Evaluation of the online pharmaceutical market and counterfeit medicines: Development of a Risk based safety mapping of online pharmaceutical market

Doctoral (Ph.D.) Thesis

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List of abbreviations and acronyms

PPT - parallel pharmaceutical trade

GTDP - Good Trade and Distribution Practice

EAEPC - European Association of Euro-Pharmaceutical Companies

UK - United Kingdom

FMD - Falsified Medicines Directive

EU - European Union

GMP - Good Manufacturing Practice

GDP - Good Manufacturing Practice

POM - Prescription only medicines

DQSA - Drug Quality and Security Act

DSCSA - Drug Supply Chain Security Act

U.S. - United States of America

FDA - Food and Drug Administration

OTC - Over-the-counter

URL - Uniform Resource Locator

PMB - Pharmacy benefit management

DIMDI - German Institute of Medical Documentation and Information

GPhC - General Pharmaceutical Council

NABP - National Association of Boards of Pharmacy

VIPPS - Verified Internet Pharmacy Practice Site

WHO - World Health Organization

FBI - Federal Bureau of Investigation

TLDs - Top-level domains

PDE-5 - Phosphodiesterase type 5

ADRs - Adverse Drug Reactions

RFID - Radio-frequency identification

TAMC - Total aerobic microbial count

TYMC -Total yeast and mold count

IT - Information Technology

EDQM - European Directorate for the Quality of Medicines & Health-Care

FFCm's - Falsely labelled, falsified (counterfeit) medicines

NIPN - National Institute of Pharmacy and Nutrition

ISP - Internet service providers

SSL - Secure socket layer

VAWD - Verified-Accredited Wholesale Distributors

hGH - Human growth hormone

EAHP - European Association of Hospital Pharmacists

ASHP - American Society of Health-System Pharmacists

API - Active pharmaceutical ingredient

CZE - Capillary zone electrophoresis

ESI-MS - Electrospray ionisation-mass spectrometry

BGE - Background electrolyte

FIP - International Pharmaceutical Federation

EMA - European Medicines Agency

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Introduction and review of online pharmaceutical market and counterfeit medicines

The closed drug supply chain and new global threats in the drug distribution systems

Specifically, we define the legitimate supply chain as "any supply chain that is either regulated/ licensed by a ministry of health or other regulatory body [or] any supply chain where a patient would reasonably expect to obtain authentic product, supplied via a controlled supply chain, from the manufacturer of the product to the point of dispensing." [1, 2].

It is well known that the pharmaceutical supply chain is a very complex and tightly regulated network where the pharmaceuticals must be delivered at the right time to right place in a standard condition. The availability and accessibility of pharmaceuticals is crucial for every health care system and government, and if there is a minimal incompliance with the standards of production and distribution (Good Manufacturing Practice, Good Distribution Practice) it is highly likely that it will negatively effect individuals and the public as well [3].

The globalization of the pharmaceutical supply chain, the reduction of trade barriers and the augmentation of parallel pharmaceutical trade (PPT) practice have led to an extremely complex European pharmaceutical supply chain with many actors and participants. These include full-line European level distributors, European-level parallel distributors, national full-line distributors, European- and national-level short-line distributors, national-level parallel distributors, pharmacy distributors, distributor manufacturers, and micro-distributors (e.g.: short-line wholesalers, secondary wholesalers and wholesaling retailers, small import/export firms). The situation is even more complicated when processes like horizontal and vertical integration are taken into consideration. The supply chain now can be characterized as a transnational, interconnected and digital platform with various participants from all over the World [4-7].

As the complexity of the supply chain grows the medical products undergo multiple transactions from the manufacturing until the end-user patients. Consequently, the risk of falsification and substandard product penetration is increasing [8]. However, not all of the countries are exposed to the same risk, as in high-income countries the regulation of the drug supply chain ensures that most of the patients are receiving authentic and safe products compared to low- and middle-income countries (e.g.: Southeast Asia and sub-Saharan Africa) [6, 9].

Every EU Member State has a different regulation regarding pharmacy ownerships and chains. However these liberalization processes mentioned above serve consumer benefits (e.g.: greater product portfolio and price reduction), the regulatory authorities are struggling to track and control cross-European drug distribution as beside the central regulations of European Union regarding Good Trade and Distribution Practice (GTDP), there are several jurisdiction within the member state borders. Although there is a Parallel Trader Association Good Distribution and Manufacturing Practice Guidance published by the European Association of Euro-Pharmaceutical Companies (EAEPC), this document does not replace central legislation. This structure of the European drug distribution system is highly susceptible to the entrance of illegal and criminal actors/distributors. With the increasing complexity the practice of multiple repackaging and relabeling is growing. Not all EU countries implement regulation regarding these procedures and this practice is not consistent across Europe [7, 10].

These tendencies show similarities with the pharmaceutical supply chain of the United States which is a highly multi-layered system without consistent regulations between the different states and leading to the appearance of counterfeit medicines (e.g.: bevacizumab) with potential public health threat [10-13].

The challenge of providing effective and safe pharmaceutical distribution system in Europe is now further complicated by the rapid growth of internet and mail order pharmacy services [13]. Other unexpected complication to the European drug supply chain is the possible consequences of the fact that the United Kingdom (UK) will leave the European Union in March 2019. (This will happen 1 month after the realization of the Falsified Medicines Directive.) The phenomenon called BREXIT will impact the whole European drug supply chain with the potential threats of drug shortages and illegal counterfeiters that will hit UK citizens [14].

Regulations against counterfeit medicines and for the security of medicine supply chain in the EU

The core element of the European Union is the Internal Market (Art. 3 TEU) supported by different legal actions such as Directives (towards EU harmonization), shared competencies (legal actions by the European Parliament and the Council and the Member States against public health concerns in order to protect the health of the population), the full movement of goods and the restriction measure by EU Member States (In some cases the Member States can restrict the basic elements – such as free movement of goods – of the EU law e.g.: distance and cross border sale of prescription only pharmaceuticals; parallel exportation and drug shortages) [15, 16].

Therefore the European Union owns a legal framework that strongly regulates licensing, manufacturing and distribution of medicines. Only licensed pharmacies and approved retailers are allowed to sell medicines offline and online as well. In July 2011, the EU adopted the Falsified Medicines Directive (FMD, Directive 2011/62/EU of the European parliament and of the council) that aims to prevent the entrance of falsified medicines into the legitimate supply chain with the introduction of harmonized safety and strengthened control measures across Europe (**see Table I**.). The FMD will require most of the prescription only and some of the over-the-counter medications (black list) to have a unique 2D barcode identifier, (while the majority of the nonprescription medicines - white list - will not be included in serialization) tamper-proof seals will be used on their packaging and their authenticity must be verified before being dispensed to patients. The authenticity of the medicines will be verified by scanning a barcode on the pack of medicine against a central or national database (repository systems). The challenge of the implementation of this system can be highlighted with the number of 6000 pharmaceutical manufacturers and the approximately 10 billion packages of prescription only medicines (POM) dispensed annually in the EU [17, 18].

Beside the FMD, MEDICRIME (CETS No. 211) is another international instrument that is aiming the criminal law field on counterfeiting of medical products and similar crimes involving threats to public health. It helps to create and establish the legal protection of the victims of criminal activities such as medicine counterfeiting in the EU Member States [19].

Table I: Overview of the regulations against counterfeit medicines in the European Union [17, 18]

Safety features	Interpretation	Legislation
Safety features of medicines to guarantee medicine authenticity	A unique identifier (a 2-dimension barcode) and an anti-tampering device. Marketing authorization holders must place these on the packaging of most prescription medicines and certain non-prescription medicines no later than 9 February 2019.	Commission Delegated Regulation (EU) 2016/161
Supply chain and good distribution practice standards	New responsibilities for wholesalers and companies practicing brokering activities*. The EudraGMDP database includes information on good distribution practice (GDP).	Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 68/01)
GMP standards to active substances and excipients	From July 2013, all active substances manufactured outside the EU and imported into the EU have to be accompanied by a written confirmation from the regulatory authority of the exporting country. The EudraGMDP database includes information on good manufacturing practice (GMP).	Directive 2001/83/EC of the European parliament and of the council
Regulation of internet sale – common logo for authorized online pharmacies and approved retailers	The Directive has introduced from July 2015 an obligatory logo that will appear on the websites of legally operating online pharmacies and approved retailers in the EU. Clicking on the logo will link to the national regulatory authority websites, where all legally operating online pharmacies and approved retailers in their respective countries will be listed.	Directive 2011/62/EU of the European parliament and of the council

** A 'broker' is a person involved in activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.*

Regulations against counterfeit medicine and for the security of medicine supply chain in the United States

The Drug Quality and Security Act (DQSA) was enacted by Congress on November 27, 2013. Title II of DQSA, the Drug Supply Chain Security Act (DSCSA), outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. It will include the implementation of practices to improve detection and removal of potentially dangerous and counterfeit medications from the drug supply chain and establishment of national licensure standards for wholesale distributors and third-party logistics providers. The main elements of the security measures that will be implemented in the following years are summarized in **Table II.** [20, 21].

Other initiatives also exist to protect the consumers from the exposure to substandard or counterfeit medicines. These include (1) BeSafeRx, (2) Know Your Source and (3) Letters to doctors to ensure safe purchasing practices among consumers and health care professionals in the regular drug supply chain and through the internet [17]. Furthermore several guidance have been published by the FDA, such as the "Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry" [22]. The **Figure 1.** shows the overview of the different security measures and elements that are going to be implemented in the future in the developed countries to ensure patient and public health safety [23].

Table II: Overview of the major provisions of the Drug Supply Chain Security Act (USA) [20, 21]

Name of the provision	Explanation
Product identification	Manufacturers and repackagers are obliged to put a unique product identifier on certain prescription drug packages, for example, using a bar code that can be easily read electronically.
Product tracing	Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) in the drug supply chain to provide information about a drug and who handled it each time it is sold in the U.S. market.
Product verification	Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) to establish systems and processes to be able to verify the product identifier on certain prescription drug packages.
Detection and response	Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) to quarantine and promptly investigate a drug that has been identified as suspect, meaning that it may be counterfeit, unapproved, or potentially dangerous.
Notification	Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) to establish systems and processes to notify FDA and other stakeholders if an illegitimate drug is found.
Wholesaler licensing	Wholesale drug distributors to report their licensing status and contact information to FDA. This information will then be made available in a public database.
Third-party logistics provider licensing	Third-party logistics providers, those who provide storage and logistical operations related to drug distribution, to obtain a state or federal license.

Figure 1: Main elements of supply chain security [23]

Drug shortages – a global phenomenon

Drug shortages mean a complex global public health crisis [24-28] and have a great impact on provision of healthcare services from the early 2000s [29] as they are posing a challenge to ensure medication and patient safety [30]. Although there are different approaches in defining drug shortages all definitions emphasize a critical drug supply issue requiring change and affecting patient care [25, 28, 31-33]. We have to differentiate between general definition of a shortage (to designate a shortage event) and definition of drug shortages for reporting purposes. In case of the European Medicines Agency (EMA) the two definitions are the followings:

- EMA drug shortage definition: When the delivery of a medicine cannot comply with the needs of the patients, whether this is local, national, or international.
- EMA drug shortage reporting system definition: Medicines shortages that affect or are likely to affect more than one EU MS, where the EMA has assessed the shortage and provided recommendations to patients and healthcare professionals across the EU.

De Weerdt et al identified between October the 6th 2014 and April the 31th 2015. 26 unique definitions from legislator, governmental and professional organization perspective, in scientific articles and as a part of shortage reporting systems (national and European). An additional and detailed survey including 28 countries in 2017 by Bochenek et al found that only four countries are having (Belgium, France, Italy, and Spain) comprehensive descriptions. Also in Hungary there is not any concrete formal definition, it only appears as a term in the legislation, including the act requiring the Marketing Authorization Holders to report in case they are not able to supply a drug product [28, 31].

A uniform definition for drug shortages (general and reporting) is important to establish at national and at international level, as not only the data collection and shortage reporting, but the legal actions that can be made by the medicine agencies and other supply chain participants to mitigate drug shortages can be based on a concrete and accepted nomenclature [28, 31].

Causes and contributing factors of drug shortages may vary in countries and show a multidimensional nature both on the supply and demand side. Despite the variation there are similarities in the primary drivers, such as manufacturing problems, economic and health policy decisions [25, 32-40]. In Europe the leading cause of drug shortages can be linked to manufacturing and GMP compliance problems [40].

As the shortage of drugs is still a problem in Europe and the systemic data collection is lacking the European Cooperation in Science and Technology (COST), a European framework supporting trans-national cooperation among researchers, engineers and scholars across Europe, created a European Medicines Shortages Research Network in order to achieve a systematic sharing of information and research about past, ongoing and future shortages of medicines and nutritional products [41].

Shortages can result in compromised quality, safety and efficacy in the supply chain, with numerous negative therapeutic and financial consequences on patient care. In the United States 15 deaths happened due to shortages between 2010 and 2011 [25, 40-43].

Managing drug supply problems can lead to additional expenses (purchasing cost, labor cost, and cost of under-treatment) and higher workload as well. Latter may decrease direct patient care activities which can lead to the increasing number of medication errors [25, 26, 40, 41, 42, 46, 47]. Furthermore, other consequences not necessarily involved in the traditional supply chain also exist, such as the acquisition of unapproved or falsified medication from alternative sources [48-50].

The characterization of the online pharmaceutical market

Nomenclature, participants and categorization of online pharmacies

In recent years the Internet has changed every aspect of our lives, including communication and trade [51]. With the increase in the Internet use the online health information searches are also expanding. A U.S. survey found that 64% of the online population, while a European survey showed that 71% of Internet users searched for health information at least once in the previous 12 months [52, 53]. These tendencies are further facilitated by mobile devices [54]. Internet today is not only a resource for health information but an actual opportunity to obtain health services and products [55]. According to several surveys the percentage of people purchasing medicines online varied between 1 and 6% (published data differs due to type of product, sample population, educational and income status or substance abuse status) [56, 57].

During the last two decades the pharmacy supply chain has developed a new segment beside traditional "brick and mortar" pharmacies. The expansion of the Internet, consumer experience in online purchases, the ease of mail order trade and distance selling has facilitated the growing market of online pharmacies [58]. Changes in health seeking behaviour, patient empowerment and openness to self-diagnosis and self-treatment have also contributed to the phenomenon.

Different types of online drug sellers have been published earlier, and the authors have classified online pharmacies mainly according to legality and patient safety considerations [59-66]. As Internet pharmacies show a great diversity, it is most likely that no distinct categories can be specified, rather pharmacies on the Internet can be categorized by multiple aspects. In **Table III.** key aspects of categorization are summarize to describe different vendors on the Internet.

The terms Internet pharmacy, online pharmacy, e-pharmacy, mail order pharmacy, e-commerce pharmacy or cyber pharmacy have sometimes been used interchangeably. Although there is no clear definition, online/Internet pharmacies are entities that offer and dispense pharmaceuticals through an Internet website [55, 63, 67]. Mail order pharmacies have existed in the United States for more than a century [68] and during the past decades have extended their services online, becoming online retail mail order pharmacies. As the two categories today are closely related "mail order and Internet pharmacy" channel is considered as an entity in this thesis.

