incongruity, and other key structural and payment features match, but we note that the order numbers returned in all subsequent Pharmacy Express transactions are only five digits long, and that over nine months pass between this initial outlier and all subsequent purchases. Consequently, we might reasonably explain the discrepancy by a decision to reset the order number space at some point between January and October.

Finally, we find a group of four early GlavMed purchases whose order numbers are roughly the same magnitude, but occur out of sequence (i.e., given the rate of growth seen in the other GlavMed order numbers, these four are from a batch that will only be used sometime in 2013). These all occurred together in the last two weeks of January 2010. This small outlier group remains a mystery, and suggests either that GlavMed might maintain a parallel order space for some affiliates, or that they reflect a "counterfeit" GlavMed operation. The remaining 21 GlavMed purchase samples, as well as the 122 opportunistically gathered order numbers (occurring both before and after January 2010), all use consistent order numbering.

While we cannot completely explain these few outliers, they represent less than 2% percent of our dataset. We also have found no unexplained instances within the last 12 months. We remove these six data points in the remainder of our analysis.

3.4 Order rates

Under these assumptions, we can now estimate the rate of orders seen by each enterprise. Figure 4 plots the 2011 data points for each of the 10 programs. We also plot the least squares linear interpolation as well as the slope parameter of this line—corresponding to the number of orders received per day on average. During this time period, daily order rates for pharmacy programs vary from a low of 227 for Rx–Promotion (recall that their order IDs increment by two for each order) up to a high of 887 for EvaPharmacy (software programs range between 49 and 749). Together, these reflect a monthly volume of over 82,000 pharmaceutical orders and over 37,000 software orders. Again, these numbers reflect upper bounds on completed orders, since undoubtedly some fraction of these attempted orders are declined; however, it seems clear that order volume is substantial.

We also note that while order volume is quite consistent across January and February, there are significant fall offs for some programs when compared to the data gathered earlier. For example, during 2010, the average number of Rx–Promotion orders per day was 385, 70% greater than during the first two months of 2011. Similarly, 2011 GlavMed orders are off roughly 20% from their 2010 pace, and EvaPharmacy saw a similar decline as compared to October and November of that year. Other programs changed little and maintained a stable level of activity.

4 Purchasing behavior

While the previous analysis demonstrates that pharmaceutical affiliate programs are receiving a significant volume of orders, it reveals little about the source of these orders or their contents. In this section, we use an opportunistic analysis of found server log data to explore these issues for one such affiliate program.

4.1 EvaPharmacy image hosting

In particular, we examine EvaPharmacy, a "top 5" spam-advertised pharmacy affiliate program.[6] In monitoring EvaPharmacy sites we observed that roughly two thirds "outsourced" image hosting to compromised third-party servers (typically functioning Linux-based Web servers). This behavior was readily identifiable because visits to such sites produced HTML code in which each image load was redirected to another server—addressed via raw IP address—at port 8080.

We contacted the victim of one such infection and they were able to share IDS log data in support of this study. In particular, our dataset includes a log of HTTP request streams for a compromised image hosting server that was widely used by EvaPharmacy sites over five days in August of 2010. While the raw IP addresses in our dataset have been anonymized (consistently), they have first been geolocated (using MaxMind) and these geographic coordinates are available to us. Thus, we have city-level source identifiability as well as the contents of HTTP logs (including timestamp, object requested, and referrer).

Through repeated experimentation with live EvaPharmacy sites, we inferred that the site "engine" can use dynamic HTML rewriting (similar to Akamai) to rewrite embedded image links on a *per visit* basis. On a new visit (tracked via a cookie), the server selects a set of five compromised hosts and assigns these (apparently in a quasi-random fashion) to each embedded image link served. During the five-day period covering our log data, our crawler observed 31 distinct image servers in use.

[5] We have found third parties contracting for custom GlavMed templates on popular "freelancer" sites, giving reason to believe that independent innovation exists around the SE2 engine created by GlavMed.

[6] Our page classifiers [16] identified EvaPharmacy in over 8% of pharmacy sites found in spam-advertised URLs over three months, with affiliates driving traffic to over 11,000 distinct domains.

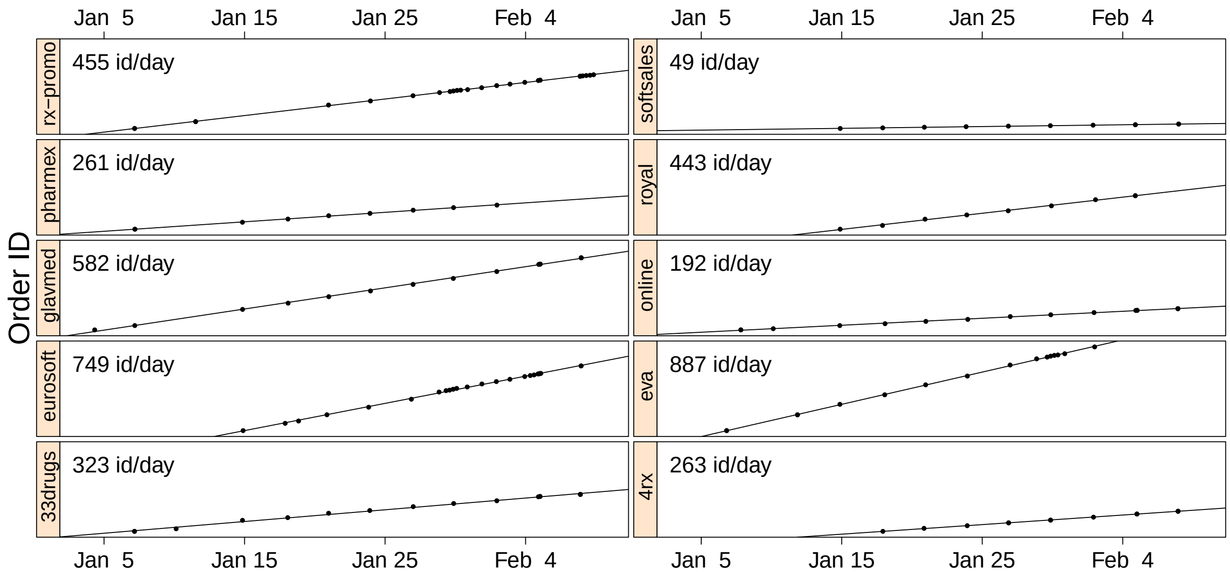

Figure 4: Collected data points and best fit slope showing the inferred order rate for ten different spam-advertised affiliate programs. Order numbers are zero-normalized and the vertical scale of each plot is identical.

However, our particular server was apparently disproportionately popular, as it appears in 31% of all contemporaneous visits made by our URL crawler (perhaps due to its particularly good connectivity). In turn, each image server hosts an nginx Web proxy able to serve the entirety of the image corpus.

4.2 Basket inference

Since the log we use is limited to embedded Web page images, and in fact only includes one fifth of the images fetched during a particular visit, there are considerable challenges involved in inferring item selection purely from this data. We next discuss how this inference technique works (illustrated at a high level in Figure 5) as well as its fundamental limitations.[7]

We mapped out the purchasing workflow involved in ordering from an EvaPharmacy site, and observed that all purchases involve visiting four key kinds of pages in order: landing, product, shopping cart, and checkout. The landing page generally includes over 40 distinct embedded images. Thus, even though images are split among five servers, it is highly likely that multiple objects from each landing page are fetched via our server (each with a referrer field identifying the landing page from which it was requested).[8] We observe 752,000 distinct IP addresses that visited and included referrer information during our five-day period.

When a visitor selects a particular drug from the landing page, the reply takes them to an associated product page. This page in turn prompts them to select the particular dosage and quantity they wish to purchase. The precise construction of product pages differs between the set of site templates (i.e., storefront brands) used by EvaPharmacy. However, all include at least a few new images not found on the landing page, and the most popular template fetches five additional images. The number of additional images varies on a per-template basis, not a per-product basis within each template. Thus, for some templates we may have less opportunity to observe what product the user selects, but this does not affect our estimate of the *distribution* of products selected, because the diminished opportunity is not correlated with particular products.

Next, upon selecting a product, the user is taken to the shopping cart page, which again includes a large number (often a dozen or more) of new images representing *product recommendations*. We observe 4,879 cart visits from 3,872 distinct IP addresses. This allows us to estimate a product-selection conversion rate: the fraction of visitors who select an item for purchase. Based on the total number of visitors where we have referrer information, the conversion percentage on an IP basis is 0.5%.[9] Of these, 3,089 cart additions have preceding visits to prod-

[7] This general approach is similar in character to Moore and Clayton's inference of phishing page visits from Webalizer logs [20].

[8] We validated this observation using our crawled data, which showed that the landing pages using :8080 image hosting always used five distinct servers. Thus, any image server assigned to a particular visit is guaranteed to see the landing page load for that visit.

[9] For comparison, in our previous work we measured a visit-to-product-selection conversion rate of 2% [10].

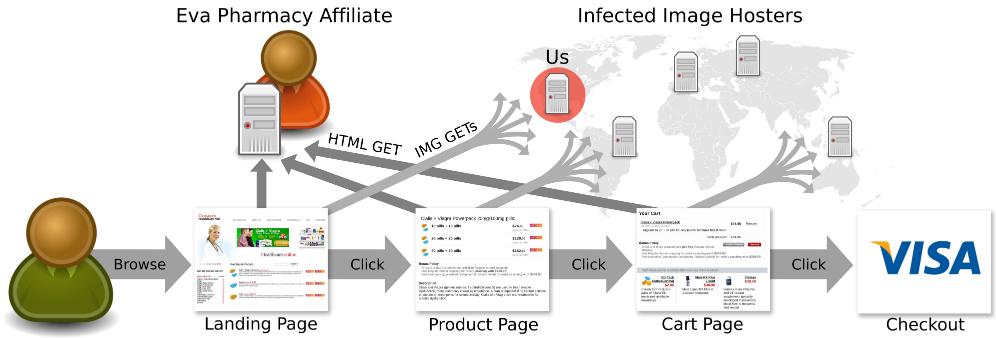

Figure 5: How a user interacts with an EvaPharmacy Web site, beginning with the landing page and then proceeding to a product page and the shopping cart. The main Web site contains embedded images hosted on separate compromised systems. When a browser visits such pages, the referrer information is sent to the image hosting servers for every new image visited.

uct pages, which allows us to infer the selected product. To quantify overall shopping cart addition activity, we compare the total number of visits to the number of visits to the shopping cart page. To quantify individual item popularity, we examine the subset of visits for which the customer workflow allows us to infer which specific item was added to the cart.

There are three key limitations to this approach. First and foremost, the final page in the purchasing workflow—the checkout page—generally does not include unique image content, and thus does not appear in our logs (even if it did, our approach could not determine whether checkout completed correctly). Thus, we can only observe that a user inserted an item into their cart, but not that they completed a purchase attempt. In general, this is only an issue to the degree that shopping cart abandonment correlates with variables of interest (e.g., drug choice). The second limitation is that pages typically use the same image for all dosages and quantities on a given product page, and therefore we cannot distinguish these features (e.g., we cannot distinguish between a user selecting 120 tablets of 25mg Viagra tablets vs. an order of 10 tablets, each of 100mg). Finally, we cannot disambiguate multiple items selected for purchase. When a user visits a product page followed by the shopping cart page, we can infer that they selected the associated product. However, if the visitor then *continues* shopping and visits additional product pages, we cannot determine whether they added these products or simply examined them (subsequent visits to the shopping cart page add few new recommended products; recommendations appear based on the first item in the cart). We choose the conservative approach and only consider the products that we are confident the user selected, which will cause us to under-represent those drugs typically purchased together.

Another issue is that pharmacy formularies, while largely similar, are not identical between programs. In particular, some pharmacy programs (e.g., Online Pharmacy) offer Schedule II drugs (e.g., Oxycodone and Vicodin). However, since EvaPharmacy does not sell such drugs, our data does not capture this category of demand.

Finally, our dataset also has potential bias due to the particular means used to drive traffic to it. We found that 45 of the 50 top landing pages observed in the hosting data also appeared in our spam-driven crawler data, demonstrating directly that these landing pages were advertised through email spam. While these pages could also be advertised using less risky methods such as SEO, this seems unlikely since spam-advertised URLs are swiftly blacklisted [14]. Thus, we suspect (but cannot prove) that our data may *only* capture the purchasing behavior for the spam-advertised pharmacies; different advertising vectors could conceivably attract different demographics with different purchasing patterns.

Given these limitations, we now report the results of two analyses: product popularity (what customers buy) and customer distribution (where the money comes from).

4.3 Product popularity

Our first analysis focuses on simple popularity: what individual items users put into their shopping carts (Table 3a) and what broad (seller-defined) categories of pharmaceuticals were popular (Table 3b) during our measurement period. Although naturally dominated by the various ED and sexually-related pharmaceuticals, we find a surprisingly long tail; indeed, 38% of all items added to the cart were not in this category. We observed 289 distinct products, including popular mass-market products such as Zithromax (31), Acomplia (27), Nexium (26), and Propecia (27); but also Cipro (11; a commonly prescribed antibiotic), Actos (6; a treatment for Type 2 diabetes), Buspar (12; anti-anxiety), Seoquel (9; anti-schitzophrenia), Clomid (8; ovulation inducer), and Gleevec (1; used to treat Leukemia and other cancers).

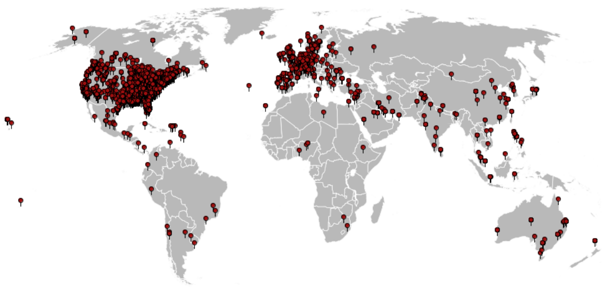

Figure 6: The geographic distribution of those who added an item to their shopping cart.

Country	Visits	Cart Additions	Added Product
United States	517,793	3,707	0.72%
Canada	50,234	218	0.43%
Philippines	42,441	39	0.09%
United Kingdom	39,087	131	0.34%
Spain	26,968	59	0.22%
Malaysia	26,661	31	0.12%
France	18,541	37	0.20%
Germany	15,726	56	0.36%
Australia	15,101	86	0.57%
India	10,835	17	0.16%
China	8,924	30	0.34%
Netherlands	8,363	21	0.25%
Saudi Arabia	8,266	36	0.44%
Mexico	7,775	17	0.22%
Singapore	7,586	17	0.22%

Table 2: The top 15 countries and the percentage of visitors who added an item to their shopping cart.

This in turn explains why such online pharmacies maintain a comprehensive inventory: not only does a full formulary lend legitimacy, but it also represents a significant source of potential revenue.

We also comprehensively crawled an EvaPharmacy site for pricing data and calculated the *minimum* estimated revenue per purchase (also shown for the top 18 products in Table 3a). Combining this data with our measurement of item popularity, we calculate a minimum weighted-average item cost of $76 plus $15 for shipping and handling. This weighted average assumes visitors always select the minimum-priced item for any given purchase, and that the final purchases have the same distribution as for items added to the user's shopping cart.

4.4 Customer distribution

We next examine the geographic component of the EvaPharmacy customer base. Figure 6 shows the geolocated origin for all shopping cart additions. We observe that EvaPharmacy has a vast advertising reach, producing site visits from 229 distinct countries or territories. However, this reach is not necessarily all that useful: the population *actively engaging* with EvaPharmacy sites and placing orders is considerably less diverse than the superset simply visiting (perhaps inadvertently or due to curiosity). For example, the Philippines constitutes 4% of the visitors, but only 1% of the additions to the shopping cart. Overall, countries other than the U.S., Canada, and Western Europe generate 29% of the visitors but only 13% of the items added to the shopping cart. Conversely, the vast majority of shopping cart insertions originate from the U.S. and Canada (80%) or Europe (6%), reinforcing the widely held belief that spam-advertised pharmaceuticals are ultimately funded with Western Dollars and Euros.

The United States dominates both visits (54%) and cart additions (76%), and moreover has the highest rate of conversion between visit and shopping cart insertion (0.72%). Table 2 well illustrates this, listing the activity from the countries originating the most visits. This observation reinforces the conclusion that non-Western audiences offer ineffective targets for such advertising.

Finally, we also notice significant differences between the drug selection habits of Americans compared to customers from Canada and Western Europe. In particular, we divide the EvaPharmacy formulary into two broad categories: lifestyle drugs (defined as drugs commonly used recreationally, including "male-enhancement" items plus Human Growth Hormone, Soma and Tramadol) and non-lifestyle (all others, including birth control pills). We find that while U.S. customers select non-lifestyle items 33% of the time, Canadian and Western-European customer selections concentrate far more in the lifestyle category—only 8% of all items placed in a shopping cart are non-lifestyle items. We surmise that this discrepancy may arise due to differences in health care regimes; drugs easily justified to a physician may be fully covered under state health plans in Canada and Western Europe, leaving an external market only for lifestyle products. Conversely, a subset of uninsured or under-insured customers in the U.S. may view spam-advertised, no-prescription-required pharmacies as a competitive market for meeting their medical needs. To further underscore this point, we observe that 85% of *all* non-lifestyle drugs are selected by U.S. visitors.

5 Revenue estimation

Combining the results from estimates on the order rate per program and estimates of the shopping cart makeup, we now estimate total revenue on a per-program basis.