Table III: Categorization aspects of pharmacies on the Internet

Online and offline presence	The "**click and brick**" pharmacies offer online and offline services, while the "**pure online/Internet-only**" Internet companies do not have a physical pharmacy that patients can enter. There are also **corporate websites without e-commerce**.
Legality	**Legitimate pharmacies** are verified, monitored and adhere to laws and regulations. **Illegitimate/rogue vendors** fail to comply with national or international standards and regulations.
Prescription requirement	**Prescription only pharmacies** requests valid prescriptions written by independent medical doctor to be submitted, in contrast to **prescribing/online consultation pharmacies** where individuals must consult with clinician employed by online pharmacy to obtain prescription drugs. **No-records online pharmacies** dispense prescription drugs without any prior documentation necessary.
Operator and business model	Internet pharmacies can be operated by **local independent pharmacies**, by **pharmacy and/or drugstore chains**, or by a **mail order pharmacy** (USA) extending its service online. **Central pharmacy portals** are operated by a trade association, distributor or franchise partner involving independent pharmacies that offer order online and collect in-local store service. **Affiliate sites** are operated by individuals or companies and market another company's products or divert traffic to the merchant's site for a commission.
Product categories offered	Limited number of Internet pharmacies offer **solely non-prescription products** (OTC medication, herbal, personal care, cosmetics), as most sell both **prescription drugs and non-prescription products.** Some online pharmacies specialize on **lifestyle and embarrassment drugs** (erectile dysfunction, hair loss, obesity, etc.) or veterinary products.
Delivery of pharmaceuticals	Online pharmacies may offer **in pharmacy pick-up** or cooperate with **non-pharmacy pick-up points** (e.g. retail druggist chains). The logistical function can be provided by **mail or courier delivery**.
Geographical service orientation	Pharmacies can provide their services to the **local community**, to **domestic customers** within a country, or **trans-border** to reach international markets.
Digital/technical presentation	Majority of online pharmacies are **web based (e-commerce)** but popularity of mobile phones inspire companies to provide **mobile application (m-commerce)** services.

Language	Websites focusing on domestic customers are **monolingual**, as others serving international markets are **multilingual**.
Money transaction method	Payment occurs **within the website's URL** (e.g.: pharmacyglobalrx.com) or the **directs to another URL** for the transaction (e.g.: pharmashop-online.com to safecheckout.com)

Internet supply of pharmaceuticals has developed in numerous ways and according to different models in each part of the world due to diverse regulatory, economic and cultural environments. Globalization and the desire to increase market share has led to mergers in the industry which will likely blur international differences and facilitate the penetration of online services within the pharmaceutical supply chain.

North America

The drug distribution system in the USA is complex as drugs prescribed to outpatients can be filled by two channels: community and mail order pharmacies. Mail order pharmacy channel is well developed and takes a notable share of the pharmaceutical market in the United States, representing 21% of the outpatient expenditures [69].

As opposed to numerous other countries the distance sale of pharmaceuticals is well established in the US and the online mail service is well integrated to the distribution network [70]. Patients in the United States take advantage of the cost savings and convenience from buying 90-day quantities of prescription drugs for their chronic conditions. The US online prescription medicine market is driven by pharmacy benefit management (PMB) companies and patients are usually offered co-payment reductions if they use mail order pharmacies instead of retail pharmacies. The former is considered as the least expensive channel for the management of prescriptions due to lower dispensing and administrative costs. Although patients benefit from lower co-payments, there are mixed results in the literature regarding the savings that third-party payers realize, the effect on drug utilization and the generic drug dispensing ratio by mail order compared to community pharmacies [68, 69, 71-74].

The importation of drugs from Canadian online pharmacies, an estimate of 1 billion USD per year, is surrounded by debate [75-76]. Americans have realized that retail prices of brand-name drugs are significantly cheaper in Canadian pharmacies [76-78].

Canadian Internet pharmacies have received much attention about a decade ago and are considered as a controversial issue [79-84] as: in most circumstances it is unlawful for individuals to import prescription drugs for personal use from Canada to USA, importation threatens the integrity of the US drug supply chain and may also lead to Canadian drug shortages, Canadian pharmacies should receive a prescription of a Canadian licensed physician before dispensing [61, 76, 85]. Because authorities had limited resources for enforcement patients have been able to import prescription medications for personal use [61, 86]. The problem became even more complex as it was discovered that numerous rogue online operators aimed to take advantage of the positive discrimination of being Canadian [78, 80]. The tactic "hiding under the maple leaf" refer to websites that advertise themselves as Canadian but are actually registered in other countries. These fraudulent pharmacies sell drugs made in foreign countries or ones that are unauthorized in Canada [67]. In 2011 search engine Google has agreed to pay a fine of 500 million USD for allowing online Canadian pharmacies to place advertisements through its AdWords program targeting consumers in the United States [87].
In the United States only national and licensed pharmacies can dispense drugs via the Internet and it is illegal for non-US pharmacies to ship prescription drugs to the country. Typically, US patients are required to be examined by medical practitioner in person. In a similar manner only domestic storefront pharmacies with provincial license can operate Internet pharmacies and fill online orders in Canada. It is illegal for foreign websites to sell drugs to Canadian patients. As mentioned previously patients must see a Canadian physician in person in order to obtain a prescription [88].

European Union

While the mail order Internet pharmacy market in the United States is mainly prescription based, the European market is forming according to a non-prescription based model [70]. Comparison to the US is somewhat difficult due to different legislative and socio-economic background in EU countries. Online pharmacies are not covered by a specific EU legislation and Community legislation gives a framework at national and international levels [59]. In some "conservative" EU countries Internet pharmacy market is just starting to develop during the past years and individual pharmacies only have information websites without e-commerce. At the same time in other countries Internet driven distance marketing is present.

For example in the United Kingdom, Germany, Sweden, or Poland large pharmacy and druggist chains collaborate and operate e-commerce websites for numerous products including prescription only medicines. Online pharmacies in these countries develop online consultation services and promote in-store or even non-pharmacy pick-up opportunities [70].

Despite the fact that several EU countries - like the Netherlands or the UK - have legalized online pharmacy trade from the early 2000s, Internet sale of pharmaceuticals was not allowed in Austria and Finland until 2012, France permitted solely non-prescription drug sales in 2013, while Italy legislated e-commerce for national pharmacies in 2014 [70]. Some EU countries, such as Slovakia, Hungary, Italy, Belgium or France, do not allow e-commerce of prescription drugs. On the other hand the Swiss Internet pharmacy market is led by reimbursed prescription medicines [70]. European countries have different national regulations on online pharmacy services and the dispensing of prescription drugs over the Internet. The 2011/24/EU Cross Border Directive requires member nations to respect other nations' laws regarding online drug sales, consequently trans-border sale of prescription drugs within EU is typically not allowed [89].

In Europe probably the German online drug market has received the most attention in the literature, primarily due to the DocMorris case in 2004 [59, 90].

In late 2003 the European Court made a decision regarding the legality of cross border B2C mail order trading in pharmaceuticals. The case DocMorris challenged the German courts and is a historical milestone in the Internet pharmacy industry. I was said that the domestic control of online pharmacy marketing of nonprescription medicines in the EU both illegal and impractical, furthermore distance selling of prescription only medicines can only be prohibited on the grounds of public health safety and not for the protection of the local pharmacy monopoly. The rule of 'what is legal for sale in one Member State is legal in all others' is one of the founding 'freedoms' of the European internal market. This has been upheld in the European Courts ruling in the DocMorris case [70].

After the European Court of Justice ruling regarding the DocMorris case, restrictions on Internet sale and mail order of pharmaceuticals have been lifted and distance selling of medicines has become legal in Germany and consequently in numerous European countries. It is interesting to note that later in 2012 DocMorris was acquired by the Swiss pharmaceutical distributor Zur Rose Group, making it the one of the largest Internet pharmacy in Germany, Switzerland and Austria [70]. Currently it is legitimate to operate "only online" pharmacies (without a storefront pharmacy) in Germany, similarly to the UK [88].

Internet pharmacies shipping medicines to Germany from abroad or within the borders of the country must be licensed by the German Institute of Medical Documentation and Information (DIMDI) [88]. Years before the European Commission adopted the common logo for legally operating online pharmacies in 2014, the German DIMDI logo and the Registered Pharmacy logo of the UK General Pharmaceutical Council (GPhC) have existed [91].

United Kingdom is probably one of the most "permissive" countries in Europe from the aspect of Internet pharmacy market. Legal status of online pharmacies was established in 1999, and the same year Pharmacy2U the oldest solely online pharmacy in United Kingdom began its operation. GPhC registers pharmacies that are physically located in the UK and supply prescription drugs to UK citizens. Prescribing medications through online consultations is permitted, but this service is limited to customers within the United Kingdom [89]. In 2010 Boots.com while in 2011 Lloydspharmacy.com launched online doctor consulting and private prescription services [70]. Non-UK pharmacies – with permission – can ship prescription drugs to the country [88].

The European online pharmaceutical market is complex due to member states' different legislative, pricing and reimbursement background. It has emerged that e-commerce allows an indirect way of parallel trade for pharmaceuticals [90], that decreases transparency of the supply chain and raises patient safety issues [86, 93, 94].

Regulation and verification

Primarily legislative and economic background influences what customer segments legitimate Internet pharmacies target in different regions of the world. Websites can be viewed globally, thus subject to every country's law. Online pharmacies generate regulatory confusion as pharmaceuticals and health services "move" between jurisdictional boundaries [95]. In case of trans border trade, the country of operation and the country of delivery must be evaluated. The former determines the licensing regulations and the quality assurance standards for online pharmacy practice. The latter is just as important, because mail order must be performed in accordance with destination country's specific legislations on distance sale of pharmaceuticals. However, as many illegitimate websites are unwilling to indicate their real-world location, one cannot be sure of the regulatory framework under which the Internet pharmacy is operating [96]. Further, it is reprehensible when websites accept no responsibility for their dispensing practice and overcome legal differences and issues by placing burden of proof on consumers to check legislation for the country of delivery [97]. Unfortunately national authorities are typically powerless outside their own borders [98].

Although it has been mentioned that safety issues of Internet pharmacies originate from lack of regulation [62, 99], today it is not the case as license/registration and regulation is available in most developed regions. Indeed regulation may vary from a country or a state to another [85]. Despite the national legal differences there are a few internationally accepted obligations: *(a) prescription drugs shall not be dispensed without valid physician order, (b) medications authorized as controlled substance, medications not authorized or not approved for sale by national drug authority cannot be distributed, (c) pharmacies shall also be registered or licensed in the destination country, (d) sale of counterfeit, adulterated and illegal medications is considered a crime.*

Accordingly legitimate online pharmacies must comply with jurisdictions of the country of operation and also the country of delivery. Legality and safety of online consultations with physicians who have no personal face-to-face contact with their patients is a sensitive and debated issue [61].

One of the most important differentiating factors of online pharmacies is legality. Accredited and regulated online pharmacies allow consumers to purchase medications with confidence, while unregulated websites clearly present a danger. Further, verification/registration is of key importance, however does not necessarily correlate with clinical and patient safety issues as verification systems are not mutually recognized by countries. Regulated online pharmacies have been defined as those websites that are approved and verified, display and correctly link a regulatory logo [96], thus verification systems should be discussed briefly.

There are numerous verification systems worldwide but unfortunately legitimacy and verification system don't necessarily work trans-border [67]. Beside national governmental organizations private agencies also certify drug-selling websites. These services differ in certification standard, coverage, business model and certification outcome [85].

In the USA the National Association of Boards of Pharmacy (NABP) organizes the Verified Internet Pharmacy Practice Site (VIPPS) programme since 1999. The US-based online pharmacies must comply with laws of the business operation and the states that the pharmacy ship medications to. NABP requires voluntarily application and payment of a verification fee. Of the 55 accredited websites in the NABP's database majority are open to all customers, these include chain pharmacies (like walgreens.com) and pure online pharmacies (such as drugstore.com). The remaining are membership only sites that belong to PMB companies (caremark.com). The NABP reviews fraudulent operators and publishes the "Not recommended sites" list containing more than ten thousand entities [50, 85, 100, 101].

LegitScript.com is a private company that also only approves US based Internet pharmacies requiring valid US license, registration, contact information, user privacy protection and dispensing of drugs approved by the US Food and Drug Administration. LegitScript is a free service, not requiring application and consequently has a much larger database of more than thirty-five thousand active Internet pharmacies (0.7% legitimate, 5.8% potentially legitimate and 93.4% not legitimate) [85, 102].

Online pharmacies in the UK must register with the GPhC and can display the voluntary Registered Pharmacy logo which is verifiable on the authority's website [96, 103]. The German DIMDI registers pharmacies that have an official permit for mail order of medicines [104].

As of mid-2015 European countries have implemented the falsified medicines directive (2011/62/EU), consequently all mail-order pharmacies across the EU must be registered by national authorities and display the common security logo [105].

PharmacyChecker is an international certification agency requiring voluntarily application and certification fee. It is a private organization that allows price comparison among verified members that meet the criteria of: local pharmacy board license, prescription requirement, confirmed contact information, personal information protection and encrypted data transmission [105]. The organization's website does not provide complete list of approved members or unapproved rogue sites. It has been published that the private agency has less stringent requirements and has certified suspect online drug sellers previously [63].

Advantages and disadvantages

For many consumers who have no experience in purchasing medication and health related products from the Internet, online ordering may seem to be a vague or unnecessary option. Most likely due to the lack of experience some health-care professionals and participants of the pharmaceutical supply chain may underestimate the potential of this new segment. Then again, millions have realized the opportunity and benefits of obtaining drugs online. These customers are open to buy medications from the Internet but are generally not well informed about the potential unwanted effects [57]. For this reason the benefits/opportunities and the disadvantages/challenges of the online pharmaceutical market are explored briefly in multiple levels in order to unfold perceptions and activity of major stakeholders. Accordingly pros and cons are summarized from the patients', the drug distribution channel members' and the public health system's perspective to give a comprehensive review of this complex and also controversial issue.

Throughout the review the aim is to emphasize positive aspects as that Internet pharmacy market is developing rapidly and will play an important role in the future of drug distribution. As a matter of course there are numberless questions, debates and also dangers, which are also listed based on previously published papers [59, 61, 63, 96, 99]. It should be noted that majority of the articles emphasize public and patient safety concerns or regulatory issues, but the benefits and opportunities have not received adequate attention.

Patient and consumer benefits

Majority of the published articles mention the widely accepted benefits for customers, such as discounts, convenience, 24/7 ordering, big variety of available products, opportunity for price comparison [57, 59, 80, 93, 99, 106, 107]. Ordering online and picking up previously selected products in store allows fast and convenient service. By purchasing from foreign websites customers can exploit price differences between countries or access drugs affected by national shortages. If internet pharmacy websites are publishing professional information in additional to their web shops function, the provided online health and drug information resources may increase health literacy and provide opportunity for patients to ask health or drug related questions at any time of the day [61]. As there is no face to face contact with pharmacists, the "assumed anonymity" in case of sensitive personal questions can be an added value for customers [61, 62, 99]. An online pharmacy software can integrate modules that provide additional services, such as refill reminder programme, automatic drug-interaction detection for prescription only and over the counter products [61, 63], or facilitate online adverse drug reaction reporting [61]. By integrating in store, online and mobile channel companies can provide seamless shopping experience, the same experience online as in stores [70]. Although contradictory to mention it as a benefit, but patients can illegally access medication without prescription [108].

Opportunities for pharmacies

Naturally e-commerce allows pharmacies to reach broader clientele with a less costly infrastructure [59]. Compared to conventional in store sales pharmacies can achieve reduction in product cost due to rebates, lower inventory costs and dispensing fees. Computerization can reduce prescription errors and identify drug interactions [66].

Further, the digital world offers new marketing opportunities (brand building, personalized communication, loyalty programmes, analysis of the "big data" and consumer behaviour, conversion rate optimization, etc.) and services (refill programme, online chat, purchase online and pick up in store service, etc.) [70].

Benefits for health systems

Online pharmacies, similarly to mail order pharmacies make drug supply accessible in remote areas [66]. Third party payers can expect health care cost savings as a consequence of discounts, active generic substitution, volume control and formularies [66].

Internet pharmacies can efficiently handle and dispense drugs for chronic conditions prescribed on electronic prescriptions. Readability of electronic orders and e-prescriptions compared to paper prescriptions is undeniably better, accordingly Internet based commerce may reduce prescribing and transcribing errors within the healthcare system [109].