5.1 Average price per order

The revenue model underlying our analysis is simple: we multiply the estimated order rate by the average price per order to arrive at a total revenue figure over a given unit

Product	Quantity	Min order
Generic Viagra	568	$78.80
Cialis	286	$78.00
Cialis/Viagra Combo Pack	172	$74.95
Viagra Super Active+	121	$134.80
Female (pink) Viagra	119	$44.00
Human Growth Hormone	104	$83.95
Soma (Carisoprodol)	99	$94.80
Viagra Professional	87	$139.80
Levitra	83	$100.80
Viagra Super Force	81	$88.80
Cialis Super Active+	72	$172.80
Amoxicillin	47	$35.40
Lipitor	38	$14.40
Ultram	38	$45.60
Tramadol	36	$82.80
Prozac	35	$19.50
Cialis Professional	33	$176.00
Retin A	31	$47.85

(a)

Category	Quantity
Men's Health	1760
Pain Relief	232
Women's Health	183
General Hearth	135
Antibiotics	134
Antidepressants	95
Weight Loss	92
Allergy & Asthma	85
Heart & Blood Pressure	72
Skin Care	54
Stomach	41
Mental Health & Epilepsy	33
Anxiety & Sleep Aids	33
Diabetes	22
Smoking Cessation	22
Vitamins and Herbal Suppliments	18
Eye Care	15
Anti-Viral	14

(b)

Table 3: Table (a) shows the top 18 product items added to visitor shopping carts (representing 66% of all items added). Table (b) shows the top 18 seller-defined product categories (representing 99% of all items).

of time. However, we do not know, on a per-program basis, the actual average purchase price. Thus, we explore three different approximations, all of which we believe are conservative.

First, for on-line pharmacies we use the static value of roughly $100 as reported in our previous "*Spamalytics*" study [10]. However, this study only considered one particular site, covered only 28 customers, and was unable to handle more than a single item placed in a cart (i.e., it could not capture information about customers buying multiple items).

We also consider a second approximation based on the minimum priced item (including shipping) on the site for each program under study. Since sites can have enormous catalogs, we restrict the set of items under consideration as follows. For pharmacy sites, we consider the top 18 most popular items as determined by the analysis of EvaPharmacy in § 4 (these top 18 items constituted 66% of order volume in our analysis). For each of these items present in the target pharmacy, we find the minimum-priced instance (i.e., lowest dosage and quantity) and use the overall minimum as our per-order price. For small deviations between pharmacy formularies (e.g., different Viagra store-brand variants) we simply substitute one item for the other. We repeat this same process for software, but since we do not have a reference set of most popular items for this market, we simply use the declared "bestsellers" at each site (16 at Royal Software, 36 and SoftSales and 76 at EuroSoft)—again using the minimum priced item to represent the average price per order.

Finally, we calculate a "basket-weighted average" price using measured popularity data. For pharmacies we again consider the 18 most popular EvaPharmacy items and extract the overlap set with other pharmacies. Using the relative frequency of elements in this intersection, we calculate a popularity vector that we then use to weight the minimum item price; we use the sum of these weights as the average price per order. Intuitively, this approach tries to accommodate the fact that product's have non-uniform popularity, while still using the conservative assumption that users order the minimum dosage and quantity for each item. Note that we implicitly assume that the distribution of drug popularity holds roughly the same between online pharmacies.[10]

We repeated this analysis, as before, with site-declared best-selling software packages. To gauge relative popularity, we searched a large BitTorrent metasearch engine (isohunt.com), which indexes 541 sites tracking over 6.5 million torrents. We assigned a popularity to each software item in proportion to the sum of the seeders and leechers on all torrents matching a given product name. We then weighted the total prices (inclusive of any handling charge) by this popularity metric to arrive at an estimate of the average order price.

[10]One data point supporting this view is Rx–Promotion's rank-ordered list of best selling drugs. The ten most popular items sold by both pharmacies are virtually the same and ranked in the same order.

Affiliate Program	orders/month	*Spamalytics*		Min product price		Basket-weighted average	
		single order	rev/month	single order	rev/month	single order	rev/month
33drugs	9,862	$100	$980,000	$45.00	$440,000	$57.25	$560,000
4RX	8,001	$100	$800,000	$34.50	$280,000	$95.00	$760,000
EuroSoft	22,776	N/A	N/A	$26.50	$600,000	$84.50	$1,900,000
EvaPharmacy	26,962	$100	$2,700,000	$50.50	$1,300,000	$90.00	$2,400,000
GlavMed	17,933	$100	$1,800,000	$54.00	$970,000	$57.00	$1,000,000
Online Pharmacy	5,856	$100	$590,000	$37.00	$220,000	$58.00	$340,000
Pharmacy Express	7,933	$100	$790,000	$51.00	$410,000	$58.75	$460,000
Royal Software	13,483	N/A	N/A	$55.25	$750,000	$133.75	$1,800,000
Rx–Promotion	6,924	$100	$690,000	$45.00	$310,000	$57.25	$400,000
SoftSales	1,491	N/A	N/A	$20.00	$30,000	$134.50	$200,000

Table 4: Estimated monthly order volume, average purchase price, and monthly revenue (in dollars) per affiliate program using three different per-order price approximations.

5.2 Revenue

Finally, to place a rough estimate on revenue, we multiply the 2011 order volume measurements shown in Figure 4 against each of the previously mentioned approximations, summarized in Table 4. In general, the approximation from our prior "*Spamalytics*" study is the largest, followed by basket-weighted average and then minimum product price. However, for pharmaceutical programs the difference between product prices is not large, and thus the minimum and basket-weighted estimates all lie within 2X of one another. Software programs see much more variation in price, and hence the difference between the minimum and basket-weighted revenue estimates can be substantial.

Using the basket-weighted approximation, we find that both GlavMed and EvaPharmacy produce revenues in excess of $1M per month, with all but two over $400K. Surprisingly, software sales also produce high revenue—less due to high prices than high order volumes. It remains for future work how to further validate how closely order volumes track successfully completed *orders* for this market niche.

5.3 External consistency

While we put considerable care into producing these estimates, a number of biases remain unavoidable. First, while our order volume data has internal consistency (and consistency with order number implementations in common shopping cart software), we could not capture the impact of order declines. Thus, we have a somewhat optimistic revenue estimate, since surely some fraction of orders will not complete.

On the other hand, our estimates of average order revenue are themselves conservative in several key ways. First, they assume that all purchasers select only a single item. Second, they assume that when purchasing an item, all users select the minimum dosage and quantity. Finally, for pharmaceuticals we need to keep in mind that EvaPharmacy does not carry "harder" drugs found at other sites, such as Schedule II opiates. We have found anecdotal evidence that these drugs are highly popular at such sites, but our methodology does not offer any means to consider their impact. Such items are also typically more expensive than other drugs (e.g., the cheapest Hydrocodone order possible at one popular pharmacy is $186 plus shipping). Thus, this other factor will cause us to *underestimate* the true revenue per order.

Our intuition is that such factors are modest, and our estimates capture—within perhaps a small constant factor—the true level of financial activity within each enterprise. However, absent ground truth data for program revenues, it is not generally possible to validate our model and hence verify that our measurements actually capture reality. In general, this kind of validation is rarely possible since the actors involved are not public companies and do not make revenue statements available.

Due to an unusual situation, however, we were able to acquire such information for one program, Rx–Promotion. In particular, a third party made public a variety of information, including multiple months of accounting data, for Rx–Promotion's payment processor.[11] While we cannot validate the provenance of this data, its volume and specificity make complete fabrication unlikely. In addition, given that our research covers only a small subset of this data, it seems further unlikely that any fabrication would closely match our own independent measurements.

Unfortunately, we do not have payment ledgers precisely covering our 2011 measurement period. Instead, we compare against a similar period six months earlier for which we do have ground truth documentation, 27 consecutive days from the end of Spring, 2010. These

[11] While our legal advisers believe that the prior public disclosure of this data allows its use in a research context, we chose not to unnecessarily antagonize the payment services provider by naming them here.

two periods are comparable because during both times Rx–Promotion had significant difficulty processing orders on "controlled" drugs (indeed, during the 2011 period such drugs had been removed from the standard formulary on Rx–Promotion affiliates).[12]

Based on this data, we find that between May 31 and June 26, 2010, Rx–Promotion's turnover via electronic payments was $609K.[13] Using our estimate of 385 orders per day in 2010 (see § 3), this is consistent with an average revenue per order of $58, very similar to our basket-weighted average order price estimate of $57. While we suspect that both estimates are likely off (with the number of true June 2010 orders likely less due to declines, and January 2011 price-per-order likely higher due to conservatism in our approximation), they are sufficiently close to one another to support our claim that this approach can provide a rough, but well-founded estimate (i.e., within a small constant factor) of program revenue.

6 Conclusion

When asked why he robbed banks, Willie Sutton famously responded, "Because that's where the money is." The same premise is frequently used to explain the plethora of unwanted spam that fills our inboxes, pollutes our search results and infests our social networks—spammers spam because they can make money at it. However, a key question has long been how much money, and from whom? In this paper we provide what we believe represents the most comprehensive attempt to answer these questions to date. We have developed new inference techniques: one to estimate the rate of new orders received by the very enterprises whose revenue drives spam, and the other to characterize the products and customers who provide that same revenue. We provide quantitative evidence showing that spam is ultimately supported by Western purchases, with a particularly central role played by U.S. customers. We also provide the first sense of market size, with well over 100,000 monthly orders placed in our dataset alone. Finally, we provide rough but well-founded estimates of per-program revenue. Our results suggest that while the spam-advertised pharmacy market is substantial, with annual revenue in the many tens of millions of dollars, it has nowhere near the size claimed by some, and indeed falls vastly short of the annual expenditures on technical anti-spam solutions.

[12] During periods when such drugs were sold *en masse*, the overall Rx–Promotion revenue was frequently doubled.

[13] Interestingly, this data also provides useful information about refunds and chargebacks (together about 10% of revenue) as well as processing fees (roughly 8.5%). Thus, the gross revenue delivered to Rx–Promotion in June 2010 was likely closer to $489K. Finally, since roughly 40% of successful order income is paid to affiliates on a commission basis, that leaves only $270K (44% of gross) for fulfillment, administrative costs, and profit.

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Not a good buy: Value for money of prescription drugs sold on the Internet

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ABSTRACT

In this note we study the value for money of purchases of fluoxetine made through on-line pharmacies without prescription. We show that this channel is not good value from an economic point of view and that it can be dangerous in medical terms because of the poor quality of the drugs received and the lack of prescribing instructions.

1. Introduction

Economic globalisation and web-based resources have considerably increased the opportunities for patients to buy drugs without asking for advice, or perhaps even against their physician's judgment.

The rapid development of on-line pharmacies is due to several factors ranging from economic arguments (better value for money, easy access, home delivery) to patient empowerment, but it may also represent a serious health hazard. On-line drugs are available to anyone having an Internet access; the web has no geographical barriers, and its global dimension makes it virtually impossible to control on-line pharmacies.[1]

The growth of this unregulated global market may increase the risk of inappropriate intake of drugs [3], and the spread of counterfeit and low quality drugs that may harm patient health [4]. In addition, many on-line pharmacies sells drugs without a medical prescription, and this can expose patients to the risks associated with the intake of inappropriate drugs [5,6]. Finally, buying drugs on the Internet may not be good value from an economic point of view. In a comparison between traditional pharmacies and on-line pharmacies, several studies found no economic advantage in buying on-line, in both 1999 and 2006 [7,8].

In May 2007 the University of Brescia investigated the selling characteristics of four active principles which were selected as "marker drugs" because of their high intrinsic risk if used without medical control. The study by Ref. [1] reports the results of this study and shows that on-line pharmacies charge higher prices for drugs, especially when they are sold without a prescription.

In this, as in most studies, the missing dimension is the evaluation of the quality of the product. As a follow-up to the first investigation we studied the quality and the value for money of a prescription drug bought on the Internet without prescription. Ref. [9] presents a multidimensional evaluation of the quality of the drug we purchased; in this

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[1] See Refs. [1,2] and references therein.

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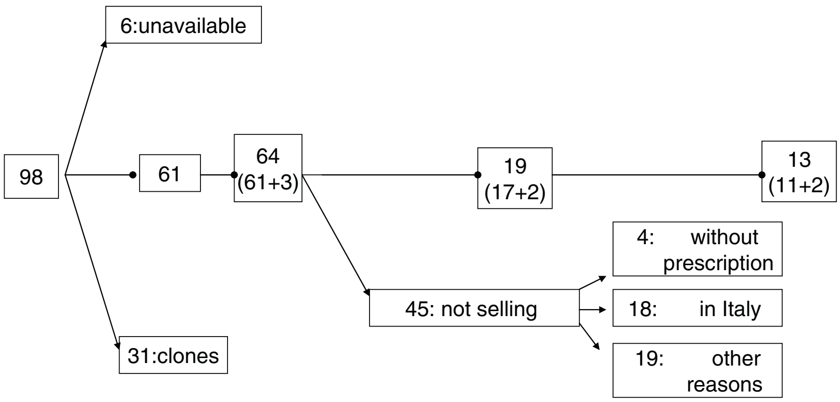

Fig. 1. From websites to drugs received.

note we investigate the value for money of this purchasing method. Our experience was fairly negative: the price paid is much higher than using traditional pharmacies and the consumer faces several risks, in both financial and medical terms.

2. Methods

At the beginning of 2011 fluoxetine was bought from on-line pharmacies without a prescription. The choice of this active principle is justified on several grounds: it is a typical prescription-only drug, it is commonly used, but it is not a "life-style drug" like Viagra.[2] An Internet search was performed using keywords to identify pharmacies selling drugs on-line.[3] A list of 98 websites claiming to sell fluoxetine worldwide, with or without prescription, was obtained. Our sample deliberately included four "prescription only" pharmacies to check if they were actually refusing orders made without a prescription.

The Italian Consumer Association Altroconsumo made the purchases on our behalf using a prepaid credit card; an email address and a P.O. Box dedicated to this project were also created. Each purchase followed a standardised protocol: orders were placed for the quantity required to perform quality tests,[4] and a standard health profile aimed at maximising the probability of receiving the drug was outlined to answer the questions some pharmacies ask about the patient's state of health.

As shown in Fig. 1, we could initialise transactions only from 61 sites. In 31 cases, closer inspection before making the purchase showed that these pharmacies were clones of other sites; 6 sites were no longer available, even though the time between search and purchase was fairly limited. We made a repeated purchase of fluoxetine from two sites, and from one pharmacy we bought both the generic and the brand drug. Branded drugs sold without prescriptions were not the target of our analysis; for this reason we attempted to buy Prozac only from one website. The total amount of initialised transaction was 64 as shown in Fig. 1. We were able to finalise 19 transactions from 17 sites. In 45 cases the transaction could not be concluded because the pharmacy was not shipping to Italy (18 cases), or for other administrative reasons (13 cases).[5] Only in four cases was the purchase refused because we did not produce a prescription. However, we did not find a perfect match between the "prescription only" requirement and being able to finalise the transaction. In fact only three "prescription only" pharmacies did not allow us to buy the drug. The fourth simply required a "fax later" option for the prescription. We received 13 samples from 11 websites. The samples we did not receive were either stopped by Customs, went lost or were (probably) never sent. One of the sample received comes from the prescription only pharmacy in spite not having sent the prescription by fax.

The samples received were inspected and the quality of the drug was evaluated using three sets of indicators: packaging appearance, microbiological analysis and chemical analysis using an approach similar to Ref. [4]. The specific protocol and the results for this analysis are presented in Ref. [9]. Below we focus on the value for money of the purchases made.

3. Results

The lack of transparency that characterises this market means that most pharmacies on-line are simply a website address, usually registered in countries that offer little consumer protection. The first column in Table 1 identifies the pharmacy, the second the country where the pharmacy is said to be located and the third the country where the website is registered. In some cases, even this basic information could not be retrieved. Few of the pharmacies that declare they are located in a specific country are actually registered there as shown in Table 1. In this case we think that the pharmacies are trying to mislead the consumer:

[2] See Ref. [10] for more details.

[3] A detailed description of the protocol can be found in Ref. [11]. The initial choice was to buy from the same on-line pharmacies described in Ref. [1], but most of the websites we used in that study had changed name or address, or were no longer available.

[4] For fluoxetine the minimum quantity is 80–20 mg tablets.

[5] In some cases the transaction could not be concluded for no apparent reasons, in other cases the purchase was not confirmed and the credit card was not debited.

Table 1
Synopsis of the analysis of the completed transactions.

PH	PL	DR	PR	CO	Q	Mails	Elapsed time	Shipping costs (€)	Hidden costs(€)	Expected price(€)	Actual price(€)	Quality
Generic fluoxetine												
1	UK	CZEC	A	India	90	2	15	28.83		0.55	0.83	X
4	CAN	CAN	B	India	90	7	21			1.13	1.17	b
6		RUS	B	India	90	5	68/o	11.07		1.47	1.60	X
8		LUX	C	India	100	2	83/o	0		0.41	0.41	b
12		UKR	D	India	90	9	23	8.68	3.92	0.55	0.64	b
15	CAN	RUS	E	India	90	2	20	12.45		0.56	0.62	X
16		POR	F	NZ	168	2	28	7.01		0.27	0.31	*
17	CAN		E	India	90	2	21	12.45	4.11	0.56	0.66	X
18		Malaysia			90	4		20.12		0.25	0.47	NR
19		USA			90	2		18		1.34	1.54	NR
20		USA			90	2		18.36		1.36	1.55	NR
34		CAN	C	India	90	5	21/o	22.14		1.47	1.71	b
45	UAE	Mauritius			90	6		21.59		0.25	0.49	NR
51	Vanuatu	AUS	F	NZ	84	3	41/o	7.38		0.88	0.97	*
54		CAN			90	7		12.03		0.57	0.63	NR
58	THAI	THAI			112	4		30		3.30	2.64	NR
61	CAN	USA	G	India	90	3	15	12.45	4.11	0.56	0.67	X
62	UK	CZEC	C	India	90	3	13	28.83		0.55	0.83	X
Brand fluoxetine (Prozac)												
64	Vanuatu	AUS	H	Turkey	144	2	21	10		1.36	1.05	X

PH identifies the pharmacy; PL the country where the pharmacy declares it is located; DR the country where the website domain is registered; PR identifies the producer of the drug (A to G to protect identity) and CO the country where it is located; *Q* is the quantity ordered; mails is the number of mails needed to complete the order; /o means delayed arrival from stated delivery time; * denotes good quality drugs; X means that the drug cannot be sold according to current pharmacopoeia; b: means that basic current pharmacopoeia requirements are met. NR means that we did not receive the drug.
Note: 62 is a repeated purchase from on-line pharmacy 1, 51 and 64 are bought from the same on-line pharmacy.

the location of the pharmacy may be perceived by the consumer as a proxy for the quality of the product received and for the protection of his consumers right. However, these expectations are not fulfilled: pharmacies choose to be registered in countries were a void in the legislation make it possible to legally operate. The picture is quite different on the production side. Most of the drugs received were produced in India, by a few industries that are probably selling drugs which are intended for the domestic market to on-line pharmacies.

Buying drugs on the Internet is a risky and costly business. The price of the drug, although very high, is only a part of it. We can identify two different cost sources:

- Monetary costs: they are made up of the price of the drug, shipping costs, customs duties and unexpected differences between the amount actually debited on the credit card and the bill shown on the website at the end of the transaction. Only the price of the drug is clearly stated on the website; the exact amount of shipping costs is often not known until the end of the transaction and other costs have sometimes been added to the bill (insurance for shipping the goods and administrative costs). In our sample these costs add an average mark-up of around 20%. It is interesting to note that the actual price paid is known only after the credit card has been debited: in our experience making transactions using these website is equivalent to sign a blank check. Column 11 shows the amount that was stated at the end of the transaction (cost of the drug plus shipping costs, insurance and administrative charges) while in column 12 we have recorded what has in fact been charged on our credit card; in some cases this difference does not simply depend on the variance in the exchange rate.
- Non-monetary costs: they relate to the time spent waiting to receive the drug and the opportunity cost of the time spent in dealing with the transaction itself. In our experience buying through these pharmacies is a costly business in terms of time as shown in Table 1, column 8. It takes on average 25 days to receive the drug and the purchaser has to reply to several emails from the seller, often originating from unknown addresses. In most cases only a very careful reading allows the purchaser to differentiate them from the spam. Although the purchases are made from Italy, most pharmacies send their mail in English, even when they ask for further information. This may be a serious hurdle to most Italian buyers whose level of literacy in English is still very poor.

Buying on the Internet is a risky business: the consumer has to trust the seller to send the drug knowing that little can be done to get the money back if the good is not delivered. On top of this, buying prescription drugs without a prescription is illegal in Italy and Customs may stop the package; in this case, the consumer loses his money since the drug will not be delivered. This risk further increases the price of the tablets received; in our case we were charged €1828 (1677 for generic and 151 for brand) and we received 1306 tablets (1162 generic, 144 brand) out of the 1868 we ordered and paid for (1724 generic, 144 brand). The average price we paid for a generic tablet was €1.44. At the time we did our study, the price for a 20 mg tablet of generic fluoxetine bought on prescription in Italy was €0.30[6]; on the Internet we paid about five times more for the drugs than in traditional pharmacies. If we proxy the extra paid for the tablets with the value of the prescription, the Internet latter is about €1.14 per tablet.

The external appearance of the drugs is often good: drugs were in sealed blisters and arrived in good condition, but without any prescribing information.[7] This represents a big health hazard because the use of fluoxetine should be strictly controlled by a physician using a dosage tailored to patients health conditions.

On average, the quality of the drug received was poor; although the tablets were all well preserved, the chemical analysis clearly showed that the technological production processes were usually not up to standard. The active principle was always in the tablets, but in variable quantity, and the analyses detected the presence of metals and other possibly carcinogenic agents (IARC2B). The quantity was always very limited, but for most of these agents a clear safety level does not exist as shown in Ref. [9] which present the complete analysis. For our study we classified the drugs received in three categories: we gave a * to the products that can be considered in each aspect (ranging from packaging to content) equivalent to the generic fluoxetine we bought in a traditional pharmacy. Only two samples met these requirements and were produced by the same manufacturer in New Zealand. We marked **X** the products that cannot be sold according to the current European pharmacopoeia. The third category is represented by products that can be sold according to current pharmacopoeia standards, but whose quality is lower than products bought in the traditional pharmacy because they contain impurities. We have labelled them with **b** which stands for basic requirements for commercialisation met.

The price paid for drugs produced by the same supplier may vary significantly as shown in Table 1, furthermore the difference in price does not depend on the producer or on the quality of the drug.

4. Discussions and conclusions

In spite of their catchy names that sometimes recall affordability, buying on the Internet without a prescription is a risky costly business, in both medical and economic terms.

Buying drugs without prescription on the Internet means that the patient is not sure that the package will arrive (because it may not be shipped or it may be stopped and detained by customs) and cannot control the quality of the drug received. The price on this market is not an indication of the quality of the product received, or a guarantee that it will be received. In our experience a third of the orders were not delivered, and no money was refunded. The price is not a good predictor of the probability of receiving the drug, at least in our sample: for the tablets that we

[6] This is the price for February 2011.

[7] In our sample only the branded variety of fluoxetine had prescribing information, but *it was* written in Turkish.

actually received the average price we paid was €0.83[8]; for those that were not delivered the average price we paid was €1.27.[9] Drugs purchased on the Internet are mostly produced by suppliers in developing countries possibly using production processes with poor quality standards, which in some cases may undermine the safety of the product. Also in this case, the price is not a good indicator of the quality of the drug sold. In our experience only the drugs commercialised by a New Zealand producer could be considered equivalent in all respects to the fluoxetine bought in a traditional pharmacy. However, for this same drug we paid one of the lowest prices (€0.31) from an on-line pharmacy whose website is registered in Portugal and three times as much from a Vanuatu pharmacy. In both cases the product came without a prescribing information leaflet.

Finally, even the producer is not a guarantee in itself. Pharmacies 8, 34 and 61 use the same producer (C), but only two of the samples received passed the quality test.

Our sample is too small to allow for a quantitative analysis on the price; our data seem to show that the price is established by the pharmacy according to its potential market irrespective of the quality of the drug sold. Most "Canadian" pharmacies charge €0.56 per tablet (3 cases out of 4). In our experience there does not seem to be any ex-ante characteristic of the on-line pharmacy that may allow potential consumers to discriminate among sellers; and price is certainly not a good predictor. In this respect our results differ from what was found by Ref. [12] who tested prescription drugs received using a prescription. We can therefore conclude that on top of the risk related to using a drug without any medical guidance, the potential patient faces the further health risk of using a drug of low to poor quality. In spite of this, the price is very high and this should be another good incentive to ask for medical advice.

Several are the strategies that the regulator can use to reduce the risk related to buying drugs on the internet without prescription. The "command and controls" measures are often not very effective to reduce the risk. The global market nature of on-line pharmacies means that national rules banning the sale of drugs without prescription can be easily overcome by a strategic choice of the location; the same mechanism can be used to commercialise drugs of poor quality: it is in fact sufficient to locate in a country with lower quality standards to trade without any legal restriction. National governments can make (as in Italy) the purchase of drugs without prescription illegal. An increase in customs and mail control may allow to reduce the purchase of drugs through the internet, but its impact may be limited since it is virtually impossible to stop any incoming package containing "illegal" drugs.

In this case some soft paternalism measures may be more effective: regulators may increase the information on the risk deriving from drug misuse or they may sponsor specific advertising campaign to induce patients to avoid on-line purchases without a prescription. The reinforcement of the doctor–physician relationship along the line of the emotional agency [13] may also produce beneficial effects in the long run: if the patients feels that the physician shares his views and concerns about his well-being, it will be induce to trust and seek the physician's advice instead of being attracted by alluring marketing messages of illegal sellers.

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[8] The pharmacies that *sent* the 1162 tablets we *received charged* us €960.99.

[9] We *ordered* (and paid for) 562 tablets that we did not receive. We paid €716.25.

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Critical Issues Bulletin

Price Controls, Patents, and Cross-Border Internet Pharmacies

Risks to Canada's Drug Supply and International Trading Relations

by Brett J. Skinner

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Price Controls, Patents, and Cross-Border Internet Pharmacies

Risks to Canada's Drug Supply and International Trading Relations

Brett J. Skinner

Contents

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- *Definitely Not the Romanow Report: Achieving Equity, Sustainability, Accountability and Consumer Empowerment in Canadian Health Care* (2002). Halifax: Atlantic Institute for Market Studies (AIMS).
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Executive summary

Measuring the cross-border Internet drug trade between Canada and the United States

This study finds that sales of drugs through Canadian-based cross-border Internet pharmacies to American consumers remain significant despite the rising value of the Canadian dollar. According to IMS Health Incorporated data, the moving annual total (MAT) value of sales to the United States through the 278 confirmed or suspected Canadian-based Internet pharmacies identified as of June 2005 was estimated at CDN$507 million measured at standardized manufacturer-level prices. This is down 18% from estimated total sales of CDN$618 million over the 12 months ending June 2004. (The value of sales measured at the final retail prices in US dollars charged to American consumers by Canadian Internet pharmacies was unavailable to this study but is certainly much higher than the figures reported above. These figures also do not include "foot traffic" sales to American consumers through regular "brick-and-mortar" border pharmacies in Canada.)

Sales of generic products rising while sales of brand-name products falling

Data from IMS Health Incorporated on annual sales for the 500 top-selling cross-border drug products between July 2003 and June 2005 show that generic products that are less expensive than brand-name products are displacing brand-name products in the volume of drugs being traded over the Internet to Americans, thus largely explaining the drop in the overall value of sales. Of the 500 top-selling cross-border drugs between July 2004 and June 2005, 302 (60%) were brand-name products representing 72% of the total value of Internet sales and 198 (40%) were generic products representing 28% of the total value of Internet sales.

Cross-border Internet pharmacies violating US patent (intellectual property) rights

The large and rising proportion of cross-border drugs accounted for by generic products is very surprising given that previous research has shown that 74% of the 100 most commonly prescribed generic products that were available in both Canada and the United States in 2003 were priced higher in Canada than in the United States with the average price difference for this group of high-priced generics being 116% greater in Canada after adjusting for currency equivalency.

Why would Americans be buying so much of Canada's generic drug supply if these kinds of drugs are almost always cheaper in the United States? The answer is found in an analysis conducted by IMS Health Incorporated for this study of the patent status in Canada and the United States of drug products sold through cross-border Internet pharmacies. The analysis shows that nearly half (47%) of the value of sales for generic products sold through cross-border Internet pharmacies was accounted for by drugs that were not yet genericized in the United States. In most cases, the lack of a generic equivalent in the United States means that these drugs were still under active patent protection there. The data suggest that Canadian-based Internet pharmacies are engaged in a massive theft of intellectual property by selling drugs to Americans in violation of active US patent rights.

These findings make it highly probable that American patent holders have legal recourse in US courts to stop the cross-border trade. The US government certainly has the legal and moral authority to ban imports of these generic drugs in order to enforce its own property-rights laws. The findings also imply that US politicians who promote the legalization of the cross-border resale drug trade are inadvertently encouraging the massive theft of US intellectual property and therefore might be legally liable for the losses suffered by patent holders.

It is not certain that the Canadian government is legally or morally obligated to impose an export ban on drugs that are genericized in Canada but still under patent protection in the United States because patent laws differ nationally and are not enforced across international borders. This study does not attempt to provide a legal opinion on this matter. However, if such a policy could be enforced without adding a cost to Canadian taxpayers, then the gesture would be consistent with Canada's commitment to protecting intellectual property and, at the least, maintain respect for the patent rights of our trading partners as implied in international trade agreements on intellectual property (e.g., TRIPs & NAFTA). Such a move could bolster Canada's international trading relationship with the United States in the process.

Threats to Canada's drug supply

Although the total value of drugs being diverted from Canadians to Americans through Internet pharmacies has levelled off, political events south of the border suggest there is a real threat that demand in the United States for cross-border drug sales could soon expand dramatically. The cross-border resale drug trade is currently illegal in the United States. Yet since the trade began in 2002, many federal, state, and local American politicians have been attempting to make it legal for individuals to purchase resale drugs from Canadian Internet pharmacies. The number of attempts to pass legislation at the federal and state level has grown from three per year in 2002 to 84 per year by September 2005. Many of the proposals would allow the bulk buying of drugs from Canadian Internet pharmacies to supply employees for federal, state, and local governments in the United States as well as recipients of US public-health programs like Medicaid and Medicare.

When the potential individual and bulk demand from the United States for cross-border drugs is totalled, the number of American consumers that might compete for access to the Canadian drug supply is conservatively estimated to be almost 119 million, nearly four times the size of Canada's entire population of approximately 32 million.

Government policies are the problem. What are the solutions?

This study identifies Canadian drug-price regulations and provincial leveraging of the monopsony buying power of public drug programs as the causes of the cross-border trade. Such policies do not allow normal upward price adjustments in response to increased demand by American consumers for Canadian resale drugs from cross-border sales and the threat that the trade represents for global pharmaceutical price-differentiation strategies. This study argues for the repeal of public policies that distort normal drug pricing and create artificial incentives for cross-border Internet pharmacies to divert Canada's drug supply to a competing American consumer population.

Previous research suggests that, when there is no large-scale cross-border resale drug trade between Canada and the United States, federal price regulations and provincial monopsony buying power are not necessary to keep Canadian prices low relative to those in the United States as lower Canadian incomes would already lead to lower prices. In the presence of the cross-border resale trade, however, government price controls and monopsony buying power cause market distortions by prohibiting drug companies from making temporary price adjustments that would narrow the differences between Canadian and American prices to the point where there are no significant savings to be gained from cross-border drug sales for Americans.

Government prohibitions on flexible pricing cause drug makers to choose the next least costly option, which is to restrict their supply of medicines to Canada, capping shipments at normal Canadian consumption levels. This could seriously threaten access to necessary medicines in Canada as the limited Canadian drug supply is diverted to Americans through Internet pharmacies; a result that would be much worse than a temporary increase in the prices of some drugs.

Therefore, it is recommended that federal price regulations be repealed and provincial monopsony buying power replaced with more efficient cost-control mechanisms like consumer cost sharing and drug programs targeting only catastrophic needs so that normal market pricing can occur in Canada. Previous research has demonstrated that removing price controls and similar misguided public drug policies would correct a host of other market distortions that are harmful to Canadian consumers. Repealing such policies would also eliminate the conditions that drive the cross-border Internet drug trade between Canada and the United States.

The only circumstances under which this study would recommend a general export ban are if governments stubbornly cling to misguided pharmaceutical price controls and insist on leveraging a provincial monopsony buying presence. If this were the case, then in order to protect the Canadian drug supply, an export ban would be appropriate also for all prescription drugs whose prices are regulated by the federal Patented Medicines Prices Review Board (PMPRB) or affected by provincial monopsony buying power.

Summary of findings

Scale of the cross-border internet drug trade

- The moving annual total (MAT) value of sales to the United States through Canadian-based Internet pharmacies as of June 2005 was estimated at CDN$507 million measured at standardized manufacturer-level prices; down 18% from total sales of CDN$618 million over the 12 months ending June 2004.
- As of June 2005, there were 278 Internet pharmacies in Canada that were confirmed or suspected of being primarily cross-border retailers serving mainly American consumers. Nearly 70% of the total business generated through these 278 Internet pharmacies was accounted for by cross-border sales.
- The estimated provincial distribution of the cross-border Internet drug trade as a percentage of the total value of sales can be broken down as follows: Manitoba (39%), British Columbia (20%), Alberta (20%), Ontario (19%), Quebec (3%) and all other provinces (less than 1%).

Threat to Canada's trading relationship with the United States: Patent status of the top 500 cross-border drugs

- Defined by estimated dollar value of sales, the top-selling 500 drug products sold through Internet pharmacies represented CDN$468 million for the year ending June 2005 and accounted for 92% of all estimated cross-border Internet pharmacy sales.
- Of the 500 top-selling cross-border drugs between July 2004 and June 2005, 302 (60%) were brand-name products representing 72% of the total value of Internet sales and 198 (40%) were generic products representing 28% of the total value of Internet sales.
- Generic products have been accounting for a larger share of the top-selling 500 products over time, displacing brand-name products; this explains the shrinking dollar value of the trade.
- Nearly half the value of sales (47%) in generic products sold through cross-border Internet pharmacies was accounted for by drugs that were not yet genericized in the United States. Most of these drugs were likely still under active patent protection in the United States.

Potential threat to Canada's drug supply

- Canadian Internet pharmacies are targeting an American consumer segment (seniors and the uninsured) that is nearly twice as large (approx. 59 million) as the entire population of Canada (approx. 32 million).
- American seniors groups are particularly active in promoting Internet drug sales from Canada and represent a consumer segment that is nine times as large (approx. 36 million) as Canada's own population of seniors (approx. 4 million).
- Since the beginning of the cross-border trade in 2002, many federal, state, and local American politicians have been attempting to legalize bulk buying of drugs from Canadian Internet pharmacies to supply employees of federal, state, and local governments in the United States, as well as recipients of US public health programs like Medicaid and Medicare. The number of attempts to pass such legislation at the federal and state levels has grown from three per year in 2002 to 84 per year by September 2005.
- When the estimated potential individual and bulk demand from the United States for cross-border drugs is totalled, the number of American consumers that might compete for access to the Canadian drug supply is nearly four times (approx. 119 million) the size of Canada's entire population.
- Ten of the largest brand-name drug companies have already begun to restrict the Canadian supply of their drug products to the level of normal domestic consumption in order to avoid facilitating the cross-border drug trade.
- Pharmacy associations have reported that drug shortages are occurring in Canada, though there is no independent data available to confirm this (Woodend, K., et al., 2004).

What this study is about

This study measures and analyzes the export trade in prescription drugs between Canadian Internet pharmacies and American consumers. It does not directly measure the additional value of the cross-border drug trade that also occurs between physical "brick-and-mortar" retail pharmacy locations and pedestrian consumers, nor does it consider international flows in the cross-border resale drug trade beyond Canada and the United States.

Using the most recent, detailed, and authoritative data sample yet published on the subject, this study examines the total value of the cross-border Internet drug trade between Canada and the United States over time. The value of the trade is also measured according to the location of the Internet pharmacy by province, the therapeutic classification of the drugs being traded, and the brand name or generic status within Canada of the drug products being traded. The potential for future growth in the cross-border prescription drug trade is examined.