Threats for patients and consumers

Most commonly communicated disadvantage is the lack of personal interface and personalized information exchange or counselling from a pharmacist. There are some added services of in-store professionals (blood pressure monitoring and blood glucose testing, motivational interviewing, etc.) which cannot be managed over the Internet. Online consultation clinics and pharmacies examining patients' self-reported medical history are argued to provide substandard medical practice due to no prior doctor-patient relationship and personal examination [61, 63]. Mail or courier service typically requires few days for delivery. Consequently customers either have to wait more time compared to purchasing drugs in storefront pharmacies, or have to pay additional fees for faster service [59, 110]. Patients can receive delayed answers for their online questions [99]. Customers may not be aware that the use of websites is not actually anonymous as "cookies" collect information about visitors [61, 80, 111, 112]. Mail order delivery can negatively affect the integrity and product quality of medications due to inappropriate storage and handling conditions (e.g. extremes in temperature, humidity or mechanical effects) [62, 99]. These negative consequences apply to legitimate Internet pharmacies, as such disadvantages originate from distance sale and the lack of personal encounter with the pharmacist.

Challenges for the legitimate pharmacies

Online pharmacies result in loss of market share for their offline counterparts and the competition for the market may lead to lower margins due to lower prices. Because there is a limit regarding the number of orders that pharmacists can dispense or supervise daily beside their regular routines, pharmacies may have to employ additional pharmacists to process growing volumes of online orders. Similarly, immediate availability of a pharmacist for the online questions requires extra effort and workload. Packaging, handling and mailing account for additional special costs. Losses, theft or late delivery may accompany mail or courier delivery resulting in additional expenses and customer dissatisfaction.

Moreover the illegal vendors and problems associated with the Internet trade of pharmaceuticals may have a bad influence on the reputation of the pharmacy profession and the legal Internet sale of medication as well [113, 114].

Challenges for health systems

Availability of medications on the Internet can directly or indirectly increase health expenditures. Online pharmacies and corporate websites advertising prescription drugs for consumers facilitate prescription drug use [115]. Most countries have developed closed drug supply chains, thus the untraceable importation of drugs threatens the integrity of these well-regulated national systems [61]. The tax fraud and money laundering committed by fraudulent websites may have further substantial economic consequences [116]. It must be stressed that public confidence in health systems are also eroded and credibility of the regulatory and law enforcement agencies are undermined because of bad experiences from ineffective or harmful counterfeit products [116]. When purchasing prescription drugs from illegal websites without health care supervision the individual becomes a consumer instead of being a patient. Rogue operators do not offer continuous oversight or responsibility of the therapy and health status, and as a complication or health problem occurs (e.g. overdose, interaction, addiction, adverse drug reactions, etc.) the consumer must turn to the traditional health care system and become patient again, with its economic consequences as well [117, 118].

According to 800 reported cases in the WHO global surveillance system since 2013, the consequences of using falsified medications can be divided in two big groups: adverse reactions account for 10% and the rest is therapeutic failures without adverse reactions (90%) [82]. According to estimations these adverse reactions and therapeutic failures originate from counterfeit drugs causing over 1 million deaths annually in the developing countries [79, 84, 119].

Poor therapeutic outcomes for individuals and higher morbidity and mortality rate for the whole society are consequences as well [71, 79]. The illegal online purchase of anti-infective medications can contribute to the growing problem of antibiotic resistance [30, 120]. Considering the events of recent years, the risk of a terrorist attack through online pharmacies cannot be excluded [121, 122].

Because of the information asymmetry within the pharmaceutical market and the above listed complexity of Internet based drug purchases, consumers and patients are liable to overestimate actual and presumed advantages, while at the same time underestimate or ignore the risks [116].

Falsified medications and illegal online pharmacies

The characteristics of illegal online trade of counterfeit medications

Counterfeiting is one of the fastest-growing businesses in the World [79], with estimations ranging from 70 billion to 200 billion US dollars market value [119] and showing a 25% increase annually [93]. The proportion of counterfeit medicines globally is approximately 10% [123, 124] and may exceed 30% comparing to the whole medicine sale in developing countries such as Africa, Asia, India and Latin America [79, 125]. In the developed countries less than 1% of prescription medications are believed to be counterfeit [126].

Although we mainly have indirect pieces of information regarding illegitimate vendors, it is likely that illegal online pharmacies outnumber legitimate counterparts [58, 63]. Google search for the term “online pharmacy” revealed that more than half of search results were linking to fraudulent sites [127]. The Federal Bureau of Investigation (FBI) estimated in 2008 that there were up to 80 000 illegal pharmacies where patients could place orders [58].

The problems regarding these estimations originate from the followings: (1) there are several national definitions and classification systems defining counterfeit/falsified drugs; (2) the suspected cases are underreported to authorities; (3) there is a lack of validated and integrated databases; (4) illegal sites may use several URLs and have temporal presence in search engine results [63, 86].

According to the survey of the National Association of Boards of Pharmacy (NABP) in 2017, the 95,7% of 11 749 online pharmacies were noncompliant with the U.S. legislation and standards (in 2013. it was 97%) [128, 129]. These sites are listed as Not Recommended in the “Initiatives” section of the NABP website, www.nabp.pharmacy. Of the websites identified as Not Recommended, the majority were found to be dispensing prescription drugs without a valid prescription [128].

In 2016 based on industry data (LegitScript) there were 30 000 to 35 000 illicit online pharmacies and most of them offered drugs without prescription (approximately 92%). The risk is on a daily basis as it is estimated by the LegitScript that about 20 illicit online pharmacies are created each day with a possibility of slowing down in the future. 82% operated in English, 9% in Japanese, 3% in Chinese and 2,4% in Russian, and it is notable that roughly 10-15% of the internet pharmacies changed their language based on the visitor's geolocation. The large number of the illegal vendors (>85%) offer shipment to the United States, which is confirmed by the fact that the server locations are mainly in the United States (51,70%), following with 5,83% by the Netherlands [130]

Also it is worrying that 9-10% of them were selling controlled substances without any regulatory overview and prescription requirement. Notably these numbers reflect website numbers and not sellers, as actors operate multiple websites and approximately the number of the primary actors varies between 2000 and 3500. Further important characteristics include the Top-level domains (TLDs) being used by rogue/unapproved internet pharmacies and the most commonly used top-level domains are .com (59%), .net (11%) and .ru (9%) [130], highlighting global operation.

The aim of illegal operators is to by-pass prescription requirement and their marketing strategy focuses on the uncontrolled sale of prescription drugs [72]. These "rogue" vendors use selling arguments emphasizing the most commonly referred benefits of e-pharmacies (convenience, speed, discounts, privacy, etc.) augmented with the option of getting drugs without visiting a physician, special and bulk discounts, combinations of "recently bought together" products. Lack of communication regarding adverse-effects can considered to be part of the marketing communication as such misinformation is further promoting the sale of medications.

Pricing strategies include: extra price for POMs without prescription, unit cost decreases with quantity, promotion of unknown cheaper generics/brands from developing countries [72]. The main characteristics of this illegal market segment consist of trading of seemingly identical products [79] in an uncontrolled environment with no restrictions on the consumers (e.g.: no pricing and advertisement practice, people under 18 can also purchase medications via the Internet [51]) and on products (larger quantities [131]) from a large amount of virtual supply [79, 80]. Illegal online vendors operate with very high volume of transactions [1] resulting in enormous profit margins [79-81]. Owning to inappropriate regulatory circumstances, developing countries provide a good environment to the illegal Internet pharmacy operators [132]. The complexity and ecosystem of the illicit only pharmacies is highlighted in a schematic **Figure 2**. [56, 133].

There are no or minimal barriers for illegitimate individuals to enter the virtual medication market. Therefore minimal investment and expertise is required to create a website [93] and also the technologies are available on the Internet (e.g.: pharmaceutical machinery and printing technologies) [81, 134-135]. Furthermore, the ingredients to create a bogus drug can be found on business-to-business websites such as alibaba.com [136].

With the use of the same complex network (such as illegal drug dealers) and the off-shore location of operators, it is almost an impossible challenge to combat against their activity [84, 137] in the environment of insufficient international regulation and law enforcement [56].

As industrial (LegitScript database) monitoring provides valuable data since 2008 and therefore future trends and shifts can be observed in this marketplace. It is well known that illicit actors are unable to participate in online advertising through customer's search engines globally, and therefore there is an emerging trend to social media (e.g.: Facebook, Twitter, etc.) or combined activities. With the use of social media the operators of illegal internet pharmacies can reach more patients/consumers even at a younger age in a cheaper way. Also it was observed that there has been a shift from the illicit online sale of controlled drugs to the offer of "psychoactive highs" (e.g.: synthetic cannabinoids and cathinones) leading to a major public health problem [63, 130, 138-141]. Probably it is due to the fact that illicit actors are trying to hide their activities and connections.

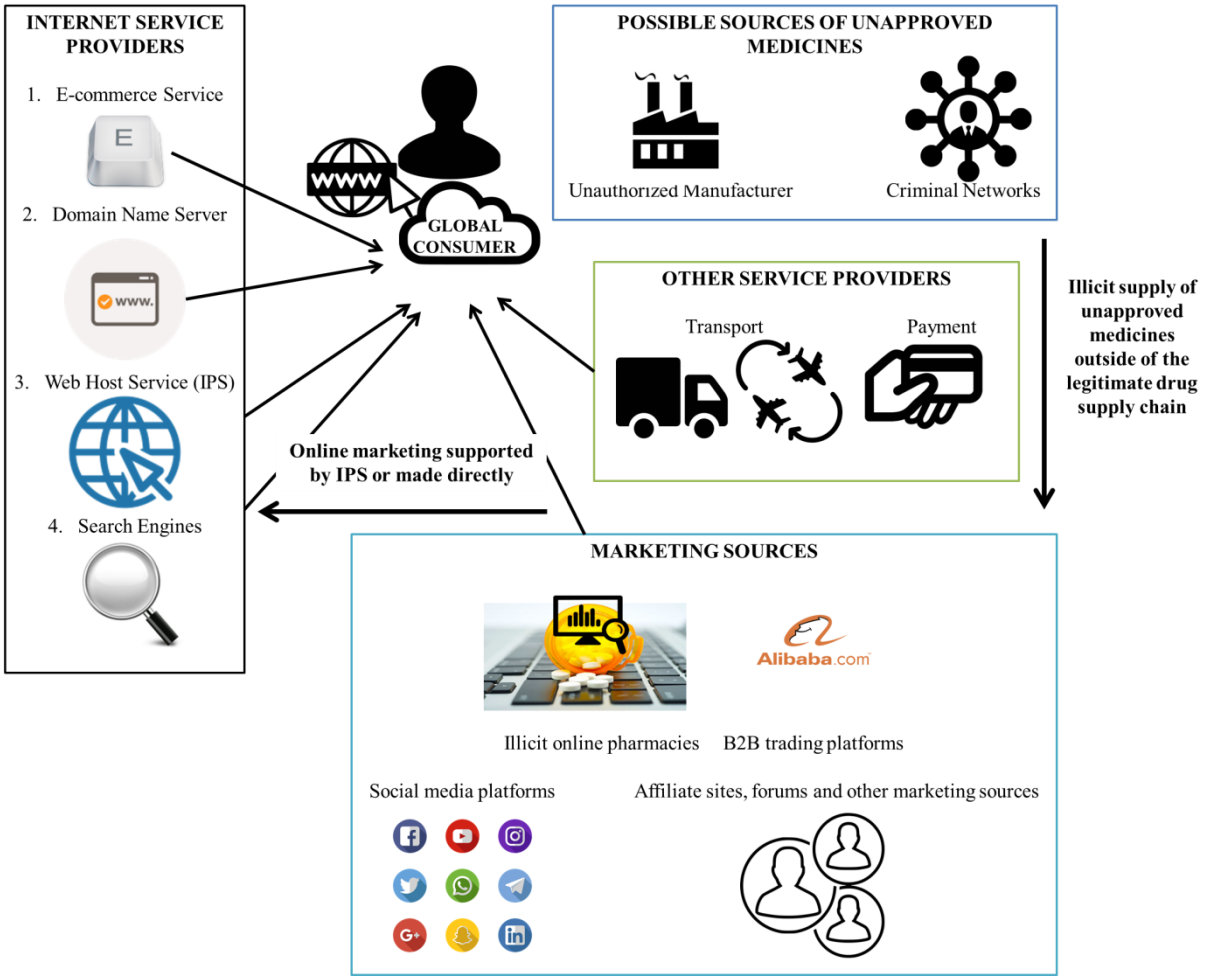

Figure 2: The ecosystem of the illicit online pharmacies [133-134]

Therapeutic and product categories available on the Internet

There are no exceptions, as almost every therapeutic class is available over the Internet. Not just the performance and image-enhancing drugs, or so called "lifestyle drugs" [142-144] such as PDE-5 inhibitors to treat erectile dysfunction [116, 145-147] or anti-baldness drugs [148], but drugs being on the WHO Essential Medicines List (life-saving medicines) as drugs to treat pain (NSAID, opioids) [60, 149], psychiatric disorders [150], obesity [151, 152], and cardiologic disorders [80] can be purchased over the Internet.

Augmented risks are associated with the online marketing of infectology and oncology drugs include the threat of infectious diseases, antimicrobial resistance and possible safety issues (e.g.: cytotoxic drug contamination) [120, 151, 153-155].

Types of drug categories include original, generic, illegal generic and biological or biosimilar pharmaceuticals (such as vaccines, heparin [156], bevacizumab [80, 153, 157, 158], etc.). Moreover drugs before approval [56, 159] or after recall by the authorities [137] can be reached by patients.

Shortage drugs (biologicals and non-biologicals) are also available for patients or health professionals on the Internet and advertised as over-the-counter preparations [56, 155, 160]. Further product categories are the herbal and dietary supplements. Beside the lack of evidence regarding efficacy, their quality and safety can be compromised originating from batch-to-batch variability, contamination or adulteration [161]. The number of herbal remedies and dietary supplements adulterated with active pharmaceutical ingredients is globally increasing [148, 162]

Types of consumers turning to illegal online vendors

The primary factor for the demand is the general accessibility of the internet, digital health and data access (social media platforms, mobile devices) leading to the increase and likelihood of searching online for health information and different health products [56, 132, 163, 164]. These changes are driving factors as more and more illegal online pharmacies adopt the practice of using 'medical questionnaires' and 'cyberdoctors' instead of prescriptions [56, 57, 165].

Different categories of the consumers turning to illegal internet pharmacies have been classified. The main motivation of *bargain hunters* is cost saving. The *elderly* with multiple chronic illnesses and medications, but limited financial opportunities may turn to the discounts promised by illegal vendors.

Lifestyle libertines mainly purchase lifestyle and embarrassment products to avoid uncomfortable primary care consultations. *Drug addicts'* motivation is to get the product to prevent withdrawal symptoms [166, 167]. These categories are complicated by the result of studies showing a link between the low health literacy and online drug purchasing [133, 168-170]. The possible health risk is even greater when we look at the risk perception of the consumers as health-related risks are ranked last [55, 72, 138, 171-173]. To map out further key characteristics of high risk consumers more robust and representative research data are required. Beside the powerful evidences of large sample studies identified and fully investigated clinical case reports are even more important as the majority of the Adverse Drug Reactions (ADRs) and therapeutic failures originated from illicit online drug purchase are left unidentified or underreported. Orizio et al identified 15 case reports in the literature in a ten year period (2000-2010) with mean age 42,8 year (18-67, SD 12,54 year) and 8:7 male to female ratio with several active pharmaceutical ingredients such as haloperidol, bentazepam, caesium chloride, carisoprodol, hydrazine sulfate, diphenhydramine hydrochloride, ephedrine, amitriptyline, tramadol, hydrocodon, anabolic steroids, butobarbital, sildenafil citrate, orlistat, γ-butyrolactone [57, 174-185].