This study also compares the patent status of the top-selling 500 cross-border Internet drugs in both Canada and the United States. The implications and risks to Canada's international trading relationships arising from findings about the cross-border patent status of the drugs being traded will be discussed.

The public policies that make the trade possible, and the economic incentives that drive it are explained. The business responses available to drug companies are explained and the risks to Canada's drug supply are assessed.

Finally, this paper documents the historical development of the trade and the special-interest politics that are encouraging its growth.

This paper is divided into two sections. Section 1 describes and explains the empirical findings about the cross-border Internet drug trade between Canada and the U.S. and the economics driving it. Section 2 describes the background to the cross-border Internet drug trade as well as the special interests associated with it.

Description of data used in this study

The data used for this study was obtained by special request from IMS Health Incorporated using their Territorial Sales Analysis (TSA) database. According to IMS Health Incorporated, "TSA tracks the sales of pharmaceutical products sold directly by manufacturers or sold indirectly through wholesalers and chain warehouses to customers in Canada" (IMS Health Incorporated, 2005). In this case, "customers" includes retail pharmacies.

TSA prices reflect those provided to IMS by each manufacturer for their own products to use as standardized national benchmarks for their own sales rep activity analysis purposes. These are applied to units of both direct sales to pharmacies and indirect sales to wholesalers, which usually have the same benchmarks. Data was not available to estimate the value of sales at either American or Canadian retail prices or the volume of the cross-border Internet drug trade by prescription volume.

The detailed sample obtained for this study included data on the value of sales (CDN$) over the top 500 drug products sold to retailers that were identified by IMS Health Incorporated as cross-border Internet pharmacies. Detailed data were not available from IMS Health Incorporated that would permit an estimate of the total value of cross-border sales through both Internet and "foot traffic" via regular "brick-and-mortar" retail pharmacy outlets located close to the border. The methodology for identifying cross-border Internet pharmacies is a proprietary secret of IMS Health Incorporated and, as such, details cannot be published in this study. IMS Health Incorporated identified 278 retail outlets as Canadian-based pharmacies confirmed or suspected of being involved in cross-border Internet activities (IMS Health Incorporated, 2005). Defined by the value in Canadian dollars of sales at TSA manufacturer-level prices, the top 500 drug products sold to these 278 cross-border Internet pharmacies accounted for 92.4%

of the total sales to these pharmacies over the period from July 2004 to June 2005 (IMS Health Incorporated, 2005).

The data includes some non-prescription drug products sold to cross-border Internet pharmacies because IMS Health Incorporated's TSA does not sort out prescription from non-prescription drug products. However, non-prescription products end up representing only an insignificant proportion of the overall sample of drug sales. A review of sales by therapeutic category indicates that the categories that could contain non-prescription products end-up ranked last toward the end of the list of 500 by value of sales. It is therefore, very safe to assume that the data sample used for this study reflects almost exclusively sales of prescription drug products.

Relying on external analyses conducted by IMS Health Incorporated on behalf of this study, additional data was provided at an aggregate level and over earlier time periods. These analyses were required because direct access to most of the detailed individual product data through the TSA database was restricted in order to protect the proprietary interests of IMS Health Incorporated and its data suppliers.

On behalf of this study, IMS Health Incorporated also identified the Canadian and US patent status of the drug products being sold to cross-border Internet pharmacies through a proxy analysis conducted in cooperation with IMS Health's US business.

1 Data and economics of the cross-border Internet drug trade between Canada and the United States

Measuring the cross-border Internet drug trade

National figures

According to data obtained from IMS Health Incorporated for this study, it was estimated that, as of June 2005, there were 278 confirmed or suspected Internet pharmacies operating in Canada whose main business was to resell to American consumers drugs that were originally distributed in Canada. Measured as a moving annual total (MAT) [most recent 12 months] current to June 2005, the total value of sales through these 278 Internet pharmacies was almost $726 million including both sales to the United States and local Canadian business (unless otherwise stated, all figures are in Canadian dollars at Territorial Sales Analysis [TSA] manufacturer-level prices). The total value of sales to Americans was approximately $507 million, while sales to Canadians amounted to $219 million over the same period. Therefore, sales to the United States accounted for about 70% of the total business generated by cross-border Internet pharmacies while local Canadian business represented only about 30% of total business (figure 1).

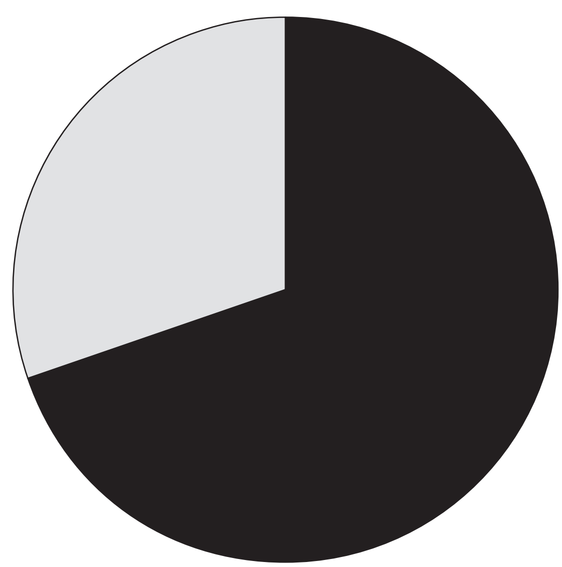
Provincial figures

The data available to this study also permitted a breakdown of Internet pharmacy sales to the United States by province (table 1; figure 2). According to this data, five provinces account for the bulk of cross-border Internet pharmacy sales to the United States. Ranked in order from highest to lowest value of sales, the five provinces are Manitoba ($196 million), British Columbia ($102 million), Alberta ($100 million), Ontario ($94 million) and Quebec ($13 million). All other provinces combined account for only about $2 million.

Cross-border Internet drug sales by therapeutic category

The data available to this study also allowed for a breakdown of cross-border Internet pharmacy sales to the United States by therapeutic category. A therapeutic category (or class) is a group of drug products that treat similar types of health conditions or that have similar effects. It is common for drugs to be sorted into therapeutic classes according to their Uniform System of Classification (USC) code. USC codes have four levels of specificity. USC2 is the broadest category, USC5 the most detailed category (Glass and Rosenthal, 2004). IMS Health Incorporated was able to group the drugs in the sample into 70 separate therapeutic classifications based on a USC2 level of description. The data show that the top 14 therapeutic drug categories are made up exclusively of prescription medications and account for 90% of the value of all sales to the United States through cross-border Internet pharmacies (table 2).

Figure 1: Canada-US distribution of total sales for the 278 Canadian-based cross-border Internet pharmacies identified by IMS Health Inc., moving annual total (MAT) to June 2005, CDN$ at manufacturer-level prices



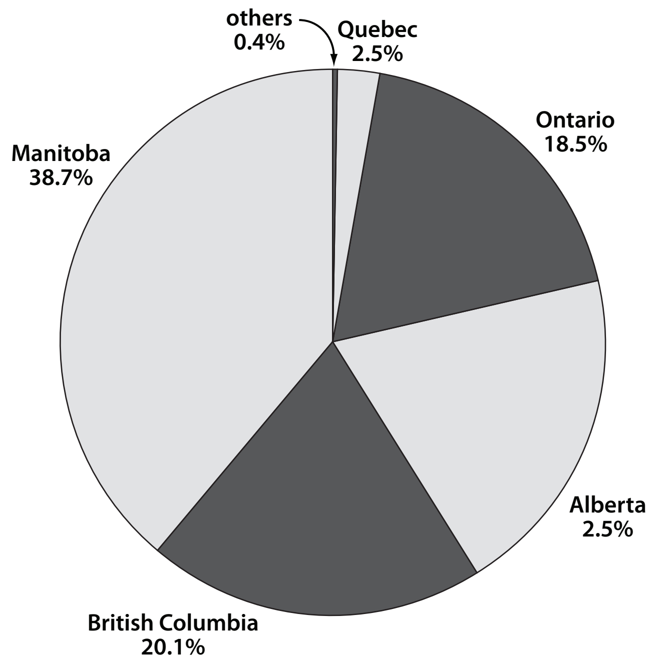
Source: IMS Health Incorporated, 2005.

Table 1: Provincial distribution of cross-border Internet pharmacy sales between Canada and the United States, as of June 2005

	Value (moving annual total [MAT] in CND$ at manufacturer-level prices)
Manitoba	$196,014,214
British Columbia	$101,808,933
Alberta	$99,902,925
Ontario	$93,882,479
Quebec	$12,818,801
Other	$2,215,441
Total	**$506,642,793**

Source: IMS Health Incorporated, 2005.

Figure 2: Provincial distribution of cross-border Internet pharmacy sales, percentage of the moving annual total (MAT) value of sales across 278 outlets, as of June 2005



Source: IMS Health Incorporated, 2005.

According to the data used in this study, the top five therapeutic drug categories ranked by value of sales to the United States through Canadian-based Internet pharmacies are cardiovascular drugs; antihyperlipidemic agents; hormones; psychotherapeutics; and antispasmodic/antisecretory medications. These five therapeutic categories account for 57% of the total value of sales to the United States through cross-border Internet pharmacies (table 2).

Drugs in these therapeutic classes are also among the most important to seniors (65 years of age and older) in particular. In fact, the data suggests that the cross-border drug trade might be heavily driven by sales to seniors because the most commonly prescribed therapeutic categories for seniors in the United States closely match the top therapeutic categories of drugs involved in the cross-border Internet pharmacy business (table 3). When ranked by annual personal expenses, the top five therapeutic classes for prescribed drugs purchased by the elderly (age 65 and older) in the United States in 2002 were cardiovascular agents, hormones, antihyperlipidemic agents, central nervous-system agents, and gastrointestinal agents. These five categories of drugs totaled US$36.5 billion and represented 73.1% of the US$49.9 billion total drug expenses of the elderly (persons age 65 and older) for prescription drugs in the same year (Stagnitti, 2005).

It should be noted that, without comparing the distribution of cross-border Internet drug sales by therapeutic category in the non-senior population to these findings, it is impossible to know for sure that there is a correlation between sales in particular drug classes and demand from American seniors. Data was not readily available to this study that would allow such an analysis. Nevertheless, the findings are consistent with the fact that the Canadian International Pharmacy Association (CIPA) openly markets to American seniors as a specific group and that seniors' advocacy groups in the United States are among the most active lobbyists in favour of the cross-border Internet drug trade.

Changes in the Canada-US cross-border internet drug trade over time

According to the detailed data sample obtained for this study, the estimated dollar value of cross-border Internet drug sales at TSA manufacturer-level prices has been steadily declining since about April 2004. IMS Health Incorporated's MAT TSA value of sales for the 12 months between July 2004 and June 2005 was nearly $507 million. This was down 18% from the MAT value of sales of approximately $618 million for the previous 12 months, between July 2003 and June 2004.

Until April of 2004, the dollar value of cross-border Internet drug sales had been rising. A monthly sales analysis over the longer term conducted by IMS Health for this study indicates that the value of sales to the United States through cross-border Internet pharmacies rose steeply from about $7.5 million per month in July 2002 to a peak of approximately $58 million per month in March of 2004. The data available to this study indicate that the dollar value of cross-border drug sales thereafter fell to about $37 million per month by June 2005, 36% below the level in March 2004 (figure 3).

Table 2. Cross-border Internet pharmacy drug sales by therapeutic category, ranked by MAT value of sales as of June 2005.

Rank	Therapeutic category*	Cross-border sales	Cumulative percent of cross-border sales
1	Cardiovascular	$80,394,797	16%
2	Antihyperlipidemic agents	$79,213,386	32%
3	Hormones	$46,473,012	41%
4	Psychotherapeutics	$41,068,262	49%
5	Antispasmodic/ antisecretory	$40,718,169	57%
6	Hemostatic modifiers	$39,380,368	65%
7	Neurological disorders, misc	$27,881,028	70%
8	Bronchial therapy	$19,175,722	74%
9	Antiarthritics	$16,752,954	77%
10	Cancer/ immunomodulators	$16,594,143	80%
11	Diabetes therapy	$16,451,244	84%
12	Anti-infectives	$15,053,745	87%
13	Ophthalmics	$8,181,106	88%
14	Anti-virals	$7,786,118	90%
15	Miscellaneous ethical	$6,884,423	91%
16	Antihistamines, systemic	$5,744,446	92%
17	Dermatologicals	$5,529,766	93%
18	Diagnostic aids	$4,112,069	94%
19	Cough/cold preps, ethical	$3,402,651	95%
20	Analgesics	$2,583,582	95%
21	Thyroid therapy	$2,280,509	96%
22	Nutrients & supplements	$1,998,131	96%
23	Muscle relaxants	$1,620,338	97%
24	Contraceptives	$1,577,577	97%
25	Diuretics	$1,420,479	97%
26	Hematinics	$1,183,521	97%
27	Sexual function disorders	$1,066,438	98%
28	Antinauseants	$944,018	98%
29	Analgesics, proprietary	$923,938	98%
30	Sedatives	$921,425	98%
31	Smoking deterrent, ethical	$914,113	98%
32	Anti-obesity ethical	$886,559	99%
33	Vitamins, ethical	$869,599	99%
34	Bile therapy	$784,231	99%
35	Biologicals	$742,405	99%
36	Cough/ cold preps, pty	$674,113	99%
37	Laxatives, ethical	$661,660	99%
38	Enzymes & digestants	$457,398	99%
39	Antimalarials	$308,724	99%
40	Infant formulas	$307,203	99%
41	Parasympathetics	$277,346	100%
42	Miscellaneous, pty	$232,702	100%
43	Hemorrhoidal preps	$222,647	100%
44	Antidiarrheals	$199,883	100%
45	Dermatologicals, pty	$196,291	100%

Rank	Therapeutic category*	Cross-border sales	Cumulative percent of cross-border sales
46	Suncare preps	$189,279	100%
47	Anesthetics	$168,973	100%
48	Antiseptics, proprietary	$143,165	100%
49	Antacids ethical	$141,539	100%
50	Lip protectors, pty	$112,085	100%
51	Antacids proprietary	$103,688	100%
52	Amebacide & trichomonacide	$102,010	100%
53	Foot preparations, pty	$99,407	100%
54	Antiseptics	$85,434	100%
55	Vitamins, proprietary	$64,829	100%
56	Denture care	$59,531	100%
57	Laxatives, proprietary	$49,666	100%
58	Anti-obesity proprietary	$47,781	100%
59	All others, unidentified	$45,123	100%
60	Hospital solutions	$42,543	100%
61	Sedatives, proprietary	$32,692	100%
62	Baby care preps, pty	$29,636	100%
63	Otic preparations	$20,215	100%
64	Fem hygiene preps, pty	$17,965	100%
65	Anthelmintics	$16,180	100%
66	Sweetening agents	$9,966	100%
67	Rubbing alcohol	$7,691	100%
68	Diuretics, proprietary	$1,102	100%
69	Asthma remedies	$47	100%
70	Antiarthritics pty	$9	100%

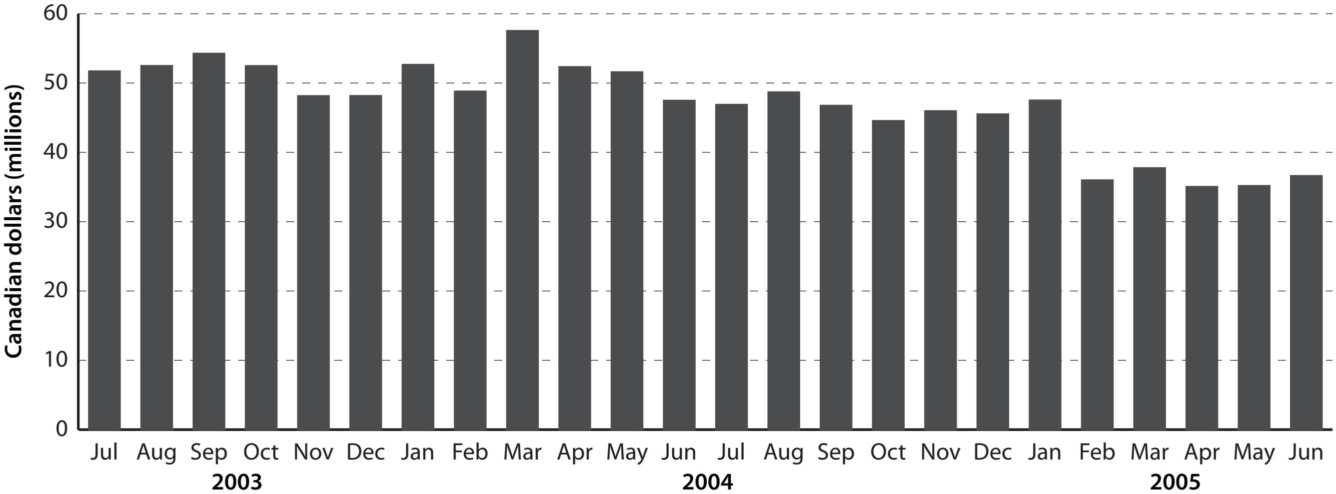
Source: IMS Health Incorporated (2005).
Notes: * USC2 description supplied by IMS Health Incorporated.

Table 3. Comparison of top therapeutic drug classes prescribed for American seniors and the top-selling drugs in the Canadian-based cross-border Internet pharmacy business to the United States.

Rank	Top selling drugs for seniors in the United States in 2002, by therapeutic category*	Top selling cross-border Internet pharmacy drugs, by therapeutic category**
1	Cardiovascular agents	Cardiovascular agents
2	Hormones	Antihyperlipidemic agents
3	Antihyperlipidemic agents	Hormones
4	Central nervous system agents	Psychotherapeutics (sub-category of central nervous system agents)
5	Gastrointestinal agents	Antispasmodic / antisecretory (for gastrointestinal related treatment of stomach cramps)

Source: Stagnitti (2005); IMS Health Incorporated (2005).
Notes: *Stagnitti's Multum Lexicon description; **IMS Health's USC2 description.