Illegal online vendors have found their ways to reach consumers in the last 25 years. They are bombing almost everyone's e-mail account with unwanted emails or spams regarding prescription drugs and bargains [186]. Another way can be the manipulation of web searching to preferentially direct consumers or to use online advertisements and pop ups [93].

Furthermore the unseen popularity of social media encourage the different e-marketing solutions [187] like direct-to-consumer-advertising for drugs in social media and other interactive Internet media or mobile technology platforms [138, 188-191]. It has to be highlighted that these illegal vendors need customers to purchase products and that their business remains profitable, thus illegal online pharmacies survive (maybe under a different name) and continue their operation. Therefore the reduction of the demand for illegal internet purchase of medication has to be prioritized in public health campaigns [64, 130].

Patient safety problems when buying drugs from illegitimate vendors

There are countless additional challenges, disadvantages and threats when customers encounter illegitimate online sellers. This is called in the literature as 'digital iatrogenesis', which is a preventable patient harm resulting from injury that occurs from use of information, services or products delivered or enhanced through the Internet and related technologies [192]. Negative aspects also can be classified according to the three basic steps of the online purchase: *information exchange, delivery and the product itself.*

Patient safety issues are:

1. **Online information exchange and operation of website:**
   - Quality of drug information provided by sellers is highly variable [99].
   - Fraudulent or misleading health claims [56].
   - Patients can be automatically redirected to other – potentially illegitimate – websites even without noticing it [67].
   - Online direct to consumer advertising of prescription drugs generates demand without evidence of health benefits (overprescribing behaviour) [22, 56].
   - Temporary or permanent unavailability of websites may disrupt continuity of drug supply and consequently the quality of care [67].
   - Financial and personal data security is jeopardized by illegal actors [96].
   - Possible infection of a personal computer with malware / viruses [56].

- No health status consultation is performed or the online questionnaires are not scrutinized by health professionals [113], which represents a risk to take contraindicated, interacting medications [93, 193-194]. This is coupled with the lack of patient follow-up [193-194].

2. **Delivery conditions:**
   - Illegal operators ship products from remote countries and the lengthy delivery increases the likelihood of inappropriate storage and handling conditions resulting in lower product quality [195].
   - Controlled substances and unapproved medications are likely to be confiscated by customs authorities [60, 63, 66].
   - Hidden costs, such as shipping and handling fees may generate higher final price than purchasing medication from legitimate storefront pharmacies [79, 80, 93, 110, 132, 194, 196, 197].
3. **Product quality and medication use:**
   - The unobservable product quality of medications by consumers is a special attribute of drugs which may lead to ineffective treatments or adverse events [79, 120, 198].
   - Non-prescription availability of controlled drugs increase the risk of opioid misuse, abuse, dependence and overdose [60, 96].
   - Pharmacokinetic and pharmacodynamic drug-drug interactions [56].
   - Customers are left with no legal recourse in case of an unwanted event [96].
   - It is an illegal activity to obtain or possess certain pharmaceuticals without the authority supervision [132].
   - No controls on the amount of medicine which can be ordered may lead to drug overuse or overdose [93, 96, 175, 199, 200].
   - There is no outer and immediate packaging or there is an inconsistency between the carton box and the blister (the batch number, expiry date, manufacturer's name) [201]. Thus, the product and ingredient cannot be identified, the proper application is not guided with information leaflets [93].
   - The self-medication with products purchased online may delay appropriate treatment [202].

Overview of the technologies to fight against counterfeit medicine in the global drug supply chain

Tool for visual inspection of medicines

The WHO checklist is designed to help health professionals in carrying out a visual inspection of medicines for any sign of counterfeiting. Questions are separated in 2 sections: (1) Packaging – e.g.: name, logo, manufacturing number, etc.; (2) Physical characteristics of tablets/capsules – e.g.: uniformity of shape, scoring, surface, smell, etc.. The main limitation of this tool that it's second half only can be used to investigate solid dosage forms [203-204].

Traditional analytical solutions

Traditional solutions consist of mainly laboratory and field-based technologies for detection and testing, medicines packaging authentication and enhanced pharmacovigilance used to test products. These methods are complementary to innovative digital solutions [205].

The growth of pharmaceutical counterfeiting results in an increase of samples need to be tested by control laboratories that chemically characterize falsified samples and assess their hazardous nature (medication safety risk).

As these laboratories are operating in almost full capacity, the reliable, fast and affordable preliminary screening methods used to decide whether further and extensive analysis is required are getting attention [206-208]. Not just the capacity problems in the developed countries but the highly affected poor income countries necessitate the development of simple, non-sophisticated portable devices. Rapid detection technologies like Near Infrared Spectroscopy, Near Infrared Chemical Imaging, Raman Spectroscopy, X-Ray Fluorescence, X-Ray Powder Diffraction, Ion Mobility Spectrometry, Ion Mobility Mass Spectrometry, Isotope Ratio Mass Spectrometry and visual analytical methods (e.g.: US FDA CD3+ counterfeit device, GPHF Minilab) can be useful tools in the preliminary screening. Some of instrumental analytical technologies (e.g.: NIR spectrometry, Raman spectrometry) can be used on the field and in laboratory circumstances or just in laboratory (e.g.: HPLC, capillary electrophoresis, mass spectrometry) [204, 209-210].

Several techniques are available to analyze composition, presence of active ingredients or impurities and crystalline arrangement of the formulation's compound [206]. In the **Figure 3.** the general steps and application of previously mentioned tools for the analysis of falsified samples are highlighted [208, 211].

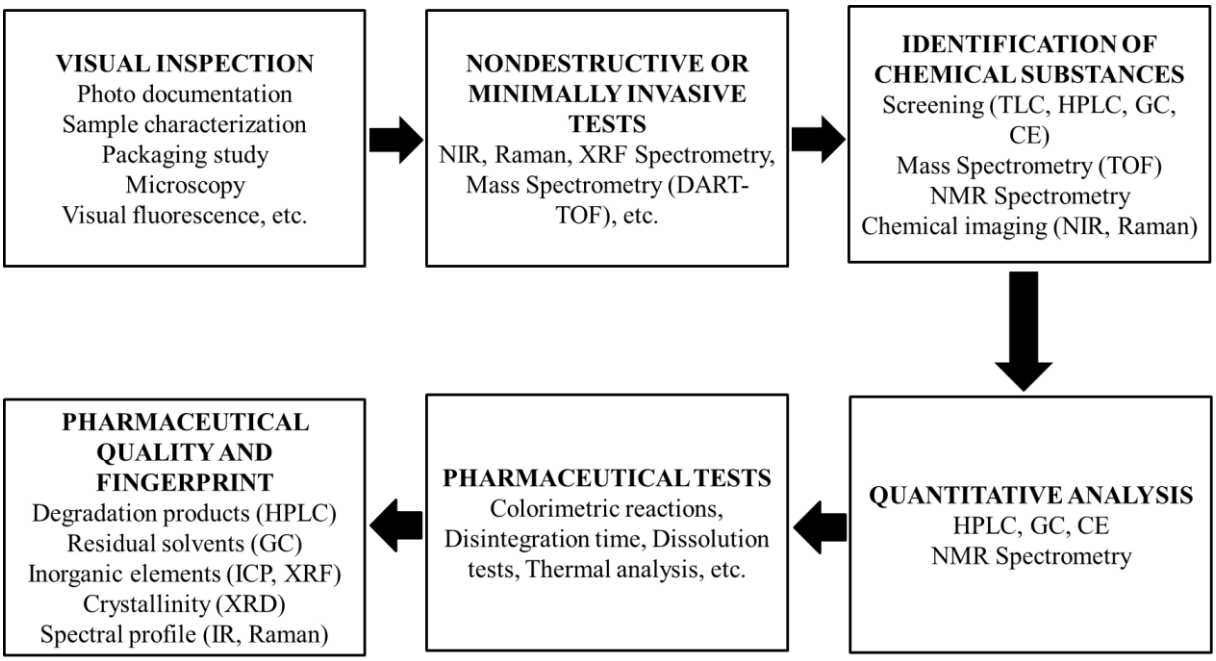

Figure 3: General analytical methodology for the analysis of falsified samples [208]

Microbiological testing

Beside the use of chemical testing to identify the exact active pharmaceutical ingredients (APIs) and impurities, adulterants in counterfeit medicine which is the main task of health authorities, serious medication safety risks may arise from the microbiological contaminations as well. This is a significant risk for individual infections and the global spread of microorganisms from developing countries to developed ones and vice versa which is originated from the poor hygienic conditions during manufacturing and distribution, especially in case of sterile dosage forms (e.g.: parenteral medications) [213-215].

A retrospective study done in Shanghai, China investigated patients undergoing intravitreal injection in 2010 and found endotoxin as the cause of intraocular inflammation after the intravitreal injection of counterfeit bevacizumab [216].

The investigation of microbiological contamination is usually based upon the standards and requirements set by the US and European pharmacopoeiae. These can be the followings: total aerobic microbial count (TAMC), total yeast and mold count (TYMC), pathogens (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella*, and *Staphylococcus aureus*), and enumeration of enterobacteriaceae and anaerobic bacteria. Products above levels or acceptance criteria of pharmacopoeial limits may lead to alterations and degradation of active pharmaceutical ingredients and cause adverse effects by infections or toxins [215].

Innovative technology-based solutions

Innovative technologies are needed to protect the complex processes (manufacturing and distribution) of medicines to ensure patient safety with the steps of serialization (identifying a medicine by using unique printed codes, images or holograms on packaging to verify authenticity), authentication (scanning a medicine product at point of supply to the patient to verify authenticity) and track and trace (logistic technology that follows the current and past locations of medical products through the supply chain) with various technological solutions. Further IT methods are aiming the public or trying to identify supply chain threats (e.g.: illegitimate online pharmacies) [204, 205, 217-219].

These emerging technologies can be divided into five main categories including (1) mobile, (2) radio frequency identification (RFID), (3) advanced computational methods, (4) online verification and (5) block chain technologies. The common feature of them is the strategy to integrate different types of anti-counterfeiting solutions [205].

Mobile technologies can be used to product authentication, track and trace and consumer or health system worker reporting to industry or authority [205, 220].

The radio frequency identification (RFID) and 2D barcodes are used to track products, manage inventory and product authentication [205, 221] as seen in the introduction.

Track and trace technologies (2 D barcode and RFID) will be the future element of the pharmaceutical supply chains in the developed countries worldwide. However there is no evidence on the effectiveness of track and trace technologies as preventive measures against counterfeit medicines. These technologies may be effective and reliable in the long run, as well according to pilot studies and not in real life operation, but the time and cost of the implementation makes it impossible to use in low- and middle-income countries. Furthermore it should be highlighted that these preventive measures will not stop this global phenomenon as authentic product can be found and ordered on the internet (e.g.: somatropin products purchased by our research group) and these techniques are also available for counterfeiters without any obstacles. Beside the uncertainties it can have a catalyzing effect on other preventive measure with proved efficacy such as new technologies (onsite inspection, pharmacovigilance systems) and the role of pharmacists (new competencies in patient safety) [205, 250].

The aim of the advanced computational methods is to detect and mitigate cybercriminal activity such as illegal internet pharmacies. These methods can be divided into 2 main categories: (1) use of machine learning algorithms to better detect and classify illicit online pharmacies through text mining and content analysis ("big data" and "infoveillance", web crawling); and (2) use of machine learning algorithms to detect irregularities or patterns of counterfeit medicine penetration into the drug supply chain (deep learning models with artificial neural networks for image recognition) [188, 191, 205].

Web-based primarily focus on the consumers to verify the legal status of an online pharmacy and educate them regarding the risks of illegal internet purchase of medicines. Technologies include the followings: (1) website seals (image, link or object like NABP and common EU logo); (2) commercially available website verification services (LegitScript); (3) and new top level domain name for legitimate pharmacies (.pharmacy domain with NABP) [100, 105, 222, 223].

Blockchain technology is a secure distributed digital ledger made up of "blocks" of continuous transaction information to provide greater transparency in the drug supply chain and to detect fake medicines [224].

Tools to identify patients harmed by illegal internet or counterfeit medicines

As the number of counterfeit products reaching patients is increasing in the EU, the European Directorate for the Quality of Medicines & Health-Care (EDQM) has therefore coordinated the development and validation of a screening tool to identify patients harmed by counterfeit medicines. The tool includes a questionnaire regarding the symptoms and risk factors (health complaints, medical history, use of medicines, use of health care products, life-styles relevant for exposure to FFCm's) and watch-list of falsely labelled, falsified (counterfeit) medicines (FFCm's) identified in Europe [225, 226]. The watch list contains 7 therapeutic classes found to be in falsified medicines in Europe such as psycho-analeptic, antibiotic, anabolic properties, as well as medicines to treat cardiovascular diseases, erectile dysfunction and obesity [227]. These kind of decision aids can be helpful to detect patients harmed by FFCm's in ambulatory care setting and in specified risk groups of patients [226].

Strategies to make the online pharmaceutical market a safer place

The problems often mentioned regarding online pharmacies and the sale of medication via the Internet is a complex issue. Based on the literature a multiple level approach focusing on consumers (demand side), members of the online pharmacy market (supply side) and strategies applied by regulators and the health systems (environment) is recommended. Another categorization concentrating on falsified medications can be seen in the **Figure 6.** as it is showing a framework for the different anti-counterfeit drug strategies including Law and regulations, Technology, Quality control and vigilance [250, 251].

Demand side: Strategies aiming the consumers, patients

1. By public awareness campaigns customers should be made aware of the importance of regulation, verifications and the identification of website characteristics that would increase the likelihood of selecting safe websites for their drug purchases [64, 80, 81, 84, 96, 99, 120, 151, 159].
2. Accreditation, verification systems are widely used to combat against illicit vendors however they seem to be ineffective as illegal actors can start their business without it [80, 83, 114, 228-231] or use fake logos. As the use of domain name extensions can be limited, the National Association of Boards of Pharmacy (NABP) introduced a ".pharmacy" generic Top-Level Domain from 2014 in order to provide an accreditation system that helps consumers to identify safe, legal and ethical Internet pharmacies [81, 223].

Supply side: Strategies aiming the online pharmacies

1. Greater the number of legitimate vendors, the more likely patients purchase medications from safe sources. In countries where there is a way to act legally and professional standards are set for Internet pharmacies, the market forces may enhance the quality of online services and products. Therefore the licensing system for online pharmacies can combat effectively against illegal participants [232].
2. Code of good practice should be set up by the pharmacy professionals and Internet pharmacy operators. By self-regulation online pharmacy operators should commit themselves to compliance with statements, directives and standards of practice [233].

3. Unregulated online pharmacies attempt to legitimize their appearance by unpermitted use of existing registration logos that are not linked to existing regulatory body or by creating fake certifications [96]. As logos can be faked websites illegally using regulation logos should be actively closed down.
4. Operation Pangea illustrates the effectiveness of international collaboration. In 2015 115 countries participated in the operation VIII that resulted in 156 arrests, 2410 websites shut down and removal of 550 illicit online pharmacy advertisements [234].
5. Search engines take into account - beside numerous factors - the number and quality of incoming links. Various algorithms, such as PageRank, TrustRank, BadRank are using linkage information to assess the quality of a webpage. When a spam page is identified the search engine no longer indexes it, consequently website are removed from search engine results pages. Similar algorithms should be developed specifically for Internet pharmacies [80, 127, 235].

Environment: Strategies aiming regulation and health care system

1. Custom authorities and agencies shall implement national policies for processing medications imported through mail order. As an example in 2004 the US Bureau of Customs policy has effectively interrupted the flow of opioid analgesics from foreign Internet pharmacies [60].
2. Governmental or professional bodies should be established with the mission to monitor online sales of unauthorized medications and initiate legal action against illegal practices. These regulatory agencies should have the power to investigate and regulate online pharmaceutical sales. A Hungarian example should be noted as the National Institute of Pharmacy and Nutrition (NIPN) has the authority to make fraudulent sites selling counterfeit or unauthorized medications temporary inaccessible by ordering Internet service providers (ISP) to shut down websites [236]. Another notable example was the proposed Stop Online Piracy Act in the USA that would have included enforcement mechanisms to require Internet service companies (ISPs, search engines and payment processors) to prohibit payment transactions for fraudulent websites [237].

3. Similarly to the international pharmacovigilance systems, every country should have its own online reporting system for websites that are believed to be illegal. Reported websites should be evaluated nationally and the collected data shall be forwarded to a central international register. Systematic collection of reports and complains will likely justify the priority of the problem for regulators. Additionally, with a searchable and transparent database national authorities, professional organizations and search engine providers could access an international authentic resource.
4. Physicians who do not prescribe in accordance with norms of practice, and pharmacists who dispense medications against the regulations and ethical norms should be subject to charges and sanctions [99].
5. Legitimate Internet pharmacy websites should focus on privacy and confidentiality issues by: (a) the use of SSL (secure socket layer) technology for maintaining the protection of customer information transmitted over the Internet, (b) registration requirement for customers before ordering, (c) not using cookies as they track other websites visited by consumers, (d) authority certifications, (e) publication of privacy policy on all pages during the ordering process, and (f) limiting number of banner ads [238].
6. Search engines, domain name registrars, hosting providers and credit card networks must effectively collaborate with pharmaceutical authorities and legislators to develop policies in order to prohibit illegal websites to use their services [80, 81, 89].
7. Due to the special nature of the Internet benefits of legitimate suppliers and disadvantages of illegal vendors need to be dealt with at international and national levels simultaneously [80, 83, 84, 120, 239].
8. Consumers, patients and health-care professionals should report adverse events associated with use of medications obtained from the Internet in order to obtain statistical data [84, 86, 119, 120, 151]. Counterfeit alert networks like Medwatch system, SafeMeds, and WHO's Rapid Alert System in the Western Pacific Region and other reporting systems also can measure the effects of anticounterfeit activities as well [86, 240-243].
9. Identical look of original and fake drugs can be misleading [79], so the development of analytical approaches and authenticity evaluation methods to differentiate between genuine and fake products is warrant [80, 93, 120, 151, 153]. Rapid, on the field analytical methods joint with the authorities' laboratory background could identify potentially dangerous products [80, 151, 244], and prevent injuries of consumers.

10. Standardized numeric identifiers, 2D barcodes or Radio Frequency Identification (RFID) for individual drug packages are in the pilot and implementation phase is in most of the developed countries to secure drug supply chains [80, 82, 83, 71, 151, 245, 246]. However, these protective measures may add cost to the product and cause logistic problems at every level of the supply chain [82]. Their effectiveness should be evaluated in the subsequent years.
11. With the improvement of supply chain management (e.g. secondary drug markets and managing drug shortages) the health care systems can decrease the probability of illegal vendors entering to the authentic drug supply chains. Implementing new supplier approval processes or verification systems (e.g.: Verified-Accredited Wholesale Distributors, VAWD in the United States) [80, 86, 151, 247] the risk of counterfeit medications entering to the legal supply chain from importers, repackagers and wholesalers can be minimized.
12. Physicians and clinical pharmacists must remember that, with easy on-line availability, a patient can be taking literally any drug and health product with no records of documentation. Proper drug history and anamnesis is one of the best technique to identify products purchased from outside the regulated supply chain [82, 107, 181, 148, 123, 229, 248, 249].

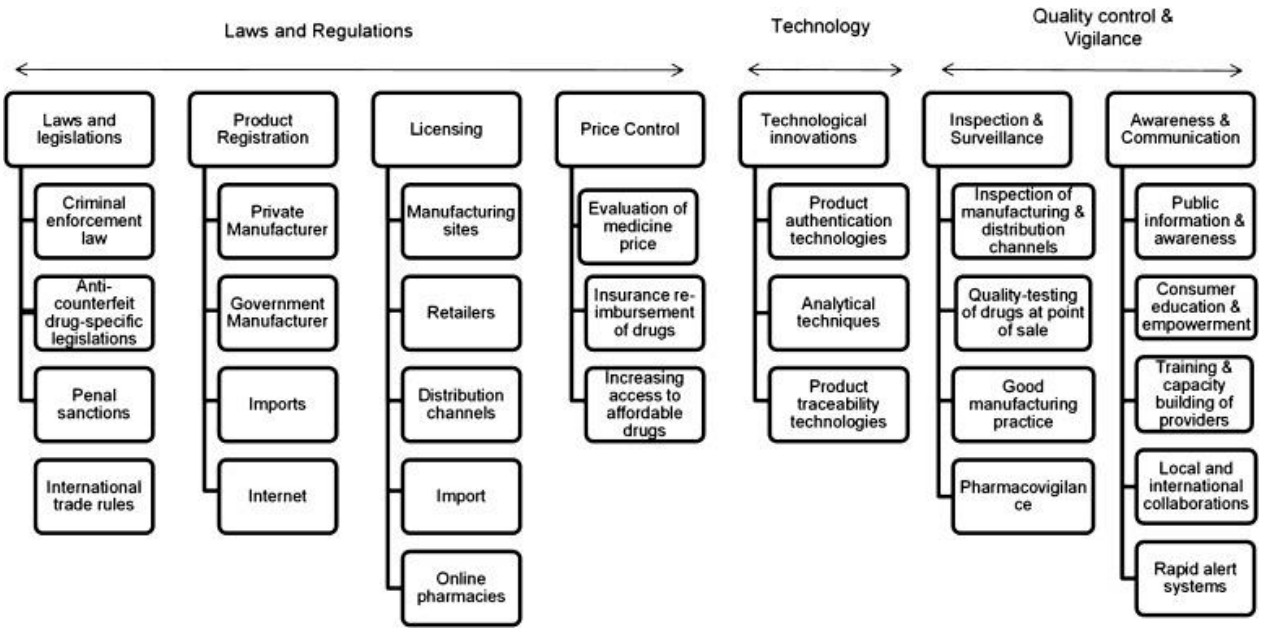

Figure 4: A framework for the different anti-counterfeit drug strategies. This framework was adopted from the study by El-Jardali et al. [250-251].

Objectives

We aimed to develop a comprehensive method that can identify patient and medication safety risk of the online pharmaceutical market in a relatively fast and reliable way, furthermore it can facilitate to find new strategies to make the online pharmaceutical market a safer place. It will be able to identify and classify high risk vendors, identify high risk products, analyze the logistic and provide initial chemical, microbiological and pharmaceutical technological evidence regarding the product quality and dosage form integrity of online purchased products.

Methods

The risk based safety mapping of online pharmaceutical market as a comprehensive methodology is consisting of three basic steps focusing on the key patient safety issues. These steps are further divided into specific questions indicating priority issues related to online medication purchases: (1) Evaluation of available information; (2) Evaluation of vendor characteristics; (3) Product analysis. The first step consists of the assessment of whether there is an increased demand for an active ingredient or product outside the traditional supply chain (high risk medicines). In case of prescription only medications (greater in case of drugs that can only be accessed in a clinical setting) or when a product has several off-label or illegitimate indications or when a drug is in shortage we suspected that patients/consumers or health professionals may turn to the online market of these products to exceed such barriers.

Selection of model product and active ingredients

The above methodology was applied for biologics (**1. somatropin**) and antineoplastic agents (**2. oncology shortage drugs**) as model products. Below I introduce our methodology for these agents.

1. Biological drugs and products on the internet

Wide range of products - such as anabolic steroids and growth hormones - have recently become available on the illicit market for those who want to enhance their physical performance and improve body satisfaction. Numerous factors, such as advances in science and pharmacology, the evolution of self-medication, and the development of Internet communication have made human enhancement drugs (e.g., weight loss, increasing lean muscle mass, cosmetic appearance or erectile dysfunction) available to a growing number of individuals [252]. Globalization, the relatively free trans-border movement of goods and the falling prices of growth hormones - due to the advent of biosimilar drugs (follow-on biologics) - have also contributed to the increasing access to this drug class [252]. Unfortunately consumers may be misled by unreliable information resources and the enormous number of illegitimate online medication vendors [64]. Furthermore, it has been reported that the Internet encourages the abuse and increase importation of human growth hormone (hGH) for personal use [253]. Additionally, the high marketing potential have contributed to counterfeit human growth hormone scandals among athletes and actors [254].

Users of human growth hormone medications for performance- and image enhancing purposes (e.g., sport and bodybuilding) are risking their health because of the possibility of obtaining counterfeit and poorly controlled injectable products [253]. Medications manufactured and distributed outside the scope of regulation bypass pharmaceutical standards ensuring quality, safety and efficacy. Although biotechnology based drugs were not the first targets of counterfeiters earlier, counterfeit somatropin drugs have been identified a decade ago [255]. Product samples of hGH obtained from the black market contained no active ingredient in three out of five hGH products in a study performed by GrahamR in 2009 [253].

1. Selection of somatropin products

To simulate the healthcare market of growth hormone products the national sales of somatropin products (ATC code: H01AC01) were evaluated for three preceding years (2011-2013). Most commonly prescribed hGH products were Norditropin SimpleXx® (Novo Nordisk), Genotropin® (Pfizer), Saizen® (Serono), Humatrope® (Lilly), Omnitrope® (Sandoz), NutropinAq® (Genentech). We hypothesized that individuals seek to obtain these popular brand name drugs from the Internet, thus the online availability of these products was evaluated.

2. The internet market of shortage drugs

Despite a growing number of legitimate Internet pharmacies are offering their services, a vast number of illegitimate vendors overwhelm the market of online pharmaceuticals [56, 63, 96, 256, 257]. The patient safety risk attached to the online purchasing of shortage drugs involves questionable sourcing, poor quality, falsification, improper storage and transportation [58, 96, 160]. Further, there are not only medical but also financial consequences associated with procuring medications from the web as the price of online drugs is documented to be much higher than offered by traditional brick and mortar pharmacies [72, 258, 259].

It has been proven in the literature that countless medications can be ordered online and uninformed consumers are unlikely to be able to differentiate legitimate websites from illegitimate actors [52, 64]. Unregulated online pharmacies are willing to supply prescription only drugs without valid medical prescriptions, use falsified verification logos and conceal their contact details [50, 56, 64, 231]. In addition, professional aspects of safe medication use are deteriorated by unethical marketing practices [259], absence of product information or valid live contact with healthcare professionals (pharmacist or physician) [55, 57, 258].

Previous studies showed that drugs in shortage (vaccines and oncology drugs) are available on the Internet from NABP not recommended vendors, however a detailed and follow up analysis of the availability of shortage oncology drugs via the Internet has not been carried out so far [155, 160].

2. Selection of oncology shortage drugs

The 2014 EAHP (European Association of Hospital Pharmacists) survey on drug shortages was the starting point to identify drug shortage information sources. We accessed these publicly available shortage databases. Inclusion criteria were: relevant shortage information on oncology medications and date of shortage events (2014 and 2016). Publicly available databases with Hungarian or English language were preferred [260]. Seven European and 4 Non-European drug shortage information sources (list, database) were included (**Table IV.**).

The query of shortage antineoplastic agents in the databases was performed by ATC code (L01) or the name of the Active Pharmaceutical Ingredient (API) from July 01. to September 30. (Q3) in 2014 and 2016. If a database only contained brand name of a drug product then the national authority's pharmaceutical product database was searched to determine the API or the therapeutic class (ATC code). ATC L01 Active Pharmaceutical Ingredients were identified according to the WHO Collaborating Centre for Drug Statistics Methodology website (https://www.whocc.no/).

An active ingredient was considered to be an *internationally significant shortage problem* if it was represented in at least one accessible European database (aside from the Hungarian) and in addition in at least one Non-European shortage database [260, 161-270]. The results of the query of the drug shortage databases can be seen in **Table S1 (Supplementary information)**.

Table IV: The selection of drug shortage databases

No.	Country or Agency mentioned to have shortage list in the EAHP 2014 survey	Drug shortage database link (if available)	Comments
1.	Austria	http://www.basg.gv.at/startseite/	Shortage drug and date could not be identified
2.	Belgium	http://www.fagg-afmps.be/fr/items-HOME/indisponibilites_de_medicaments/	Included in the study
3.	Bosnia and Herzegovina	-	-
4.	Croatia	-	-
5.	Denmark	-	-
6.	Estonia	-	-
7.	France	http://ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments	Included in the study
8.	Germany	http://www.bfarm.de/DE/Arzneimittel/zul/amInformationen/Lieferengpaesse/_node.html	Included in the study
9.	Greece	-	-
10.	Hungary	http://ogyei.gov.hu/temporary_discontinuation_of_sale_/	Included in the study
11.	Italy	http://www.agenziafarmaco.gov.it/it/content/carenze-dei-medicinali	Included in the study
12.	Lithuania	http://www.vvkt.lt/	Shortage drug and date could not be identified
13.	Malta	-	-
14.	Poland	www.leki-informacje.pl	Shortage drug and date could not be identified
15.	Portugal	http://www.infarmed.pt/web/infarmed-en/	Shortage drug and date could not be identified
16.	Republic of Macedonia	-	-
17.	Serbia	-	-
18.	Slovakia	http://www.sukl.sk	Shortage drug and date could not be identified
19.	Spain	https://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=buscarDesabastecidos	Shortage drug and date could not be identified
20.	Switzerland	https://www.swissmedic.ch/marktueberwachung/00135/00136/00140/00142/00184/index.html?lang=de	Shortage drug and date could not be identified
21.	The Netherlands	http://www.farmanco.knmp.nl/	Included in the study
22.	United Kingdom	http://psnc.org.uk/dispensing-supply/supply-chain/branded-shortages/ http://psnc.org.uk/dispensing-%20supply/supply-chain/generic-shortages/	Not available outside UK.
23.	European Medicine Agency	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6	Included in the study

No.	Non-European countries with English drug shortage database	Drug shortage database link (if available)	Comments
1.	United States of America – FDA, ASHP	http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm http://www.ashp.org/menu/DrugShortages	Included in the study
2.	Canada	https://www.drugshortagescanada.ca/	Included in the study
3.	Australia	http://apps.tga.gov.au/prod/MSI/search/	Included in the study

Analysis

Internet search methodology

1. Somatropin

The most popular search engine Google (www.google.hu) was used with search terms "buy" and "somatropin or brand name" and "online" with both the English and Hungarian equivalent. The first twenty search engine results were examined and sites offering somatropin products directly to patients (Internet pharmacies) were included in our study. Websites promoting the sale of growth hormone products were identified and analysed from June to August 2014. During searches the authors were not signed in to any account and the browser was set to standard security settings. Social media sites were not evaluated.

2. Oncology shortage drugs

We searched Google (www.google.hu) for the English and Hungarian terms of antineoplastic agents (ATC L01 class drugs) affected by shortages in July-September (the third quarter of the calendar year, Q3) both in 2014 and 2016. The name of the active pharmaceutical ingredient (API - according to the WHO terminology) and the term "buy" were used as specific search key words (e.g.: "buy bleomycin"). Web browser Firefox was used with standard security setting, with no user signed in any account during searches. By documenting the first 50 references appearing in Google for national (Hungarian) and English language search terms, we could simulate what patients can easily find and what websites they most probably would visit when searching for shortage oncology drugs. No Hungarian websites were identified, consequently only websites operating in English were included in our study. No direct searches were performed on social media sites such as Facebook, Twitter, etc..