Figure 3: Estimated monthly total cross-border Internet pharmacy sales to the United States, July 2003 to June 2005



Source: IMS Health Incorporated, 2005: special data request.

The data available to this study was not capable of measuring the volume of sales defined by the number of prescriptions dispensed or units sold so it is difficult to know exactly whether the overall volume of trade is declining or whether the individual value of the particular products being sold has changed over time. However, an analysis conducted by IMS Health Incorporated on behalf of this study indicates that the change in the value of the trade is only partially related to declining demand from American consumers.

According to IMS Health Incorporated, the four major explanations for the reduction in the value of cross-border sales since early 2004 include:

- rising value of the Canadian dollar against American currency
- increase in the penetration of generics in the 15 months previous to June 2005
- manufacturer supply management initiatives (i.e., brand-name manufacturers are restricting supply to normal Canadian consumption levels)
- pharmaceutical products for the United States being sourced from countries other than Canada.

Figure 4 shows daily changes in the value of the Canadian dollar relative to the American dollar between July 1, 2003 and June 30, 2005. The data show that value of the Canadian dollar indeed rose steadily, increasing 9% against the US dollar over the study period.

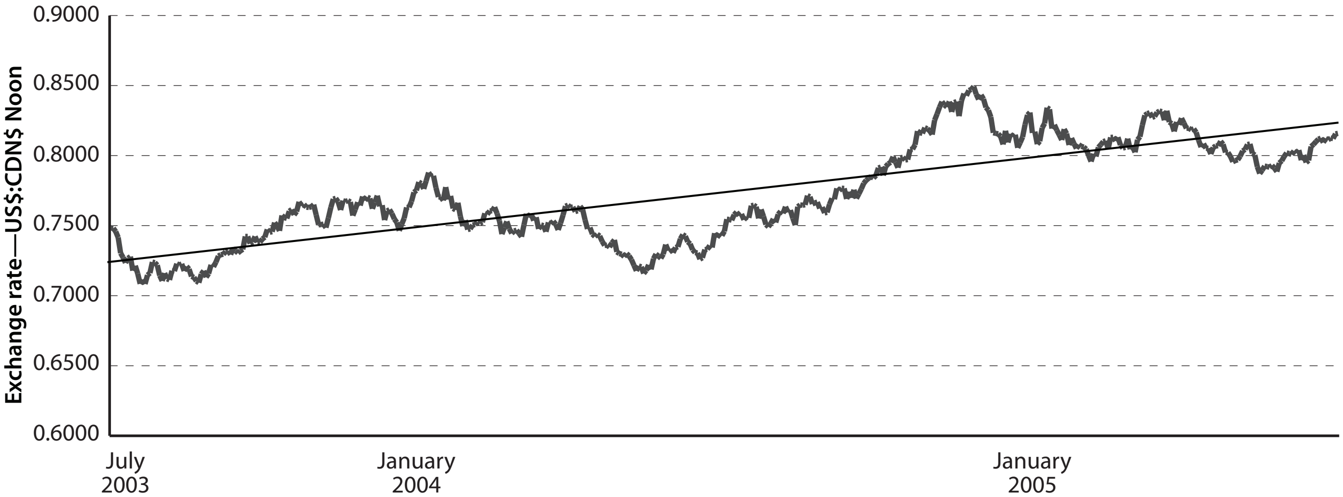
Total sales compared to generic sales

A comparison of the trend in total cross-border drug sales to the United States and the cross-border sales of generic drugs confirms another conclusion reached by IMS Health Incorporated's analysis: generic products are displacing brand-name products in the mix of drugs that are being sold through Internet pharmacies to Americans. Figure 5 shows how the monthly value of all cross-border Internet drug sales declined 29% between July 2003 and June 2005. At the same time, the monthly value of cross-border sales in generic products has steadily increased over the same time period, rising 70% between July 2003 and june 2005. Therefore, the shrinking value of cross-border sales is not solely reflective of declining unit volumes of the drugs being traded. This data indicates that generic drugs, of lower price relative to brand drugs, are accounting for a greater share of the cross-border product mix since April of 2004, thus largely explaining the drop in the overall dollar value of sales over time.

Patent status of cross-border drugs in Canada and the United States and risks to Canada's international trading relationships

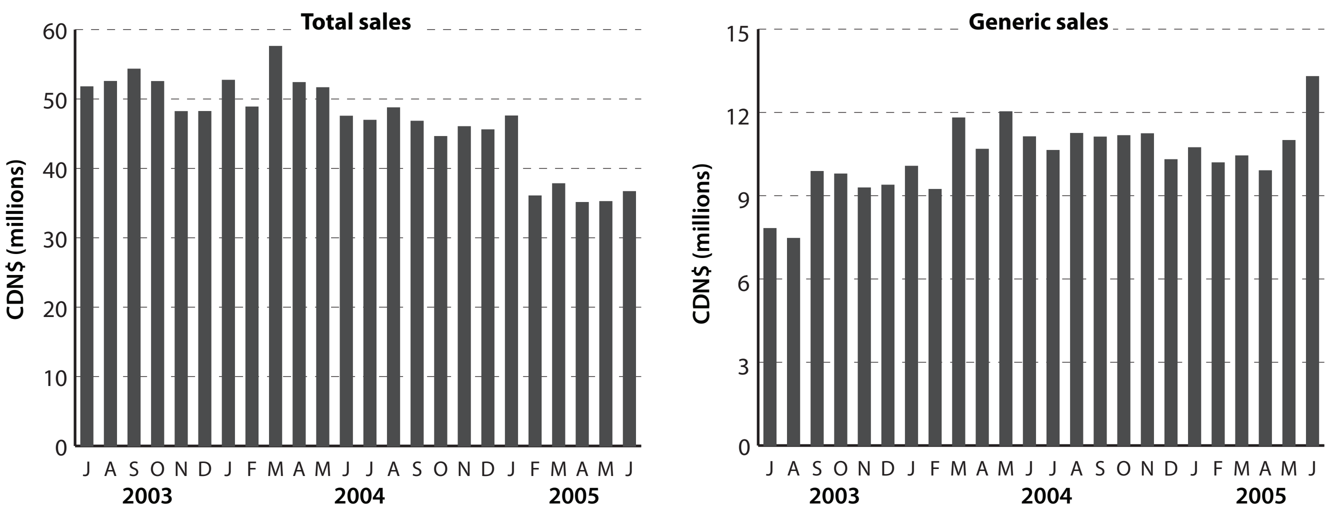
According to the data presented in figure 5, it appears that generic products are displacing brand-name products in the volume of drugs being sold to Americans through the cross-border Internet pharmacy business. The rising proportion of cross-border drugs accounted for by generic products is very surprising given that previous research has shown that 74% of the 100 most commonly prescribed generic products that were available in both Canada and the United States in 2003 were priced higher in Canada than in the United States, with the average price difference for this group of drugs being 116% higher in Canada after

Figure 4: Daily noon exchange rate of CDN$ against the US$, July 2003 to June 2005



Source: Bank of Canada, 2005.

Figure 5: Monthly cross-border Internet pharmacy sales to the United States—Total sales vs Generic sales, July 2003 to June 2005



Source: IMS Health Incorporated, 2005: special data request.

adjusting for currency equivalency (Skinner, 2005). Why would so many generic products be resold to Americans through the cross-border drug trade when they could be obtained more cheaply in the United States?

As mentioned above , one explanation is that brand-name manufacturers are restricting supply to normal Canadian consumption levels. By default, this reduction in the brand-name drug supply in Canada makes the generic proportion of cross-border drug sales rise as a percentage of the overall trade.

However, there is another explanation for the rise in the proportion of generic cross-border drug sales, an explanation that can be found in a comparison of the Canadian and American patent status of drugs sold in the cross-border trade. An analysis conducted by IMS Health Incorporated for this study indicates that 50 generic products being sold through Canadian-based Internet pharmacies to the United States have no generic equivalent south of the border (table 4). These 50 drug products accounted for $61.2 million in annual sales (MAT at June 2005) or nearly half (46.7%) the total annual value of generic cross-border drug sales to the United States through Internet pharmacies of $131.1 million (MAT at June 2005).

Clearly, it is irrelevant to American consumers that Canadian generic prices are much higher on average than American prices for the same drugs if there is

Table 4: Distribution of drug sales across 278 confirmed or suspected Canadian-based Internet pharmacy outlets by patent status in Canada and the United States, moving annual total (MAT) as of June 2005

Cross-border drug sample	Cross-border sales	Percent of total business	Canadian sales	Percent of total business	Total business
Top 500	$468,235,940	71.2%	$189,306,398	28.8%	$657,542,337
% total cross-border Internet sales	92.4%		n/a		n/a
198 Canadian generics in top 500	$131,130,748	80.0%	$32,797,777	20.0%	$163,928,525
% sales $ over top 500	28.0%		17.3%		24.9%
% total cross-border Internet sales	25.9%		n/a		n/a
50 of 198 Canadian generics non-genericized in US	$61,203,561	87.8%	$8,487,888	12.2%	$69,691,448
% sales $ over 198 Canadian generics	46.7%		25.9%		42.5%
% Sales $ over top 500	13.1%		4.5%		10.6%
% total cross-border Internet sales	12.1%		n/a		n/a
Total cross-border sales to United States	$506,642,793	69.8%	$219,089,387	30.2%	$725,732,180

Source: IMS Health Incorporated (2005).

no generic version available for the particular drug they need. Even a high-priced generic drug in Canada might be cheaper than the patented brand-name drug in the United States and so American consumers might still face a cost-savings incentive to import Canadian generic versions of drugs that are still under patent protection in the United States.

More importantly, in almost all cases the absence of a generic equivalent in the United States means that the drug in question is still under patent protection in the United States (table 5).[1] Therefore, almost half the annual value of cross-border generic drug sales going through Canadian-based Internet pharmacies are for drugs that are probably still protected by active US patents. If further research confirms this finding, the data suggests that Canadian cross-border Internet pharmacies are engaged in a massive theft of American intellectual property.

The negative implications of this finding for Canada's international trading relationship with the United States cannot be understated because the cross-border resale drug trade may violate the spirit, if not the letter, of the North American Free Trade Agreement (NAFTA), which specifically calls for member states to respect the intellectual property rights of its trading partners (Ladas and Parry, 1994). These findings could also have an impact upon Canada's global trading relationships. In fact, Canada is a member of the World Trade Organization (WTO) and is a signatory to the WTO's General Agreement on Tariffs and Trade (GATT) as well as the GATT's Trade Related Aspects of Intellectual Property Rights (TRIPS) provisions; all of which acknowledge the responsibility of member states to respect the intellectual property rights (patents) of its trading partners in these global agreements (Ladas and Parry, 1994). Canada's tacit approval of resale export activities that are primarily based on commercial advantages obtained by violating the intellectual property rights of its trading partners have the potential to damage our international trading relationships, and may be open to international legal challenges. This study, however, offers no definitive legal opinion on the matter and leaves this question to further research by experts in international trade and intellectual property-rights law.

1 In the few cases, where there was no comparable US drug product available, it was likely that the Canadian product being sold to Americans was not approved for sale in the United States, making it doubtful that these cross-border sales were even accompanied by a valid prescription issued by an American physician.

Table 5. Drugs that are not genericized in the United States (grouped by therapeutic category and active ingredient) that are being sold in generic versions (across 50 products) from Canadian-based Internet pharmacies to Americans

Therapeutic category*	Generic active ingredient	US patented brand-name version
antiarthritics	leflunomide	Arava
antiarthritics	meloxicam	Mobic
antihistamines, systemic	cetirizine	Zyrtec
antihyperlipidemic agent	fenofibrate micro	(various: Tricor, Triglide, Lofibra, etc.)
antihyperlipidemic agent	simvastatin	Zocor
antihyperlipidemic agent	pravastatin	Pravachol
anti-infectives	levofloxacin	Levaquin
anti-infectives	terbinafine	Lamisil
antispasmodic/antisecretant/antisecretory	domperidone	(no equivalent brand or generic)
bronchial therapy antispasmodic/antisecretory	salvent cfc freedomperidone	(various: similar to Albuterol) (no available product)
bronchial therapy antispasmodic/antisecretory	salbutamol hfa domperidone	(various: similar to Albuterol) (no available product)
cardiovascular bronchial therapy	carvedilol salvent cfc free	Coreg (various: similar to Albuterol)
hormones bronchial therapy	desmopressin salbutamol hfa	(various: Ddavp, Stimate, Minirin, etc.) (various: similar to Albuterol)
hormones cardiovascular	alendronate carvedilol	Fosamax Coreg
neurological disorders,hormones	lamotrigine desmopressin	Lamictal (various: Ddavp, Stimate, Minirin, etc.)
psychotherapeutics hormones	sertraline alendronate	Zoloft Fosamax
neurological disorders,	lamotrigine	Lamictal
psychotherapeutics	sertraline	Zoloft

Source: IMS Health Incorporated (2005) Notes: *USC2 description.

Canadian versus American consumer demand in the competition for Canada's drug supply

Understanding the characteristics and size of the American consumer segment competing for access to Canadian drugs through the cross-border pharmacy industry is important in estimating accurately the potential impact that this additional consumer demand might have on the Canadian drug supply. For the purposes of this study, total American demand is disaggregated and examined according to the following three criteria:

- consumer group characteristics
- individual versus bulk demand
- actual demand versus potential demand.

The distinction between individual and bulk demand is especially important because the Canadian International Pharmacy Association (CIPA) argues that they are opposed to "bulk" exports and only in favour of sales to individual American consumers (CIPA, 2005). Examining the size of the demand by individual American consumers for Canadian retail drug sales separately from bulk US demand will provide insights into whether it is feasible for Internet pharmacies to resell Canadian drugs to Americans even if they limit themselves to serving individual market demand from the United States alone.

Based on the evidence available to this study, the current cross-border demand in the United States for retail sales of Canadian drugs is largely composed of two groups that represent market demand for drugs that is individually driven:

- American seniors (65 years of age and older); and
- Americans without health insurance coverage.

Other consumer groups that have serious potential to enter the competition for access to Canadian drugs and that represent demand that is driven by "bulk" purchases include:

- federal, state, and local public employees; and
- recipients of public health insurance programs in the United States.

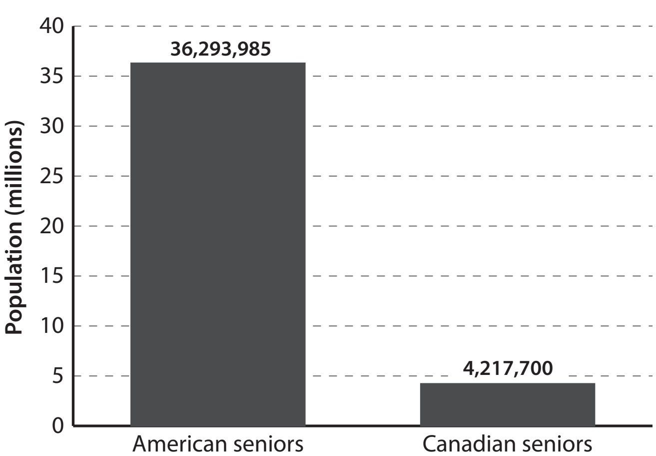
The following sections will quantify the size of these American consumer groups and compare them to the size of the current Canadian population to provide a context for estimating their impact on our drug supply.

Individual demand: American seniors and Americans without health insurance

The cross-border Internet pharmacy industry is represented by a number of trade associations, the most prominent of which is the Canadian International Pharmacy Association (CIPA). According the CIPA, their organization "is a non-profit trade association that represents 35 of Canada's leading mail-order pharmacies. CIPA's member pharmacies service about two million US patients, primarily seniors and the uninsured" (CIPA, 2005). Importantly, CIPA officials identify American seniors and Americans without health insurance as the specific target markets for its members. Based on this claim, we can estimate the size of this target market and compare it to Canada's own population of consumers.

According to the most recent data available to this study (figure 6), American seniors numbered about 36.3 million in 2004 (US Census Bureau, 2005). By comparison, Canada's current senior population is about 4.2 million (Statistics Canada, 2005). This means that there are approximately 9 times as many American seniors as there are Canadian seniors in the competition for a limited Canadian drug supply.

Figure 6: Population 65 years of age and older in the United States and in Canada, 2004



Source: U.S. Census Bureau, 2005; Statistics Canada, 2005.

However, the recent implementation of the US Medicare Modernization Act (MMA), which extended publicly subsidized drug benefits to most American seniors, may reduce the need for many American seniors to shop for drugs in Canada. There are three main publicly funded health-insurance programs that together cover most of the nearly 45% (Bureau of Labor Statistics, 2004) of total annual health-care expenditures accounted for by public funding in the US:

- Veterans Administration
- Medicaid
- Medicare.

Veterans Administration provides medical benefits specifically for American military combat veterans. Medicaid is a program that provides health-care benefits for those with low income, usually welfare recipients. Medicare provides medical benefits specifically for seniors (although there are some eligible non-senior recipients like the disabled).

In 2003, Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 to create new public drug benefits under Medicare that did not previously exist for seniors. The MMA established a basic out-patient drug benefit as Part D of Medicare and made it available on a voluntary basis to all Medicare beneficiaries; making eligibility for the Medicare drug benefits more universal than existing Canadian programs for seniors.

According to the US Congressional Budget Office (CBO), the standard drug benefit specified by the MMA for calendar year 2006 will have a $250 annual deductible; pay 75% of covered drug costs between $250 and $2,250; provide no further coverage until an enrollee has incurred $3,600 in out-of-pocket drug costs for the year; and pay about 95% of covered drug costs beyond that catastrophic threshold. The catastrophic threshold is defined in terms of the out-of-pocket costs that enrollees actually incur (CBO, 2004: viii).

The US Congressional Budget Office (CBO) estimates that 87% of current Medicare beneficiaries will participate in the drug benefit once it becomes available in 2006. Some of these would receive subsidized drug coverage through a former employer and thus would technically not be enrolled in Part D. This leaves an estimated 29 million seniors as recipients of the new benefit as of 2006 (Mays and Brenner, 2004).