A search engine result was classified as relevant if the title and/or short description (so called title- and meta-description tags) indicated possible purchase option for the given active pharmaceutical ingredient. Accessed websites were categorized as *Internet pharmacies* (direct online sellers), *intermediary sites* (websites that were not direct vendors but acted as sources of information to purchase drugs), *social media sites* (blogs and forums); *research only sites* (companies offering active ingredients for research), and the remaining as *others* (e.g.: wholesalers) similarly to previously published studies [64, 256, 258]. Only Internet pharmacies were included in our study for detailed evaluation, while vendors offering non-finished products, raw materials or chemicals for scientific use were excluded.

Evaluation of internet pharmacy websites

1. Somatropin

Internet vendor sites were evaluated by the authors based on the following pharmaceutical and professional criteria indicating possible patient and medication safety concerns: (a) no prescription requirement; (b) inaccessibility of adequate medical information; (c) lack of address and location of the website operator/vendor; (d) absence of regulatory body logo; (e) illegitimate internet pharmacy verification status according to the LegitScript.com database; (f) cheap prices and discounts as marketing messages.

2. Oncology shortage drugs

The identified direct online drug sellers were assessed according to the following characteristics: *Operational characteristics* (website category, year of accessibility, oncology specific domain name: a domain name containing expressions related to oncology e.g.: cancercurepharmacy.com, contact information: address/location, telephone number), *Distributional characteristics* (drug availability, price, quantity limit), and *Patient safety characteristics* (requirement for a medical prescription, possibility of information exchange with healthcare professionals, LegitScript [102] and VIPPS [100] legitimacy certifications). Data were documented according to previously defined methodology by the research group. Websites were identified by domain name, domain name was used during survivability and legitimacy evaluations.

Sample acquisition and delivery

1. Somatropin

Samples were purchased with money transfer from international markets to a research group memberr's personal address during October 2014. The reference legitimate product for the quantitative and qualitative analysis was obtained from the Central Clinical Pharmacy (University of Pécs, Hungary). Delivery time, storage conditions, packaging and attached product information for patients were assessed.

2. Oncology shortage drugs

The authors assessed the possibility of purchasing products by placing an order for an oncology shortage medication and aiming to proceed to the checkout page, but no product purchase was made due to financial, ethical and safety concerns.

Quality assessment of the obtained products

1. Somatropin

Samples were evaluated by assessing inner and outer packaging of medications to find signs of counterfeit production, inappropriate storage conditions and mechanical damage. Batch number, expiry date and country of marketing authorization were documented. The identification of somatropin according to the United States Pharmacopoeia (USP 37.) shall be done by chromatographic purity test and peptide mapping [272], while according to the European Pharmacopoeia (Ph. Eur.7th Edition) the capillary electrophoresis and peptide mapping are the first choice [273]. Application of these methods would have required the purchase of a reference standard, greater sample size and a laborious analytical technique. As our aim was to apply a reliable, fast and convenient analytical method with reasonably low cost, the qualitative and quantitative analysis was performed with capillary zone electrophoresis (CZE) and electrospray ionisation-mass spectrometry (ESI-MS) method based on previously published data [274-276].

Statistical analysis

1. Somatropin

No statistical analysis was performed.

2. Oncology shortage drugs

The data was summarized by descriptive analysis. Mann-Whitney test and Chi-Square test were used to evaluate correlations.

Ethical considerations

1. and 2. Somatropin and oncology shortage drugs

No ethical approval was sought as there was no patient involvement in our studies.

Results

Comprehensive evaluation of the online pharmaceutical market of different active ingredients

1. Online availability of somatropin

Growth hormone products were mentioned in numerous websites during our searches. All brand name drugs included in our study were advertised for sale directly to patients. The authors documented 26 relevant search engine results (see **Table V.**). Online presence and national market share seem to correlate, as Norditropin SimpleXx was the most commonly prescribed hGH in Hungary in 2011-2013. period. As hGHs are available in several concentrations the product price is indicated in USD per International Units. **Table V.** illustrates that price may vary significantly among vendors.

Table V. Online marketing of somatropin products

Proprietary name (manufacturer)	Number of relevant search engine results*	Average online price and price range (USD/IU)
Norditropin SimpleXx® (Novo Nordisk)	8	10.4 (4.5-20.0)
Genotropin® (Pfizer)	7	16.1 (6.5–51.0)
Saizen® (Serono)	4	19.3 (8.1-34.0)
Humatrope® (Lilly)	3	26.1 (13.9-21.3)
Omnitrope® (Sandoz)	3	6.9 (6.6-7.1)
NutropinAq® (Genentech)	1	90.0

** among the first 20 hits in Google search engine*

1. Characteristics of vendor sites selling somatropin

Among the twenty-six search engine results a total of 17 individual Internet vendor websites were identified excluding duplicates (see **Table VI**.). Prescription requirement was in accordance with previous studies [57, 64] as majority (94%) of websites did not require a valid medical prescription before dispensing these otherwise prescription only products.

On the contrary, numerous (35%) vendors aimed to facilitate purchases by marketing cheap prices and easy accessibility. The design and the appearance of the websites also indicated that body-builders were the targeted customers.

Only three (17.6%) vendors displayed postal address on their websites, while just one (6%) made its phone number available to customers. Typically, websites operated in English, although some used automated machine translation of content to national language. Such low quality and biased information most likely causes communicational barriers and can be a definite source of medication errors. Limited health related product information was displayed on the websites and majority (70%) provided no medical information for visitors. The online vendors in our study sample did not display any regulatory body logo or verification. According to the LegitScript.com pharmacy verification database one site was classified as unapproved while all the remaining (94.1%) were identified as rogue Internet pharmacies.

Table VI. Characteristics of websites offering somatropin for sale direct to patient

website URL	Prescription requirement	Sales and discounts	Geographical location indicated	Phone number displayed	Healthcare professional access	Regulatory/ monitoring body logo	LegitScript's approval status	Cheapest listed product price (USD/box)
hgh-humangrowthhormone.com	Yes	No	No	No	Not available	Not available	Rogue	514
humangrowthhormonesales.com	No	No	No	Yes	Not available	Not available	Rogue	277
hgh.bz	No	No	No	No	Not available	Not available	Unapproved	n.a.
steroid4u.org	No	No	No	No	Not available	Not available	Rogue	390
1buyhghonline.com	No	No	No	No	Not available	Not available	Rogue	385
buy-hgh-hormones.com	No	No	No	No	Not available	Not available	Rogue	201
thebodypeople.com	No	No	No	No	Not available	Not available	Rogue	621
canadasteroids.com	No	No	Yes (Canada)	No	Not available	Not available	Rogue	361
rxtank.com	No	No	No	No	Not available	Not available	Rogue	181
steroid-online.com	No	No	No	No	Not available	Not available	Rogue	481
steroid-europe.com	No	No	Yes (Europe)	No	Not available	Not available	Rogue	195
steroidsone.eu *	No	Yes	No	No	Not available	Not available	Rogue	96
hghinjectionsforsale.net	No	Yes	No	No	Not available	Not available	Rogue	141
steroidsftw.eu *	No	Yes	No	No	Not available	Not available	Rogue	180
muscledevelop.co *	No	Yes	No	No	Not available	Not available	Rogue	224
discountsteroidsuk.com	No	Yes	Yes (UK)	No	Not available	Not available	Rogue	308
showyourmuscles.com	No	Yes	None	No	Not available	Not available	Rogue	306

*websites selected for test purchase indicating increased health risk and likelihood of purchase by visitors due to lower box price

1. Online purchase and delivery of somatropin products

Samples were purchased from three Internet pharmacy websites via bank or Western Union money transfer. None of the websites (0%) requested any health information during the ordering process or before payment. Delivery time ranged between 6-15 days (average 9 days). Only one injection was adequately protected from mechanical injury as it was shipped in a box, while the other two were delivered in bubble mailer envelope. All products seemed to be authentic by visual examination of the packaging and the ampules (However verification with the use of batch number and expiration date with the help of the manufacturers is the only method to identify the origin of a product has not been carried out. From 2019 February the serialized packages will be an additional and feasible option to track and trace pharmaceuticals through the European supply chain.).

According to European regulations distance sale of prescription only medicines through the Internet is illegitimate – including Hungary as well. Further, medicinal products must comply with the national legislation of the Member State of destination [275]. Consequently according to national law medicinal products must be supplied with Hungarian language package leaflets. Neither (0%) of the obtained somatropin products had any national (Hungarian) or English written information enclosed. The two Genotropin® samples (online sample C and D) had Greek, while the Omnitrope® sample (online sample B) had Italian language labelling and package information (**Figure 7**.).

Biological drugs may require special precautions for storage and administration. Omnitrope® 10 mg/1.5ml solution for injection must be stored and transported refrigerated (2°C - 8°C). Genotropin® 5.3 mg powder and solvent for solution for injection shall be stored in a refrigerator (2°C - 8°C), or for a maximum of 1 month at or below 25°C before reconstitution. These products are not allowed to freeze. As storage temperature was not highlighted on the packaging of the samples there is no guarantee for adequate storage temperature during delivery which evidently influences product quality. Although appropriate preparation and administration would require it, no injection or reconstitution device was supplied with either of the two-chamber cartridge Genotropin® products (online samples C and D).

Favourable price is a commonly hypothesized benefit of online medication purchases. In our study sample only one product had lower price (excluding shipping and transaction costs) than the national retail price. Total price including shipping fees was significantly (40-65%) higher in the case of sample B and D, while sample C was only moderately (2.7%) cheaper than reference national pharmacy retail price (see **Table VII**).

Table VII. Purchase and shipping characteristics of somatropin samples obtained from the Internet

Product name (Sample ID)	Price (USD/ampule)		Payment method	Seller information, website URL	Lot No. & Expiration date	Sender's name and address (Country)	Market Authorization holder	Shipping method, -cost and brief package description
	Online	National						
Omnitrope 10mg/1,5ml injection (Online sample B)	215	159	Western Union	Shihua Hou (China) muscledevelop.co	DU6434 Feb 2015	Not highlighted on envelope (United Kingdom)	Sandoz Spa (Italy)	Regular air mail (8.5 USD) Bubble mailer envelope with no storage temperature indicated and no attached documentation inside.
Genotropin 5,3 mg/ml powder and solvent for injection (Online sample C)	106	127	Bank wire	Interloop Ltd (Slovakia) steroidsftw.eu	Y07747 Apr 2015	Name and address displayed (Slovakia)	Pfizer Hellas A.E. (Greece)	First class mail (18 USD), Cardboard box with no storage temperature indicated and no attached documentation inside. No injection/reconstitution device supplied.
Genotropin 5,3 mg/ml powder and solvent for injection (Online sample D)	202	127	Bank wire	Seo Master Ltd (Slovakia) steroidsone.eu	Y07747 Apr 2015	Name and address displayed (Slovakia)	Pfizer Hellas A.E. (Greece)	First class mail (7.4 USD), Bubble mailer envelope with no storage temperature indicated and no attached documentation inside. No injection/reconstitution device supplied.

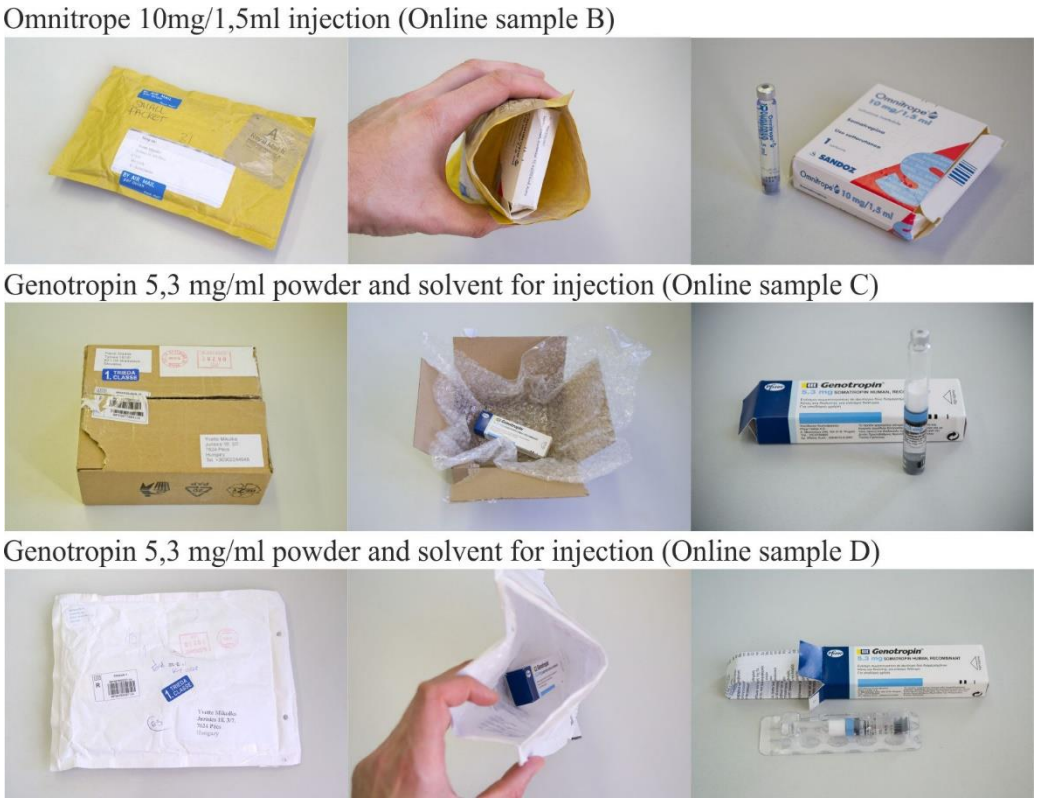

Figure 5. Packaging of somatropin products obtained from the Internet. Presenting the mail delivery conditions with the tertiary, secondary and primary packaging.

1. Qualitative and quantitative analysis of somatropin products

Liquid preparations of somatropin products obtained from internet were analysed by capillary zone electrophoresis (CZE) with UV detection. In order to gain further information on the identity of the protein content of the preparations, the samples were also analysed by electrospray ionization-mass spectrometry (ESI-MS) in the positive ion mode (**Figure 8.**). For quantification of the protein content, a calibration curve was constructed by dilution of the standard preparation (3.33, 2.50, 1.67, 0.83 mg/mL), which showed a satisfactory linearity (R^2=0,9978) in this range. All the calibration points were measured by the CZE method for four times (SD < 1%). All online samples had significantly ($p < 0.001$) lower somatropin concentration than indicated on the obtained products as listed in **Table VIII**..

1. Chemicals and samples used for the qualitative and quantitative analysis

Tris(hydroxymethyl)-aminomethan was purchased from Merck (Darmstadt, Germany). Background electrolyte (BGE) was prepared by diluting Tris to around the double of the desired concentration with LC-MS grade water (Fluka, Switzerland), adjusting the pH of solution to 8.0 with hydrochloric acid (Scharlau Chemie S.A., Barcelona) and diluting to the final concentration (200 mM) with water. BGE was passed through a 0.45 µm filter (PVDF.) before use. The liquid preparation *reference sample A* (Omnitrope 5mg/1.5mL injection, Sandoz GmbH, obtained from the legitimate national drug supply chain) and *online sample B* (Omnitrope 10mg/1.5mL injection, Sandoz Spa, from muscledevelop.co) contained mannit, poloxamer 188, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate heptahydrate and benzyl alcohol. The lyophilized powder *online samples C and D* (Genotropin 5.3mg/mL powder and solvent for injection, Pfizer Hellas A.E., C form steroidsftw.eu and D from steroidsone.eu) were reconstituted before analysis with the provided solution. They contained glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, m-cresol. Sample solutions were not diluted before analysis.

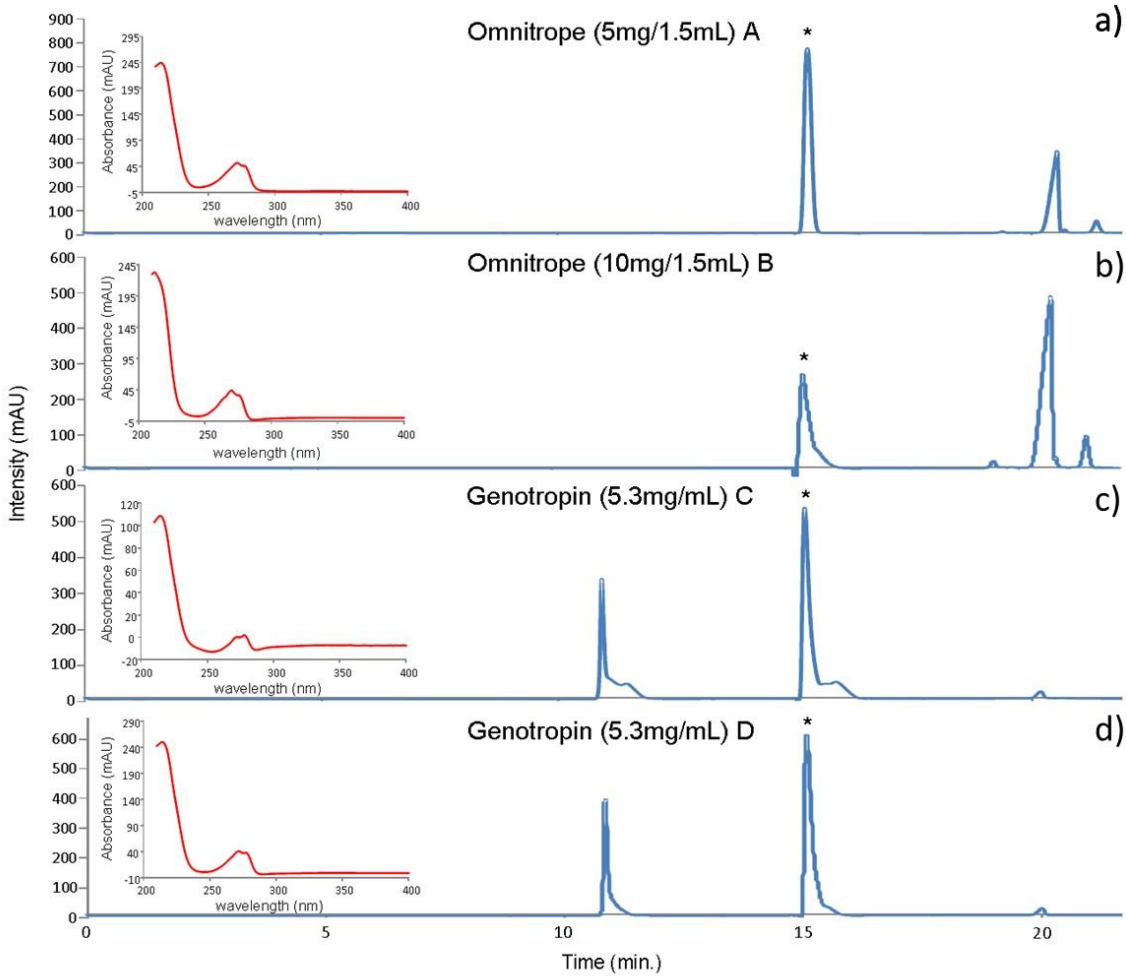

Figure 6: CZE-UV analysis of undiluted liquid preparations of somatropin: a) standard reference preparation, b-d) online ordered preparations.

Peaks with an asterisk above were assumed to be the protein components of the preparations, as only those components showed an absorption maximum at 270-280 nm (inset UV spectra are displayed on the left). The unmarked peaks most probably belong to the other UV active constituents of the preparations. Electropherograms of samples with the same brand showed highly similar separation profiles (i.e. number of peaks and migration times). Although, the area of the protein peak in the reference sample A (Omnitrope) was higher than those obtained from Internet, even though sample B (Omintrope), C and D (Genotropin) had higher nominal somatropin concentration. CE-UV experiments were performed on a 7100 Capillary Electrophoresis system (Agilent Technologies, Waldbronn, Germany).

Bare fused-silica capillary (50 µm i.d.) (Polymicro Technologies, Phoenix, USA) was used with a total length of 60 cm and effective length of 51.5 cm. 200mM Tris-HCl (pH 8.0) was used as background electrolyte. Capillary was termostated at 25 °C, the separation voltage was 15 kV and the detection wavelength was 210 nm. Samples were injected hydrodynamically for 3 s at 50 mbar. Electropherograms were analyzed using ChemStation Software, version B.04.03. New bare fused-silica capillary was rinsed with acetone for 2 min, 1 M sodium hydroxide for 25 min and with deionized water for 10 min with pressure of 1000 mbar. Capillary was rinsed between analysis with 200 mM sodium hydroxide for 10 min and then with the BGE for 5 min.

Table VIII. Quantitative analysis of active pharmaceutical ingredient in somatropin products obtained from the Internet

Sample	Lot No.	Label claim mg/ml	Measured concentration average ± SD mg/ml (n=4)	Recovery (average)
Omnitrope 10mg/1.5ml (Online sample B)	DU6434	6.67	2.34±0.04	35.1%
Genotropin 5.3 mg/ml (Online sample C)	Y07747	5.3	2.78±0.09	52.50%
Genotropin 5.3 mg/ml (Online sample D)	Y07747	5.3	2.81±0.18	53.22%

2. Online access and characteristics of vendor sites offering shortage oncology drugs

All evaluated oncology drugs affected by shortages were available on the Internet as each API included in our study (100%) was offered by online pharmacies both in 2014 and 2016. As it can be seen from **Figure 9.**, numerous search engine results (13.8% and 12.1% in 2014 and 2016 respectively) contained relevant information about purchasing shortage oncology medications. Of these relevant links 221 led to 112 individual websites in 2014, while 230 to 98 websites in 2016. The average number of websites per API somewhat decreased from 7 (2014) to 5.15 (2016). The ratio of online pharmacy sites actually offering finished products for sale within all relevant websites has risen from 66.1% (2014) to 80.6% (2016) ($p<0,001$).

About every fourth online vendor (n=14) was listed within the first fifty search engine results in both years of our study. Consequently, these sites were active, relatively easy to access and continuously available for patients in those years. In one case, a different domain extension was used for the same domain name (e.g.: buy-pharma.com & buy-pharma.co), indicating multiple (bulk) domain name operation. The accessibility of all Internet pharmacy websites (n=74) identified in 2014 was evaluated two years later and one fourth (n=19. 25.5%) were functioning in both years which is a clear sign of continuous operation. An online pharmacy was considered to be an active/functional vendor if payment options were displayed on the website (e.g. credit information was requested) as the final step of purchase during the checkout procedure. Sixty-four (86.5%) Internet pharmacies in 2014, while seventy-seven (97.5%) in 2016 vendors were active/functional.

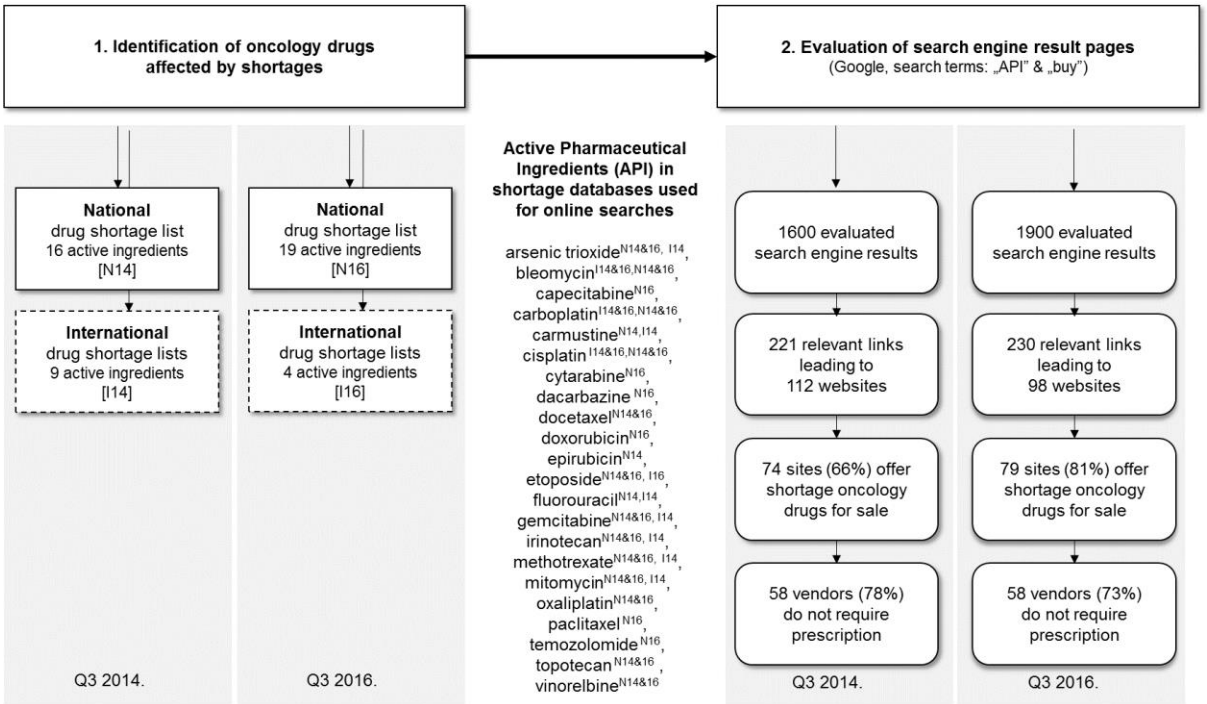

Figure 7. Flowchart illustrating methodology and main results regarding online availability of and prescription requirement for shortage oncology active pharmaceutical ingredients.

Letters indicate geographical localization of evaluated databases N: national, I: international; numbers indicate year of evaluation 14 (2014), 16 (2016); third quarter of the calendar year is labelled as Q3

Online vendors generally did not require medical prescriptions as 78.4% (58/74) internet pharmacies in 2014 and 73.4% (57/79) in 2016 offered oncology medications without the necessity of such medical documentation (p=0.474). One Internet pharmacy found in 2016 emphasized "no prescription required" access on its website, while none of the websites used this marketing message in 2014. Eight (10.8%) Internet pharmacy websites have used oncology specific domain names containing the terms e.g. "cancer" or "oncology" in 2014, down to five (6.3%) in 2016 (p=0.320). The shortage oncology portfolio of websites was similar in both evaluated years. The maximum number of shortage drugs offered per website has somewhat increased from 12 to 13, while the average number of shortage oncology medications offered per website was similar: 2.12 (±2.293) and 2.15 (±2.602) in 2014 and 2016 respectively (mean±standard deviation; Man-Whitney U test p=0.784). Most of the evaluated active ingredients became available on a larger number of Internet pharmacies.

A notable decrease was observed for others: number of carboplatin ($p<0.05$) and methotrexate ($p<0,001$) products offered has significantly decreased by 2016.

In accordance with previous studies we have also documented that numerous vendors have not displayed any physical address or telephone number on their websites (20.3% in 2014 and 27.8% in 2016). Furthermore, no healthcare professionals – pharmacist or medical doctor – were accessible on most Internet pharmacies (90.5% in 2014 and 91.1% in 2016). Majority (86.5%) of the identified vendors in 2014 and all (100%) in 2016 offered shipment to European countries. There was generally no limitation by the majority (91.9% in 2014 and 97.45% in 2016) of the Internet pharmacies on the amount of medication that could be ordered.

2. Verification according to LegitScript and VIPPS

LegitScript is a private company monitoring Internet pharmacies, supplement sellers and other online merchants. The company maintains a uniquely large database of more than eighty thousand Internet pharmacies. To evaluate whether online pharmacy websites included in our study were definitely fraudulent, we checked each domain name within the LegitScript database in Q3 2014 and Q3 2016. Internet pharmacy websites are classified by LegitScript into four categories: legitimate, unverified, unapproved, and rogue. “Legitimate” Internet pharmacies have passed LegitScript certification criteria and meet the standards of the National Association of Boards of Pharmacy (a US independent and international association that assists its member boards for the purpose of protecting the public health). “Unverified” websites appear eligible for certification, but have not been subjected to LegitScript’s certification or voluntary monitoring program. “Unapproved” sites have problem with regulatory compliance or risk and do not comply with LegitScript’s verification standards or applicable laws or regulations. However, do not meet the definition of being rogue.

“Rogue” Internet pharmacies are illegitimate websites. Their primary purpose is to engage in some sort of illegal, unsafe, or misleading activity, like selling prescription drugs without requiring a prescription, defrauding customers, or selling counterfeit goods [64, 102, 278]. Websites that are not evaluated by the organization are labeled as “Not available in the database”.

In the United States, the NABP operates VIPPS, a voluntary accreditation program. “Accredited” websites address a customer’s right to privacy, authentication and security of prescription orders, adherence to a recognized quality assurance policy, and provision of meaningful consultation between customers and pharmacists.

“Not recommended” vendors appear to be out of compliance with state and federal laws or NABP patient safety and pharmacy practice standards [64, 100, 279].

Website legitimacy is most often evaluated by the LegitScript and the VIPPS Internet pharmacy verification databases in relevant literature. In our samples obtained during the two evaluated years none (0%) of the identified Internet pharmacies were classified as “Legitimate” or “Accredited” by these verification databases, and a notable number of definitely unregulated websites offered products amongst the search engine results. There is a significant difference in the categorization of websites in case of the databases between the two evaluated years (see **Table IX.**). However, realignment can be observed between the definitely unregulated participants and ones that are not available in the databases. Seemingly the ratio of illegal actors somewhat increased and the completeness of databases has simultaneously slightly improved. The legitimacy of online pharmacies was assessed in 2014 Q3 and 2016 Q3 (July-September) within 2 weeks after the identification of the online pharmacies in google searches.

Table IX. Website legitimacy according to LegitScript and VIPPS Internet pharmacy verification databases

Database	Internet pharmacy category	Time of evaluation	
		Q3 2014 n (%)	Q3 2016 n (%)
LegitScript	Rogue	23 (31.1%)	48 (60.8%)
	Unapproved	18 (24.3%)	11 (13.9%)
	Unverified	0 (0%)	0 (0%)
	Legitimate	0 (0%)	0 (0%)
	Not in database	33 (44.6%)	20 (25.3%)
VIPPS	Not recommended	11 (14.9%)	26 (32.9%)
	Recommended	0 (0%)	0 (0%)
	Not in database	63 (85.1%)	53 (67.1%)

Chi-square test: p=0.001 for LegitScript; p=0.009 for VIPPS. Note: It is *likely that not only the number of illegal websites have increased, but that the databases have evolved during the time of our study. For example the LegitScript database contained approximately 35 000 websites in 2014, while nearly 81 000 in 2016 [64, 100, 279]*.

We must mention that LegitScript website only allows the limited number of five pharmacy verifications per day, which seems to be a disadvantage from the aspect of patients seeking safe online sellers. Also, an important limitation of the VIPPS website was noticed. The online tool was not able to identify explicit illegal websites that are otherwise listed among "Not Recommended Sites" by the NABP itself [64, 100, 279]. The EU common logo for legally operating online pharmacies/retailers in the EU Member States was introduced by the Falsified Medicines Directive (2011/62/EU) and operates since the 1st of July 2015. This logo is another opportunity to recognize website legitimacy. However, the authors did not document the presence of this seal as it was not obligatory when the study was initiated in 2014 [105].

2. Comparison of the national and international shortage situation

The authors aimed to evaluate if their findings based on national shortage conditions could be generalized and if the results could characterize a global phenomenon. Internationally significant active ingredients were identified based on methods described earlier and key findings of the study were correlated with results based on the national drug shortage lists. With the assessment of the Non-European shortage lists, and the seven accessible European national shortage databases, we have identified nine oncologic drugs that were in shortage globally in 2014 (bleomycin, carboplatin, carmustine, cisplatin, fluorouracil, gemcitabine, irinotecan, methotrexate, mitomycin) and four (bleomycin, carboplatin, cisplatin, etoposide) in 2016 (see also **Figure 10.**).