The MMA also established subsidies for enrollees with relatively low income and countable assets. The subsidies will pay all, or a portion of, premiums and substantially reduce cost-sharing liabilities. It has been estimated that about 8.7 million people would be eligible for low-income subsidy benefits under the MMA (Mays and Brenner, 2004).

The MMA therefore introduces drug-benefit coverage to seniors who have until now been the target market for Canadian Internet pharmacies. This could have the effect of reducing demand from American seniors for lower-priced Canadian retail drug purchases. However, the deductible structure of the benefit and the fact that some seniors are not eligible for coverage at all under the MMA mean that seniors as a whole will still face significant out-of-pocket drug costs. This means American seniors may still demand drugs that are sold through Canadian-based Internet pharmacies. Also, as discussed later in this publication, there are accelerating legislative efforts underway in the United States to allow Medicare recipients to obtain retail drugs from Canadian pharmacies.

The other target market for CIPA is Americans without health insurance. According to the US Census Bureau's Current Population Survey (CPS), 45.8 million Americans lacked health insurance in 2004 (US Census Bureau, 2005). However, estimating the number of people without health insurance in the United States is subject to much debate because of the way that the US Census Bureau collects data on the issue. The problem is that government survey questionnaires overstate the uninsured population, possibly double counting many responses.

Table 6 illustrates the problems with the CPS. It shows the numbers for the estimated US population in each of the survey categories for health-insurance coverage. Note that the total number of people with private health insurance, government health insurance, and no health insurance exceeds the Census Bureau's estimate for the entire population of the United States, an obvious impossibility. The CPS also does not take into account the particular characteristics of the survey population, including:

(1) those who are uninsured only for a short period because they are between jobs and have temporarily lost employer-based health insurance, or who are students transitioning between family, school, and work coverage—according to National Survey of America's Families (NSAF), up to 47% of respondents (Kaiser, 2004);

(2) those who are eligible for public health insurance programs like Medicaid and SCHIP programs for children who are reluctant to enrol until the moment they require health-care services—approximately 33% of respondents (BCBS, 2005);

(3) those who have the income to buy health insurance but simply do not prioritize the purchase of health insurance—approximately 20% of respondents had annual incomes above $50,000; nearly half of this group had household incomes above $75,000 (BCBS, 2005);

(4) those who are uninsured for long periods of time because they lack employer-based insurance or the income to buy health insurance themselves—about 50% of respondents (BCBS, 2005).

The total numbers of people who are uninsured at any time for whatever reason, represent a potential market for Canadian-based Internet pharmacies of about 46 million people (US Census Bureau, 2005). However, based on the characteristics of the uninsured survey population, the best estimates of the actual long-term uninsured population in the United States is about 23 million (BCBS, 2005). Nevertheless, even this group by itself equals two thirds of the entire population of Canada of roughly 32 million (Statistics Canada, 2005).

Table 6: Inaccuracies in the US Current Population Survey (CPS) questionnaire regarding health-insurance coverage among Americans

Survey Response	Estimated population
Had private health insurance	198,262,000
Had government health insurance	79,086,000
Not covered at any time during the year	45,820,000
Total of Above	323,168,000
Total CPS US Population	291,155,000

Source: US Census Bureau, 2005.
Note: the percentages stated above do not total to 100% because some of the surveyed population is in multiple categories.

Bulk demand—US public employees and recipients of public health-insurance programs

To date, demand for bulk purchases of drugs supplied by cross-border pharmacies has not materialized due to the US federal ban on the reimportation of drugs sold outside the country. The national reimportation ban is enforced by the Food and Drug Administration (FDA) under the rationale that the safety of cross-border drugs cannot be assured because FDA-mandated standards do not apply beyond the borders of the United States. Despite the fact that the trade is illegal, numerous states have begun to mobilize support for its legalization and to lobby the

US Congress to permit states to make bulk purchases on behalf of public employees and those enrolled in public health insurance programs like Medicaid and Medicare. The size of the consumer populations targeted by the political efforts of American states to legalize the cross-border drug trade is quite substantial relative to the overall size of the Canadian population.

For instance, the US Census Bureau reports that the total number of full-time equivalent, federal, state, and local civilian employees of government is approximately 18.2 million people or approximately 57% of the entire Canadian population (US Census Bureau, 2005). It is also probable that the family members of these employees would be eligible to make cross-border purchases. The 2004 US census reports that the average American family size was 3.18 people (US Census Bureau, 2004). Therefore, the potential consumer segment represented by government employees and their families could be as high as 58 million or nearly twice as large as Canada's entire population. To be conservative, this study only includes the direct employee population of 18.2 million.

Additionally, just the number of people enrolled in state Medicaid programs (37.5 million, mainly recipients of social assistance) is 17% greater than the entire Canadian population and the number of Medicare beneficiaries (39.7 million, mainly seniors and the disabled) is 24% greater (US Census Bureau, 2005).

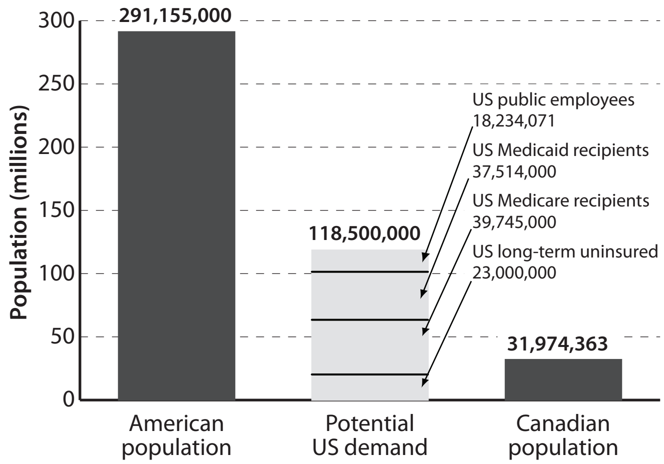
Total potential American demand for Canadian cross-border drug sales

If the estimated potential individual and bulk demand for cross-border drugs from the United States is totalled, it becomes apparent that the number of American consumers that might compete for access to the Canadian drug supply is nearly four times the size of Canada's entire population. The enormous size of the potential American consumer demand relative to Canada's population is shown in figure 7 and indicates that it is clearly not feasible for cross-border pharmacies to supply either their target markets (approximately 63 million customers between Medicare (seniors) and the uninsured populations) or potential bulk buyers (approximately 56 million customers between Medicaid and US public employees, excluding family members) (US Census Bureau, 2005).

Warning signs of increasing American demand for retail drug sales from Canada

It might be argued that the potential American demand for Canadian cross-border drug sales will not actually materialize. However, there are serious signs that the political momentum on this issue in the United States is accelerating. As mentioned earlier, legislative and political activities at the state level have been increasing dramatically in the last couple of years in an effort to put pressure on Washington to repeal its ban on the cross-border drug trade. These efforts are not limited only to the state level; the US Congress has seen the introduction of numerous bills as well.

Figure 7: Estimated size of American consumer groups competing for access to Canada's drug supply



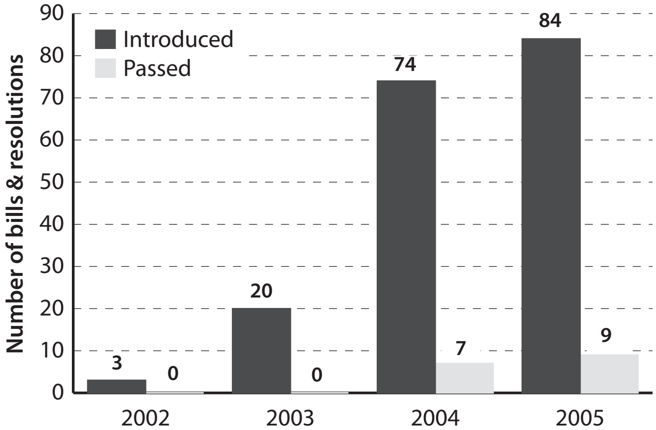
Source: U.S. Census Bureau, 2005; Statistics Canada, 2005.

One way to measure these trends is to count the number of bills that have been introduced by state and federal legislatures since the beginning of the cross-border drug trade between Canada and the United States. Figure 8 shows the number of state and federal bills introduced since 2002 (roughly the beginning of the Canada-US cross-border drug trade) that favoured the legalization of the cross-border drug trade with Canada or attempted to facilitate it. The number of bills and resolutions introduced annually has risen dramatically from three in 2002 to 84 as of September 2005.

Figure 8 also shows the number of these bills or resolutions that have passed since 2002. The data indicates that there is a build up of political momentum in favour of the cross-border drug trade with nine bills or resolutions passing by September 2005 compared with zero between 2002 and 2003.

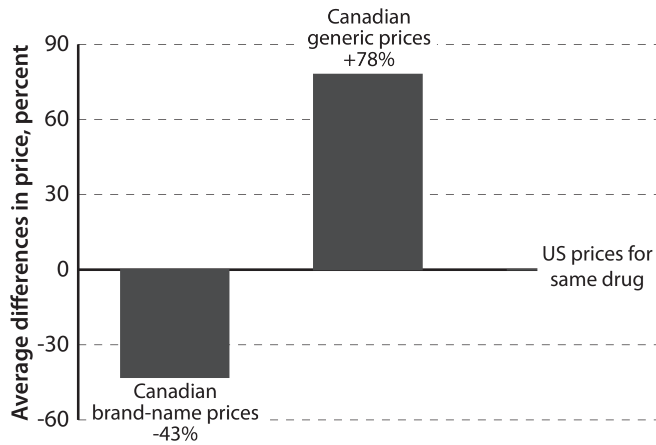
The statistics presented here are conservative because they do not even include the growing efforts of American cities and counties to legalize and facilitate the bulk purchase of drugs from Canadian Internet pharmacies for their public employees and the beneficiaries of local social programs.

Figure 8: Number of US state and federal bills and resolutions introduced and passed that favoured legalizing the cross-border drug trade, January 2002 to September 2005



Source: National Conference of State Legislatures, 2005.

Figure 9: Average differences of Canadian from US prices for the same drugs over the top 100 brand-name and top 100 generic drug products sold in Canada in 2003, PPP adjusted for currency equivalency



Source: Skinner, 2005; based on data from IMS Health Inc., 2004.

Economics of the cross-border Internet drug trade

Differences in drug prices driving the cross-border resale trade

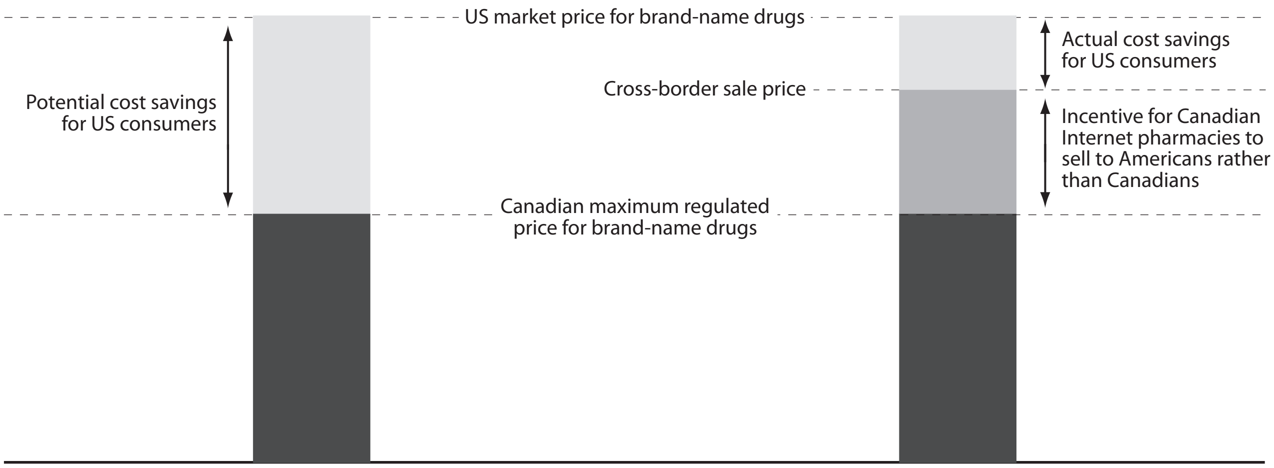
The difference between Canadian and American prices for brand-name drugs has created an incentive for Canadian Internet pharmacies to resell the Canadian drug supply to American consumers at a premium over the Canadian price. Previous research has shown that, after adjusting for currency equivalency, Canadian prices for the 100 top-selling brand-name drugs are on average 43% below American prices for the same drugs (figure 9). By contrast, the 100 top-selling generic drugs are overall, on average, priced 78% higher in Canada than in the United States (Skinner, 2005).

Not surprisingly, the data obtained for this study show that brand-name products accounted for 74.1% of the value of all cross-border Internet sales to Americans between July 2004 and June 2005, while generic products accounted for only 25.9% (see table 5). This pattern of sales is roughly consistent with the fact that 92% of the 100 top-selling brand-name products in Canada are priced lower in Canada than in the United States, while nearly 75% of the 100 top-selling (defined by the number of prescriptions dispensed) generic products in Canada (2003) are priced higher in Canada than in the United States (Skinner, 2005). As one would expect, lower prices on Canadian brand-name drugs create incentives for these particular products to be resold to Americans at a price that is below the US market price. The higher relative price of three-quarters of Canadian generic drugs explains why a relatively smaller percentage of these kinds of drugs are resold to Americans through Internet pharmacies: they can buy most of these drugs cheaper at home.

But a price incentive only accounts for about half of the sales of generic products through Canadian Internet pharmacies to Americans. Cross-border sales of generic drugs are also being driven as much by the fact that many of the drugs are still under patent in the United States. As mentioned earlier, almost half the annual value of cross-border generic drug sales going through Canadian-based Internet pharmacies is for drugs that are probably still protected by active US patents. The difference in price between an over-priced Canadian generic drug and the regularly priced patented version in the United States might still represent a significant savings to American Internet customers, but such savings are based on the theft of US intellectual property and are therefore not legitimate.

Figure 10 illustrates the components of the pricing economics that drive the cross-border resale trade in drugs. The first bar in the figure shows that the potential savings for consumers created by the difference between the American market price and the lower Canadian price create an incentive for Americans to demand drugs from Canadian retail pharmacies. The second bar in the figure shows how Internet pharmacies take advantage of Canadian government interference in the drug market that creates an artificial price ceiling for brand-name drugs sold in Canada.

Figure 10: Illustration of the pricing economics driving the Canada-US cross-border resale drug trade



Canadian Internet pharmacies buy their product at low Canadian prices, and then sell to Americans at a price that is far above Canadian prices but still much below the American price. The premium price that an Internet pharmacy can get from sales to Americans creates a profit incentive for them to favour American consumers and redirect the Canadian drug supply to them. Meanwhile, drug manufacturers are prohibited by federal price controls and provincial monopsony buying power from defending their global pricing strategies by raising Canadian prices. This fixes the differences between Canadian and American drug prices and allows cross-border Internet pharmacies to exploit the resulting market distortion at the expense of drug makers.

Explaining the differences between Canadian and American drug prices

There are valid economic reasons why drug companies charge lower prices in Canada than in the United States and also why they cannot afford to allow lower Canadian prices to be "imported" into the American market through the cross-border drug trade. Previous research indicates that across segmented free markets, the prices of drugs should be positively correlated to the average incomes in each market: that is, drug prices should be higher in wealthier markets and lower in poorer markets—a pricing relationship that is consistent for many non-pharmaceutical products as well (Danzon and Chao, 2000; Graham, 2000; Danzon and Furukawa, 2003).

Differential pricing between markets occurs because sellers find that the profit-maximizing price in a market depends on the level and distribution of income among buyers. A positive relationship between price and average income in a market is usually observed because average income is an important factor in determining consumers' willingness-to-pay in a market.[2] For the seller, the best price is the one that maximizes profits through an optimal combination of supply and demand for a product within each market (Varian, 1985). Thus, countries with higher incomes will generally pay higher prices for goods and services.

Hollis and Anis (2004) have explained how drug price differentiation between Canada and the United States has benefited Canadian consumers by providing access to drugs at lower prices; and also benefited drug companies

2 However, higher prices may sometimes be observed in poorer markets if a very wide income range characterizes the market. This is because average incomes are affected by the distribution of wealth in the market. For instance, a poor country may have a small minority of its population that is extremely wealthy while the bulk of the population is extremely poor. This will lower the average income (total income divided by population). If the domestic market cannot be segmented among consumer groups based on income or if the incomes of the poor are not high enough to buy at the lowest possible price, then it will only be profitable to sell to the smaller but wealthier population whose average incomes, if considered as a separate consumer group, are much higher. Furthermore, the profit-maximizing price will be set at the equilibrium of the wealthier consumer group. If this small group of consumers has higher average incomes than the average incomes in foreign markets, then its prices will be higher as well (Skinner, 2004).

because it allows them to maximize profits by selling their products at a price is matched to the different supply-and-demand dynamics in the Canadian and American markets. In other words, the interests of Canadian consumers and drug companies converge on the issue of differential pricing strategies. It is important to understand that lower prices on Canadian brand-name drugs are also likely just the normal result of market economics, not Canadian price regulations. There is evidence that even in the absence of price controls, the normal Canadian free-market price for drugs would likely remain much lower than American prices.

This is certainly the case with federal price regulations imposed by Canada's Patented Medicines Price Review Board (PMPRB). According to the PMPRB's 2002 to 2004 annual reports, manufacturers' prices of patented drugs fell by 1.2% in 2002, 1.1% in 2003, and 0.2% in 2004. These results continue the pattern of declines and near negligible increases in the Patented Medicines Price Index (PMPI) that began in 1993 (PMPRB, 2002: 21; 2003: 21; 2004: 22). Except during 1992, pharmaceutical prices have increased less than the general rate of inflation measured by the Consumer Price Index (CPI) in every year since 1988 (PMPRB, 2003). The 2004 PMPRB annual report again confirms that manufacturer's prices for patented (brand-name) drugs have grown slower than inflation every year since 1993 and actually decreased in eight out of the last 11 years (PMPRB, 2004). Notably, the PMPRB's price-control regulations limit price increases for patented drugs to the expected rate of increase in the CPI over a three-year period (PMPRB, 2003). Therefore, if drug prices are rising slower than they are allowed to, this would indicate that factors other than price controls are holding the prices of patented drugs down (Graham, 2000).

Federal price regulations also only apply to brand-name drugs while they are under patent protection in Canada. Once a branded drug's patent expires, PMPRB regulations no longer apply. Therefore, after a branded drug's patent expires, its price is determined by market forces, so that the price could rise if market conditions demanded it. However, research shows that branded drug prices do not rise significantly above the price-control level even after their patents expire and federal price controls no longer apply. For instance, Skinner (2005) examined a small sample of prices for Canadian brand-name drugs with expired patents (i.e., their prices are no longer regulated) and have no competition from generics or other patented or non-patented brand-name drugs in the same therapeutic class (i.e., prescription brand drugs with expired patents that have market exclusivity similar to, or stronger than, patented drugs). The research found that the prices of these drugs were at similar levels to drugs that were under price controls in Canada. This suggests that, if federal price controls on patented drugs were repealed, the price of patented drugs would not likely rise much higher than current levels in Canada. (However, such a result would only occur in the absence of a large and persistent cross-border resale drug trade.)

Hollis and Anis (2004) have also argued that Canadian federal price regulations do not adequately explain lower Canadian drug prices relative to those in the United States and suggest that a more likely answer is that provincial governments use the bulk-purchasing power of their drug programs to drive down drug prices in Canada. They attribute lower Canadian prices both to the price negotiating power of large provincial programs and the effect of lower Canadian incomes.

Problems created by federal price regulations and provincial monopsony buying power

Canadian prices should be lower than those in the United States due to the average income differences between the two countries. This should occur even if governments do not impose price controls. However, drug manufacturers can charge lower prices in Canada than they do in the United States only when the two markets are segmented; that is, when vendors can prevent customers who enjoy lower prices (Canadians) from re-selling their goods to customers who pay higher prices (Americans) (Schweitzer, 1997). If the cross-border drug trade undermines North American market segmentation, Canadian prices would be expected to adjust naturally in response to the increased market demand from the growing wave of American consumers and converge toward higher American prices.

Aside from normal demand-driven price increases, the growth of the cross-border trade should also be expected to create upward pressure on Canadian prices because drug manufacturers want to prevent Canadian prices from being "imported" to the United States, thus undermining global pharmaceutical pricing strategies. Therefore, drug companies would also have an incentive to raise the price in Canada to eliminate any artificial cost savings that are driving cross-border sales.

Existing Canadian pharmaceutical policies prevent such an increase in price. This is because Canadian regulations governing drug prices and provincial reimbursement policies prevent natural price movement above the status quo. For instance, Federal PMPRB regulations prohibit increases in patented drug prices above the annual rate of general inflation in Canada. This creates an effective barrier to normal market-driven pricing—with other negative consequences for consumers (Skinner 2005).

The large scale of provincial drug programs and the influence they have on drug prices in general is also a barrier to price increases above current levels in response to the cross-border drug trade. According to CIHI (2004), public drug programs account for about half the market (47%) for prescription drug sales in Canada. In Canada, the prices for prescription drugs in the rest of the market are similar to those obtained by provincial drug programs. This occurs because provincial reimbursement schemes act to create a single price at the wholesale level: retailers receive a fixed reimbursement from provincial drug programs; wholesalers sell at a single price to retailers; and manufacturers sell at a single price to wholesalers. But, the large market coverage of provincial drug programs coupled with the single price means that provincial programs influence the overall market price and exercise near monopsony buying power—effectively creating a price control for the market and distorting normal market pricing. In a competitive market, normal price negotiation among multiple, competitive, market buyers and sellers is perfectly legitimate. However, the monopsony power leveraged by provincial drug programs makes such negotiations unbalanced, harming the economic interests of sellers (drug makers) and distorting the market.

Economic choices facing drug companies

As illustrated above, American consumers represent an opportunity to capture a higher price and sell a larger quantity of drugs, thus creating a powerful profit incentive for Internet pharmacies to engage in reselling the Canadian drug supply to Americans. This would not be a problem if there were an unlimited supply of drugs available in Canada. However, the growth in the cross-border drug trade encourages drug makers to restrict their supply of medicines in Canada to normal domestic consumption levels in order to prevent Canadian prices from being "imported" to the United States.

Research-based drug companies cannot afford to have Canadian prices imported to the American market because their global price-differentiation strategies are designed to recover the significant research and development costs associated with bringing new drugs to market. Research indicates that inventing and developing a new drug costs on average between US$800 and US$900 million (DiMasi, 2002; Adams and Brantner, 2004). Most of the cost of this R&D is borne by Americans, who pay higher prices that match their higher average incomes.

In this context, drug manufacturers have only a few options to deal with increasing volumes of cross-border resale drugs.[3] First, in a competitive market, drug makers would simply adjust Canadian prices toward the American price level to eliminate the savings that are driving consumer demand for cross-border drugs. This is the easiest, most effective, and the least costly strategy for dealing with the cross-border resale drug trade. However, federal drug-price regulations and provincial drug procurement policies in Canada prevent this from occurring and so this option is simply not available to drug companies.

The next least expensive option is to minimize cross-border sales of drugs. The least expensive way of doing this is to supply the Canadian market only at levels that are consistent with normal Canadian demand. This would make the cross-border drug trade a zero-sum game: if Internet pharmacies were to redirect substantial portions of the Canadian drug supply to American consumers, it would result in equivalent shortages in supply for Canadian consumers. Such a strategy limits the damage that can be done to international pricing structures in pharmaceutical markets and puts the onus on the Canadian government to act to protect its domestic drug supply. Given that price regulations and provincial monopsony power is the cause of the cross-border drug trade, this assignment of the onus would seem appropriate.

The last option available to drug companies is to monitor their distribution networks and enforce wholesale distribution agreements that prohibit sales to cross-border pharmacies, assuming they can even be properly identified. This option is not realistic: it would be prohibitively expensive to implement, requires the bureaucratic assistance of Canadian law enforcement, and would do nothing to deal with "foot traffic" sales to American consumers originating from regular "brick-and-mortar" border pharmacies because there is no inexpensive way to identify whether sales were directed toward American rather than Canadian consumers among walk-in customers.

In any case, evidence exists to show that drug companies have revealed their preferences for the second option, implying that it is the least costly response. According to data obtained by IMS Health Incorporated for this study, as of June 2005 at least 10 of the largest brand name pharmaceutical companies supplying the Canadian market have implemented policies to restrict sales of drugs in Canada to normal domestic consumption levels. These companies include Abbot Laboratories, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Lilly, Merck Frosst, Novartis, Pfizer, Sanofi Aventis, and Wyeth (IMS Health Incorporated, 2005).

3 Hollis and Anis (2004) also outline some of these options.

Conclusions and policy recommendations

In previous research, Graham (2003) studied the cross-border drug trade and concluded that it posed a serious risk that research-based drug makers would stop supplying Canada with their products. Further, he calculated that importing Canadian prices generally into the United States would reduce the profits of research-based drug makers to such a degree that they would reduce annual investment in research and development (R&D) by US$5 billion to US$15 billion, the latter estimate being almost half of global pharmaceutical R&D for 2002.

More recently, Hollis and Anis (2004) studied the cross-border drug trade finding that Canada's Internet pharmacies pose a deep threat to our domestic drug supply and lower prices. They argued that the federal government should intervene and shut down the trade. Hollis and Anis acknowledged that since Canadian federal regulations prohibit drug companies from increasing prices at a rate higher than inflation, the manufacturers' only method of protecting their American profits would be to restrict supply to Canada, which could lead to shortages and eventually to higher prices. However, instead of calling for the removal of price regulations, they recommended that Canada take pre-emptive measures to prevent unauthorized exports of drugs whose prices are regulated by the Patented Medicines Prices Review Board (PMPRB).

This publications's findings agree with other research indicating that the potential growth in American demand for Canadian cross-border drug sales will seriously threaten Canadians' access to medicines. It also agrees with previous research in identifying Canadian drug price regulations and the leveraging of provincial monopsony power as the causes of the cross-border trade because such policies interfere in normal adjustments of market prices in response to increased demand by American consumers for Canadian resale drugs and threats to global pharmaceutical pricing strategies.

Remove public policies that distort the market for pharmaceuticals

The correct response to this situation, however, is the removal of the public policies that interfere in Canada's pharmaceutical market, distort drug pricing, and create artificial incentives for cross-border Internet pharmacies to divert our drug supply to a competing American consumer population.

Previous research has shown is that when there is no large-scale cross-border resale drug trade between Canada and the United States, price regulations are not necessary to keep Canadian prices low. This study has shown that when there is a large-scale cross-border resale drug trade, price regulations can cause market distortions by limiting the responses available to drug companies whose global pricing strategies are threatened by cross-border resale drug trade.

Such obstacles created by public policy force drug makers to choose the next least costly option, which is to restrict their supply of medicines to Canada. Therefore, it is recommended that federal price regulations be repealed and provincial monopsony buying power reduced so that normal market pricing can occur in Canada. Previous research has demonstrated that removing price controls and other misguided public drug policies would result in other significant benefits for Canadian consumers (Skinner 2004, 2005) in addition to eliminating the threat to our drug supply from the cross-border drug trade.

Patents and trade relations between Canada and the United States

This study also found that a large number of generic products are being sold to Americans through the cross-border Internet pharmacy business in likely violation of active US patents. These findings make it highly probable that American patent holders have legal recourse in American courts to stop the cross-border trade. The US government certainly has the legal and moral authority to ban imports of these generic drugs in order to enforce its own property rights laws. The findings also imply that American politicians who promote the legalization of the cross-border resale drug trade are inadvertently encouraging the massive theft of US intellectual property and, therefore, might be legally liable for the losses suffered by patent holders.

It is unclear whether the Canadian government is legally or morally obligated to impose an export ban on drugs that are genericized in Canada but still under patent protection in the United States because patent laws differ nationally and are not enforced across international borders. This study does not attempt to provide a legal opinion on this matter but offers some discussion points below.

Both Canada and the United States are signatories to the WTO's Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreement that was part of the World Trade Agreement of 1994. The text of Article 51 of the TRIPs agreement requires member countries to suspend the importation into their territories of "counterfeit trademark or pirated copyright goods" and permits similar action against "other infringements of intellectual property rights" (WTO 2005), which presumably would include patent rights. Article 51 thus justifies the United States banning the import of generic products identified as patent violators.

However, the requirements of TRIPs do not explicitly create a Canadian obligation to impose an export ban on generic drugs that infringe on patents in other countries. First, the text of Article 51 states that customs authorities in member countries are allowed to suspend the "release of infringing goods destined for *exportation* from their territories" but the provision does not require such action (WTO, 2005). Second, the text probably refers to goods that infringe on patents in the exporting country even though the patent-violating goods are not intended for sale in that country. But Article 51 does not necessarily refer to goods that infringe on a patent(s) in another country.

While it does not appear that Canada has an obligation under international treaty to ban exports of generic drugs that violate foreign patents, it is clear that the Canadian government could enact such a policy if it chose to do so. If such a policy could be enforced without adding a cost to Canadian taxpayers, then the gesture would be consistent with Canada's commitment to protecting intellectual property and, at least, maintain respect for the patent rights of our trading partners as implied in international trade agreements on intellectual property (e.g. TRIPs and NAFTA). Such a move could bolster Canada's international trading relationship with the United States in the process. This study makes no recommendation either way on this matter.

The only circumstance under which this study would recommend a general export ban on the resale of cross-border drugs is if governments stubbornly cling to misguided pharmaceutical price controls and insist on maintaining a provincial monopsony buying presence. If this were the case, then in order to protect the Canadian drug supply, an export ban would be appropriate for all prescription drugs whose prices are regulated by the Patented Medicines Prices Review Board (PMPRB) or affected by provincial monopsony buying power.

2 Background and special interests

Beginnings of the cross-border Internet drug trade between Canada and the United States

Andrew Strempler

American retail importation of Canadian prescription drugs via "online pharmacies" or "Internet pharmacies" emerged as a significant commercial business beginning in 2000. Andrew Strempler, a graduate of the University of Manitoba's pharmacy class of 2000, is credited with pioneering the industry. Strempler took advantage of the fact that Nicorette gum (a non-prescription pharmaceutical product that helps people quit smoking cigarettes) was cheaper in Canada than in the United States and began selling it on eBay directly to American online customers. Strempler's venture began by selling one box a week but increased to 150 sales per day within three months (Parloff, 2005).

Daren Jorgenson

At the same time, Daren Jorgenson, another graduate of the University of Manitoba's pharmacy program, began selling glucose-monitoring equipment over the Internet. Jorgenson claims to have asked US Food and Drug Administration (FDA) officials whether selling the equipment via the Internet was legal. In response, he said, an FDA official encouraged him to sell prescription drugs over the Internet due to urgent demand from American consumers and the high price disparity between Canada and the United States on brand-name pharmaceutical products (Parloff, 2005).

Exploiting the opportunity created by government price controls on prescription drugs in Canada, Strempler and Jorgenson set up profitable businesses reselling to Americans prescription drugs that were meant for distribution in the Canadian market, subsequently spawning the cross-border Internet pharmacy industry in Canada. By 2003, Internet pharmacies in Canada had developed into a big business.

The politics of the cross-border Internet drug trade between Canada and the United States

Canadian government

At the federal level, former Canadian Health Minister Ujjal Dosanjh introduced a bill late in 2005 that would have mandated that a Canadian physician personally examine each cross-border patient before signing a prescription for a medication. This would have erected serious logistical obstacles to conducting the cross-border trade. The bill also had provisions empowering the Minister of Health to monitor drug shortages related to the cross-border drug trade and to ban exports of those drugs on a case-by-case basis to protect the Canadian drug supply. The proposed legislation was not passed, expiring with the dissolution of parliament in November of 2005 and the launch of a general election.

US Government

At the federal level, officials of the Food and Drug Administration (FDA) oppose the cross-border drug industry, arguing that the practice is both unsafe and illegal. Since 2003, the FDA has taken serious measures to stem the flow of cross-border drugs into the United States (FDA News, 2003). President George W. Bush is also opposed to the cross-border drug trade and supports the FDA's stance that personal and bulk drug reimportation poses significant health risks for American consumers because of the inability of the FDA to enforce American safety standards on products that are sold through the cross-border trade.

Canadian pharmaceutical industry

The national trade association representing Canada's Research-Based Pharmaceutical Companies (Rx&D) is opposed to the cross-border resale drug trade. Their position is that the cross-border drug trade avoids normal medical and health controls that require patients to be examined by a physician before a prescription is issued. They also argue that the trade could trigger shortages of critically important medicines in Canada (Rx&D, 2003).

The national trade association representing Canada's generic companies, the Canadian Generic Pharmaceutical Association (CGPA) does not post a public statement of their position regarding the cross-border resale drug trade on their website. However, the CGPA does post their position on export restrictions in general, saying the association believes it "deserves the right to export pharmaceutical products to any countries where a product does not have patent protection and that the laws of a country where a product is being used should govern whether or not Canadian companies are allowed to sell it there" (CGPA, 2005).

American pharmaceutical industry

In the United States, the Pharmaceutical Research and Manufacturers of America (PhRMA), representing the leading research-based pharmaceutical and biotechnology companies in the United States opposes the reimportation of drugs from Canada. According to PhRMA, reimportation of pharmaceuticals creates real risks for American patients while providing no guarantee of cheaper pricing. PhRMA's position is that Federal laws banning reimportation reflect documented apprehension about the safety of imported drugs and the probability that many such drugs will be unapproved, adulterated, contaminated, or counterfeit. PhRMA's alternative solution is the expansion of drug insurance coverage for seniors under the new 2006 Medicare prescription drug benefit (PhRMA, 2005).

The US Generic Pharmaceutical Association (GPhA) is also against the reimportation of drugs that have not been under continuous supervision for safety by the FDA (GPhA, 2004).

Canadian retail pharmacies

The Canadian International Pharmacy Association (CIPA), a lobby group for online pharmacies based in Winnipeg, obviously supports the cross-border trade. CIPA's 35 member companies account for 80% of the cross-border Internet drug trade to the United States (Associated Press, 2004). CIPA is opposed to a proposal from former Canadian Health Minister Ujjal Dosanjh to require doctors facilitating the Internet pharmacy business by co-signing American prescriptions without seeing patients to conform to Canadian standards and only sign prescriptions for patients they have personally examined (CIPA, 2005).

The Canadian Pharmacists Association (CPhA), a national organization of mostly brick-and-mortar retail pharmacists, opposes the parallel drug trade due to concerns over the negative impact of this trade on Canadians, including many factors such as access to quality care, access to prescription drugs, and the threat to drug prices in Canada. CPhA also opposes the practice of co-signing prescriptions (CPhA, 2004).

In 2003, community pharmacists in Manitoba established the Coalition for Manitoba Pharmacy. Their main concern is the potential impact of the rapid growth of the parallel drug trade on Manitoba health care and access to medicines in Canada. The group is especially concerned about the prospects of state governments using Canadian pharmacies to source the bulk purchase of drugs (CNW Group, 2005).

American retail pharmacies

The National Association of Chain Drug Stores opposes the cross-border resale drug trade. Position statements of the organization indicate opposition to the cross-border trade both at the bulk and personal importation level (NACDS, 2004).

Canadian seniors organizations and other special-interest advocacy groups

In Canada, there are numerous special-interest groups endorsing the call for a ban on the cross-border drug trade. These include: The Canadian Treatment Action Council, CARP—Canada's Association for the Fifty-Plus, Canadian Pharmacists Association, Best Medicines Coalition, The Arthritis Society, Canadian Breast Cancer Network, Arthritis Consumer Experts, Canadian Hepatitis C Network, HepCURE, Canadian Arthritis Patient Alliance, Consumer Advocare Network, Manitoba Society of Seniors and the Coalition for Manitoba Pharmacy. In a joint statement, these groups asked the federal government to act immediately to end exports of prescription drugs. They also called on provincial regulatory bodies for pharmacists and physicians to monitor and, where necessary, discipline those members who are engaged in the cross-border Internet drug trade (CARP, 2005).

American seniors organizations and other special-interest advocacy groups

The Internet drug trade is largely driven by demand from American seniors as evidenced by the existence of groups like the Minnesota Senior Federation that encourage American seniors to buy drugs in Canada and lobby

American legislators to permit cross-border sales (Graczyk, 2004). Major supporters of the reimportation of prescription drugs to the United States include both the Alliance for Retired Americans (AARA) (Alliance for Retired Americans, 2005) and the American Association of Retired Persons (AARP) (AARP, 2004). These groups take the view that the cross-border trade is a safe and effective method of providing low-cost prescription drugs to American seniors who cannot afford US prices, but consider it a temporary solution.

Canadian health professionals and associations

Media releases in March and June of 2005, co-sponsored by the Canadian Medical Association, Canadian Medical Protective Association, Canadian Pharmacists Association, The Federation of Medical Regulatory Authorities of Canada, and the National Association of Pharmacy Regulatory Authorities have indicated that these groups are opposed to the cross-border resale drug trade. The main concerns of these groups are protecting Canada's drug supply, ensuring the safety of drug distribution, and ethical and safety-based worries about the practice of co-signing of prescriptions. The Colleges of Physicians and Surgeons in British Columbia, Saskatchewan, Manitoba, and Ontario are also opposed to the Internet pharmacy industry's reliance on prescription co-signing and have censured and fined doctors engaging in the practice.

The National Association of Pharmacy Regulatory Authorities (NAPRA), an umbrella association representing the members of 11 Pharmacy Regulatory Authorities (PRAs), oppose the resale of Canadian pharmaceutical products to Americans. The NAPRA wants to enforce a ban on exporting drugs via Internet sales until governments can implement systems to regulate the trade effectively (Pharmacy Post News, 2004).

American health professionals and associations

The American Medical Association (AMA), an advocate group for physicians and their patients, firmly believes that online pharmacies create threats to public health. However, the AMA is supporting prescription drug reimportation as a way to help reduce drug prices. According to AMA's policy on the issue, the association will support legalizing the importation of prescription drug products by wholesalers and pharmacies only if all drug products are approved by the Food and Drug Administration (FDA) and meet all other FDA regulatory requirements, pursuant to United States laws and regulations; the drug distribution chain is closed and all drug products are subject to reliable, electronic track and trace technology; and Congress grants necessary additional authority and resources to the FDA to ensure the authenticity and integrity of prescription drugs that are imported. The AMA is opposed to personal importation of prescription drugs via the Internet until patient safety can be assured (AMA, 2005).

The National Association of Boards of Pharmacy (NABP) supports the resale of pharmaceutical products from Canada to Americans. In response to public concern over the safety and conduct of Internet pharmacies, NABP developed the Verified Internet Pharmacy Practice Sites (VIPPS) program. The VIPPS program is a voluntary certification program available to Internet pharmacies. Through VIPPS, members of the public are provided with a means to assure themselves that the Internet pharmacy they choose is a bona fide, fully licensed, facility exercising competent Internet/interstate pharmacy practices. (NABP, 2005). The Pharmacy Boards of many states, on the other hand, oppose the cross-border trade.

First Nations

The ability of governments to restrain the cross-border resale drug trade in either Canada or the United States is complicated by the existence of semi-autonomous First Nations' reserves. For instance, Maine and Minnesota are considering the possibility of re-importing drugs from Canada by using the First Nations Sovereign status as a loophole. In Maine, Governor John Baldacci (D) gave the Penobscot Indian Nation $400,000 to build a warehouse and initiate a distribution program. In 2004, the governor requested a waiver from the US Department of Health and Human Services (HHS) to allow Maine residents to purchase their prescription drugs from Canada through the Penobscot Indian Nation (Gutknecht, 2005). US State governors have also discussed ways to facilitate the cross-border drug trade with provincial officials, reportedly offering to help build a casino and pharmacy on First Nation's territory close to where seniors travel in large numbers to local health facilities. First Nations' media sources have reported that one of the possibilities suggested was to build a pharmacy at the Seven Clans Casino in Thief River Falls to sell lower-priced prescription medications imported from Canada. According to the story, the joint Dakota Ojibwe Tribal Council already operates a pharmacy in Winnipeg licensed by the Manitoba Pharmacy Association (Miron, 2005).

Yellowhead Tribal Council (representing five First Nations groups in Alberta) is part of a broad coalition of special interests including seniors' and patients' groups that are allied in Canada to oppose the cross-border trade (CARP, 2005).

Appendix A: Legislative history of cross-border drug trade in the United States, 2002 to September 2005

Jurisdiction	Bill	Allows cross-border drug trade?	Status of law	Sponsoring political party
2002				
Illinois	S. 812	✓		Democrat
Arizona	S. 812	✓		Republican
New Jersey	S. 772	✓		—
2003				
New Jersey	A 570			Democrat
New Jersey	S 2598			Democrat
Vermont	HR 847	✓		Independent
USA	HR 780	✓		Democrat
USA	HR 2497	✓		Independent
Maine	SP 380	✓		Republican
Michigan	HB 4289	✓		Democrat
Michigan	BH 4473	✓		Democrat
Michigan	SB 69	✓		Democrat
Vermont	JRS 17	✓		Democrat
USA	HR 2427	✓		Independent
USA	HR 2769	✓		Republican
District of Columbia	B15-569	✓		Republican
New York	A 9298	✓		Democrat
Vermont	S. 276	✓		Republican
Illinois	SB 1769	✓		Republican
Massachusetts	S 494	✓		Democrat
Rhode Island	HB 5478	✓		Democrat
Vermont	H. 56	✓		Democrat
Vermont	S. 103	✓		Democrat
Florida	SB 484	✓		Republican
Pennsylvania	HR 155			—
USA	HR 2629	✓		Democrat
Nevada	SB 337		Passed	Democrat
2004				
New Jersey	A 1645	✓		Republican
USA	S 2137	✓		—
USA	S 2307	✓		Republican
USA	S 2328	✓		Democrat
New Jersey	A 2439			Democrat
New Jersey	A 3289	✓		Democrat
New Jersey	S 1231	✓		Democrat
Massachusetts	S. 2400	✓		—
New Jersey	A 3289	✓		Democrat
Virginia	HJ 199	✓		Democrat

Jurisdiction	Bill	Allows cross-border drug trade?	Status of law	Sponsoring political party
Wisconsin	SR 31	✓		Republican
California	SB 1149			Democrat
Louisiana	HB 894			Democrat
Tennessee	SR 158			Republican
Vermont	H. 502			Democrat
California	AJR. 61	✓		Democrat
California	SB 1144	✓		Democrat
California	SB 1333	✓		Democrat
California	SJR 25	✓		Democrat
Connecticut	SB 472	✓		—
Hawaii	HR 47	✓		—
Hawaii	SCR 27	✓		—
Idaho	HJM 16	✓		—
Illinois	HB 6787	✓		Republican
Illinois	HJR 56	✓		Democrat
Illinois	SB 2608	✓		Democrat
Illinois	SB 2609	✓		Democrat
Iowa	HSB 620	✓		—
Kentucky	SS-SB 7	✓		—
Massachusetts	H 4626	✓		—
Michigan	HB 5436	✓		Republican
Minnesota	HF 1998	✓		Democrat
Minnesota	SF 1966	✓		Democrat
Minnesota	HF 2293	✓		Democrat
Minnesota	HF 2697	✓		Republican
Missouri	SCR 28	✓		Democrat
Nebraska	LR 331	✓		Democrat
New Hampshire	SB 434	✓		Republican
Pennsylvania	HR 645	✓		Democrat
Rhode Island	H. 7199	✓		Democrat
Tennessee	HB 2173	✓		Democrat
Tennessee	SB 2545	✓		Democrat
Vermont	H. 728	✓		Democrat
Vermont	S. 288	✓		Democrat
Vermont	JRS 40	✓		Democrat
Virginia	HB 190	✓		Republican
Washington	HB 2469	✓		Democrat
Wisconsin	AB 785	✓		Republican
Wisconsin	AJR 71	✓		Democrat
Arizona	HM 2001	✓		Republican
California	AB 1957	✓		Democrat
Florida	HB 1347	✓		Democrat
Florida	S 3042	✓		Democrat
Hawaii	HB 1921	✓		Democrat
Hawaii	HCR 70	✓		—
Hawaii	HCR 80	✓		—
Hawaii	HCR 192	✓		—
Hawaii	HR 134	✓		—
Hawaii	SCR 125	✓		—
Hawaii	SR 63	✓		—
Hawaii	SB 2684	✓		Democrat
Hawaii	HCR 70	✓		—
Hawaii	SB 3045	✓		Democrat
Maryland	SB 167	✓		Democrat

Jurisdiction	Bill	Allows cross-border drug trade?	Status of law	Sponsoring political party
Wisconsin	SJR 46	✓		Democrat
New Jersey	A 2439			Democrat
Michigan	HB 5732	✓		Democrat
Michigan	SB 1095	✓		Democrat
New Jersey	S 1231	✓		Democrat
Florida	HR 3710	✓		Democrat
USA	S 2493	✓		Republican
USA	HR 4790	✓		Democrat
USA	HR 4923	✓		Republican
Connecticut	SB 8	✓	Passed	Democrat
Mississippi	HB 1434	✓	Passed	—
Mississippi	0	✓	Passed	Democrat
Rhode Island	H. 7320	✓	Passed	Democrat
Rhode Island	S. 2160	✓	Passed	Democrat
Vermont	H. 768	✓	Passed	—
West Virginia	HB 4084	✓	Passed	Democrat
2005				
USA	S 184			Republican
USA	HR 563	✓		Democrat
USA	HR 578	✓		Republican
USA	HR 700	✓		Republican
USA	HR 753			Republican
USA	HR 328	✓		Republican
USA	S 334	✓		Democrat
Tennessee	HB 1870	✓		Democrat
Washington	HB 1194	✓		Democrat
Connecticut	SB 45	✓		Democrat
Connecticut	SB 46	✓		Democrat
Connecticut	SB 126	✓		Democrat
Connecticut	SB 314	✓		Democrat
Connecticut	SB 1236	✓		—
Georgia	HB 887	✓		—
Hawaii	HR 139	✓		Democrat
Hawaii	HCR 187	✓		Democrat
Maryland	HB 65	✓		Democrat
Maryland	HB 231	✓		Democrat
Maryland	SB 742	✓		Democrat
Minnesota	HF 2117	✓		Republican
Minnesota	SF 1892	✓		Republican
Minnesota	SF 22	✓		Democrat
Missouri	HB 59	✓		—
Missouri	HB 859	✓		Republican
Montana	SB 310	✓		Republican
Nevada	AB 195	✓		Democrat
New Mexico	SJM. 8	✓		Democrat
Oklahoma	SB 544	✓		Democrat
Oklahoma	SB 977	✓		Democrat
Tennessee	HB 172	✓		Democrat
Tennessee	SB 841	✓		Democrat
Tennessee	HB 1096	✓		Democrat
Tennessee	SB 1112	✓		Democrat
Tennessee	SB 1989	✓		Democrat
Tennessee	HB 2021	✓		Democrat
Tennessee	SB 2134	✓		Democrat

Jurisdiction	Bill	Allows cross-border drug trade?	Status of law	Sponsoring political party
Texas	HB 173	✓		Democrat
Texas	SB 518	✓		Democrat
Texas	HB 3427	✓		Democrat
Texas	SB 601	✓		Democrat
Texas	HB 173	✓		Democrat
Texas	SB 518	✓		Democrat
Vermont	H 29	✓		Democrat
Virginia	HB 2005	✓		Democrat
Virginia	HB 2281	✓		Democrat
Virginia	HB 2348	✓		Republican
Virginia	HJR 632	✓		—
Virginia	HJR 718	✓		—
Virginia	SJR 391	✓		—
Virginia	SJR 411	✓		—
Virginia	HJR 683	✓		Republican
Virginia	SB 1246	✓		Democrat
Washington	HB 1316	✓		Democrat
Washington	HB 1884	✓		Democrat
Washington	SB 6020	✓		—
Colorado	HB 05-1152	✓		Democrat
Florida	SB 464	✓		Democrat
Florida	SB 2306	✓		Democrat
Montana	HB 364	✓		Republican
New Mexico	HB 601	✓		Democrat
California	AB 73	✓		Democrat
California	AB 74	✓		Democrat
Massachusetts	H 2748	✓		Democrat
Massachusetts	S 375	✓		Democrat
Massachusetts	S 400	✓		Democrat
Massachusetts	S 427	✓		Democrat
Ohio	SB 14	✓		Democrat
Oregon	SB 192	✓		Democrat
Pennsylvania	HB 613	✓		Republican
Pennsylvania	HB 715	✓		Democrat
Pennsylvania	HR 51	✓		Democrat
Pennsylvania	SR 43	✓		Democrat
Rhode Island	HB 5809	✓		Democrat
Rhode Island	SB 560	✓		Democrat
USA	S 109	✓		Republican
USA	S 16	✓		Democrat
Iowa	HF 610		Passed	—
Maine	HP 369/ LD 494	✓	Passed	Republican
Maine	SP 406/LD 1178 (LR50)	✓	Passed	Democrat
Maine	HP 923 / LD 1324	✓	Passed	Democrat
Nevada	SB 5	✓	Passed	Republican
Texas	SB 410	✓	Passed	—
Vermont	H 67	✓	Passed	—
Vermont	S 49	✓	Passed	—
Washington	HB 1168	✓	Passed	Democrat
Washington	SB 5470	✓	Passed	Democrat

Appendix B: Efforts by American cities and counties to facilitate the cross-border drug trade

City	Position / Situation
2003	
Montgomery, AL	Allows its 4,100 city employees and retirees to buy drugs from Canada; about 300 to 400 participate. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
New York, NY	Mayor Bloomberg has added his name to the roster of leaders calling on the FDA to permit states and cities to import prescription drugs from Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Pittsburgh, PA	Officials have expressed interest and asked State Rep. Don Walko to assist the city in reviewing its possible participation in program that involves buying drugs in Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Portland, ME	Considering and exploring the importation of drugs from Canada. Health and Human Services Department, Office of Elder Affairs, sponsored a one-day event at City Hall, during which 25 senior citizens were instructed by city staff on how to order prescription drugs from a Canadian-based mail-order company via the internet. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
2004	
Anchorage, AK	Mayor Begich is moving forward with a proposal to import prescription drugs from Canada for city employees. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Buffalo, NY	Resolution to investigate the issue of importing drugs from Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Burlington, VT	Information on city's official website, <www.ci.burlington.vt.us>. Prescription drugs from Canada are available for city employees and retirees covered by the City Health Plan, BurlingtonMed program. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Columbia, SC	Mayor has created a personal website to direct local consumers to Canadian pharmacies; city council is considering a link on the city's official site. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Newton, MA	Discussing the possibility of including re-importation of drugs from Canada in City of Newton health plan. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Palm Beach, CA	County Commissioner reported on the elements of importing plans from various government entities. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Revere, MA	About 1,700 employees, retirees, and their dependants who are enrolled in the city self-insurance health plan can begin to participate in a program that will allow them to purchase drugs from Canada; program is called Revere RX Direct; city will waive co-payments for drugs purchased through CanAm Health Source, a Montreal-based company. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>

River Fall, MA	Mayor Lambert announced a partnership with CanaRx Services to import prescription drugs to all residents and employees of the town. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Washington, DC	City’s official website <www.dc.gov> has link to Minnesota RxConnect. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Worcester, MA	Prescription drug purchasing plan for 9,000 people includes a limited option to buy medications from Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
2005	
Cambridge, MA	Exploring options on buying prescription drugs from Canada. <http://bernie.house.gov/documents/pharmbill/importation_announcement_10_20_03.htm>
Somerville, MA	Exploring options on buying prescription drugs from Canada. <http://bernie.house.gov/documents/pharmbill/importation_announcement_10_20_03.htm>
Wooster, MA	Exploring options on buying prescription drugs from Canada. <http://bernie.house.gov/documents/pharmbill/importation_announcement_10_20_03.htm>

County	Position / Situation
2003	
Caldwell County, NC	Passed resolution to encourage US government to allow US citizens to buy prescription drugs from Canada. Board of Commissioners asked the Human Resources director to research a Canadian prescription drug program. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Montgomery County, MD	Proposal to buy prescription drugs from Canada for county employees. Resolution No. 15-385 on securing lower-price prescription drugs for current and retired employees of county agencies. The resolution discussed the impact of the soaring price of prescription drugs and the arguments for and against enabling active employees and retirees to obtain these drugs from Canada. County Council voted to approve resolution to allow about 85,000 county employees, retires, and their dependents to purchase drugs from Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Westchester County, NY	Prescription drug plan includes a Canadian pharmacy option that allows residents to obtain medicines produced in America but sold at a significantly reduced rates in Canada. Program is open to all Westchester residents for an annual fee of $15 for an individual and $26 for a family. WestchesterRx is working with an intermediary that has relationships with various Canadian pharmacies. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
2004	
Lake County, IN	Under a proposed drug program, county employees would send their prescriptions by mail to Sav-Rx, which could then fill them with Canadian drugs. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Miami-Dade County, FL	Resolution directing the county manager to conduct a feasibility study regarding the importation of Canadian prescription drugs for county employees and senior citizens. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Monroe County, NY	Under a proposal, county officials would contract with Ontario-based CanaRx Services to conduct an analysis. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Orange County, CA	County Supervisor proposes to buy prescription drugs from Canada. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>
Prince George’s County, MD	County Executive Jack Johnson is reviewing the issue of importation. <http://www.gil.house.gov/issues/pdrugs/cityinfo.htm>

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