As it can be seen in **Table X.,** the main evaluated parameters show similarity for national and international shortage products. Therefore the key findings of our study are supported by data obtained based on internationally significant drug shortages.

Table X. Comparison of key findings of national shortage list APIs and internationally significant shortages

Evaluated parameters and online accessibility findings	2014 shortages		2016 shortages	
	16 national	9 internationally significant	19 national	4 internationally significant
Relevant links and websites within first 50 search engine results	221 links of 112 websites	134 links of 72 websites	230 links of 98 websites	53 links of 33 websites
Internet pharmacies within individual relevant websites	66.07% (74/112)	76.4% (55/72)	80.6% (79/98)	66.6% (22/33)
Number of shortage oncology drugs identified per pharmacy (mean±standard deviation)	2.12 ±2.29	2.33 ±2.57	2.15 ±2.602	4.36 ±4.11
Online pharmacies not requiring prescriptions for oncology drugs	78.4% (58/74)	78.2% (43/55)	73.4% (58/79)[1]	77.3% (17/22)
Oncology specific domain name	10.8% (8/74)	12.7% (7/55)	6.3% (5/79)	9.1% (2/22)
Legitimacy according to LegitScript				
Rogue	23 (31.1%)	16 (29.1,0%)	48 (60.8%)	15 (68.2%)
Unapproved/Unverified	18 (24.3%)	11 (20.0%)	11 (13.9%)	3 (13.6%)
Legitimate	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not in database	33 (44.6%)	28 (50.9%)	20 (25.3%)	4 (18.2%)
Legitimacy according to VIPPS				
Not recommended	11 (14.9%)	9 (16.4%)	26 (32.9%)	9 (40.9%)
Recommended	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not in database	63 (85,1%)	46 (83,6%)	53 (67.1%)	13 (59.1%)

Discussion

1. Characteristics of the biopharmaceutical drug market

While the share of small molecules in the new molecular entity approvals per year is stagnating, the market of specialty drugs such as biopharmaceuticals, orphan drugs and ultra-orphan drugs has been growing since the 1980s [280-284]. These characteristics are quite noticeable in the somatropin drug market as well [285-287]. Beside the challenges and unsolved issues in the official biopharmaceutical industry (e.g., terminology, manufacturing, authorization and regulation, biosimilars) [284], which can cause uncertainty in patients, there are other factors that may contribute to the illegal online marketing of biological drug products. The attractiveness of biopharmaceutical market for counterfeiters lies in the opportunity for high profit and extensive number of illegal indications. As the technological background has evolved, the falsification of more complex parenteral drugs such as biologics are threatening the patients and clients via the traditional (offline) and non-traditional (Internet) black market channels [157, 254, 255, 288, 276, 289-295].

1. Therapeutic indications, off-label and illicit use of somatropin

Beside insulin the recombinant human growth hormone (rhGH, somatropin) was the first biopharmaceutical drug approved by the Food and Drug Administration in 1987 and several products have followed Humatrope® in the United States and in Europe as well (see **Table XI.**).
The authorized human growth hormone drug products are generally indicated for the treatment of children with growth failure or short stature due to growth hormone deficiency (GHD) or other disorders (e.g.: Prader-Willi syndrome, Turner syndrome, chronic kidney disease, etc.) [296, 297]. Beside the indications and dosing regimens approved by the authorities, the hormone has numerous authorized „Off label" uses in clinical practice such as the supplementary therapy to reduce the effect of long term steroid therapy in different kind of immunological disorders [298-305].

1. The potential acute and long term adverse effects of unauthorized use of somatropin products

The claimed beneficiary effects of growth hormone have gone to extremes in the public and most likely mask the unwanted adverse effects of this hormone [306]. However, there is little evidence of the anabolic effect of somatropin in healthy individuals, as the acute application may worsen the exercise performance and lengthen recovery. One of the potential adverse effects is the cardiac arrhythmia originated from the high fatty acid level in short term use [306]. Chronic administration of high doses of rhGH may result in metabolic alterations causing cardiovascular and blood glucose disorders (cardiac instability, hypertension, insulin resistance, type 2 diabetes) and neurological disorders (carpel tunnel syndrome) [252, 306-308]. Long term abuse of hGH may represent in conditions similar to acromegaly, a state with proved increase in morbidity and mortality [309].

Table XI. Human growth hormone products with marketing authorization in Europe[1], in the United States[2] and Hungary[3]

	Drug brand name	Authorization Date	Marketing Authorization Holder	Biosimilar (According to EMA)	European Medicines Agency[2] (EU)	Food and Drug Administration [1] (USA)	National Institute of Pharmacy and Nutrition[3] (HUN)
1	Humatrope	1987.	Lilly			x	x
2	Nutropin	1994.	Genentech			x	
3	Genotropin	1995.	Pharmacia and upjohn			x	x
4	Nutropin Aq	1995.	Genentech			x	
5	Zomacton	1995.	Ferring			x	x
6	Saizen	1996.	Emd Serono			x	
7	Serotism	1997.	Emd Serono			x	
8	Norditropine Flexpro/Simplexx	2000.	Novo Nordisk Inc			x	x
9	NutropinAq 10 mg/2 ml (30 NE)	2001.	Ipsen Pharma		x		x
10	Zorbtive	2003.	Emd Serono			x	
11	Valtropin	2006.	BioPartners GmbH	x			
12	Omnitrope	2006.	Sandoz GmbH			x	
13	Omnitrope 1,3 mg/ml; 10 mg/1,5 ml; 15 mg/1,5 ml; 5 mg/1,5 ml	2006-2014.	Sandoz GmbH	x	x		x
14	Valtropin	2007.	Lg Life			x	
15	Saizen 5,83 mg/ml	2011.	Merck				x
16	Saizen 8 mg/ml	2011.	Merck				x

[1] www.fda.gov, [2]www.ema.europa.eu, [3]www.ogyei.gov.hu

1. Overview of the online accessibility of biological drugs and products

Seven articles dealing with similar research topic (illicit trade of somatropin or other protein drugs) were identified that primarily focus on the doping and black market with the description of the different analytical techniques [253, 254, 310, 311] and legal aspects of the anti-aging quackery [312, 313]. There is one article where Frank M. Jung goes through the role of comprehensive instrumental techniques and hospital pharmacists in the identification and prevention of counterfeit protein drugs entering to the closed pharmaceutical supply system based on literature overview [288]. Our sample size (3 vials) is similar to most of the studies found in the literature as generally the sample size of these researches varies from 1 to 5 vials. There is one large study that was taken under the umbrella of the Bureau of Customs Investigation. In the study more than 3500 ampules of confiscated and black market hGH products were analysed in the Cologne Anti-Doping Laboratory in a 3 year period [310]. The analytical findings of the literature shows that the black market products may contain the ingredient with different degradation profile or containing other active ingredient, or containing hGH, but not labelled as somatropin products [253, 254, 288, 310-313]. Similarly we faced with low active ingredient concentration and the joint degradation of the products. In comparison with the revealed articles our findings added a specific Internet search and the identification and characterization of vendors selling illegal human growth hormone products. Beside the quality assessment of the products ordered specifically from the Internet, a comprehensive evaluation of the Internet pharmacy websites and the sample acquisition and delivery circumstances and details were introduced.

1. Strengths and limitations of the risk based safety mapping of online market of somatropin products

The main limitation of our study is the lack of comprehensive analysis including purity test and peptide mapping. Also because of the small sample size the microbiological evaluation could not be carried out. With these techniques the magnitude of the potential health risk can be identified [288]. Also it can be seen from literature as well, that our findings are time connected as the features of the online market are constantly changing in time. However these snapshots of the illicit online marketing of medications are proving that there is a considerable and stable threat for individuals and the public as well.

As the continuous monitoring of the illegal Internet sale of pharmaceuticals is lacking, generally these cross sectional studies are the main sources of information in this field.

The main strength is that a combined method was used to give a complete patient safety characterization (prescription requirements, vendor location, regulatory body logo, verification status, packaging and product information) along with the analytical evidence of medication quality. The whole process was evaluated from the online search until the arrival of the products.

Further research opportunities include the increase of the sample size to gather further analytical and microbiological evidences and the possible continuous monitoring of the illegal vendor sites.

2. Drug shortage information sources and databases

Due to this relatively novel and serious global pharmaceutical market issue publicly available drug shortage information is needed to handle and manage product supply disruptions and their consequences [27, 38]. National online shortage catalogues can provide valuable information for healthcare personnel and policy makers on the extent and nature of the problem at a country level [46]. Additionally, available shortage information may also prevent patients from “gray market” suppliers and buying counterfeit and illicit medications through the Internet [38].

In 2011, President Obama issued an Executive Order emphasizing the importance of notification in helping Food And Drug Administration (FDA) to prevent drug shortages [80], while international recommendations by the International Pharmaceutical Federation (FIP) and the European Association of Hospital Pharmacists (EAHP) also highlighted the establishment of publicly accessible information resources on medicine shortages [24, 270]. By this time almost every health authority and medicine agency has taken steps to collect information proactively from the manufacturers and to provide shortage information on their websites. Extensive databases are available in the United States, Canada and Australia [27, 270, 314]. According to the 2014 survey of the EAHP shortage information or catalogues are also available in most European countries as well [25]. Bochenek et al in 2017 identified 31 drug shortage information sources in the European Union and the European Free Trade Association [41].

Although there is a centralized database collecting information about drug shortages in Europe that is maintained by the European Medicines Agency (EMA), unfortunately it only contains data that has been assessed by the Agency [28, 41, 267].

Following the analysis of eleven drug shortage databases, thirty seven active pharmaceutical ingredients (20% of 178 L01 ATC) were identified by the authors in 2014 and 2016. We wanted to highlight the time pattern of oncology drug shortages during the two evaluated years.

As it can be seen in **Figure 10.,** the total number of documented shortage events (active pharmaceutical ingredient on a shortage list) are nearly the same in 2014 (n=61) and 2016 (n=60) and represent a wide range of fourth level chemical ATC subgroups [80]. However, it is important to notice that the shortage status and pattern of active ingredients changed over time. We believe that systematic data collection and the analysis of shortage patterns over time support better understanding of shortage issues.

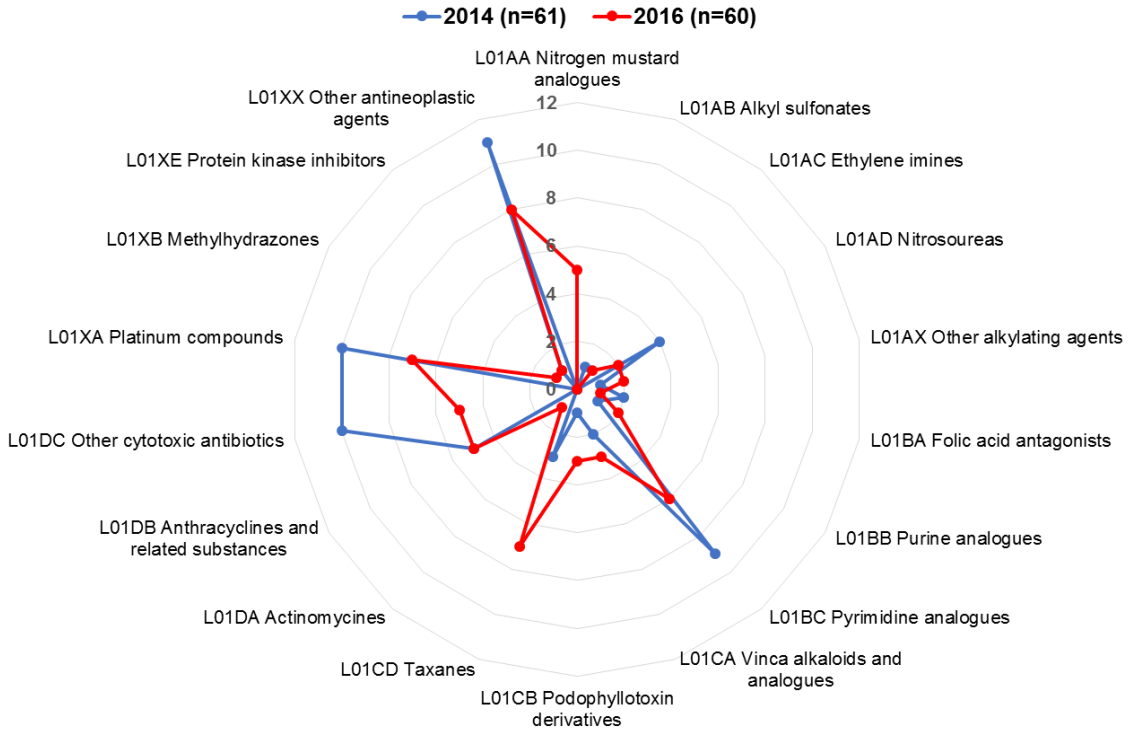

Figure 8. The pattern of identified oncology shortage active ingredients in 2014 and 2016.

2. Drug shortages and the Internet

Drug shortages turned into a global healthcare problem affecting safe and cost-effective patient care in most countries. Managing medication shortages requires a multi-disciplinary approach that integrates medical doctors, pharmacists and policy makers.

In order to combat product supply disruptions, regularly updated and publicly available drug shortage information is essential. Oncology is one of the most commonly affected therapeutic area concerning shortages in most developed countries [315-316].

The limited access to pharmaceuticals is most likely a strong motivator for patients and healthcare professionals to obtain treatments outside the traditional drug-supply-chain.

Internet trade is among the most convenient alternative purchasing options for medications. Unfortunately, the online medication market is currently dominated by illegitimate vendors offering products without medical prescriptions and adequate professional supervision [56, 64, 317]. The chance of obtaining illegitimate, substandard or counterfeit dugs from the Internet is high as currently there is no effective international supervision and law enforcement of the online pharmaceutical market. For drugs in short supply, providers and hospitals may search beyond conventional sources to obtain the medications. Thus, shortages of key medicines have created opportunities for illegitimate traders for price markups, while also increasing the chance of infiltration of counterfeits to the market [84, 318].

2. Online accessibility of oncology drugs

Our aim was to evaluate the online accessibility of oncology drugs affected by drug shortages to highlight the dangers of the unregulated sale of possibly life threatening products. Oncology drugs affected by shortages were identified by evaluating national and international drug shortage databases, while online availability was evaluated by searching for these shortage antineoplastic agents with the popular search engine Google. Direct online drug sellers were assessed for operational, distributional and patient safety characteristics.

Oncology drugs affected by shortages were generally available on the Internet. Accordingly, it seems that these vendors do not differentiate between plentiful and shortage drugs, and can offer both categories for sale. Numerous Internet vendor sites (25.5%) operated in both evaluated years, indicating illegitimate sellers' continuous service and broad product portfolio. Current findings are in line with our previously published results on long-term follow-up of Internet pharmacies [62].

Shortage oncology medications were accessible without medical prescription by the majority (73.4-78.4%) of websites. Similarly to previously published studies on Internet pharmacies we have documented that numerous (20.3% in 2014 and 27.8% in 2016) vendors have not displayed any contact information on their websites and in most cases (90.5% and 91.1% in 2014 and 2016 respectively) no healthcare professional was available for customers' consultation.

None of the evaluated websites were legitimate (approved or recommended) by the VIPPS or the LegitScript Internet pharmacy verification databases. Nearly one third of the websites (31.1%) were definitely unregulated (rogue) - thus explicitly dangerous - by the LegitScript database in the year 2014 and seemingly the ratio of illegal actors increased (60.8%) within two years. However, simultaneously the completeness of databases has improved.

The analysis of shortage catalogues showed that the drug shortages identified in Hungary are also represented internationally (Europe, North-America, Australia), although with somewhat different appearance and duration. However, the identified number of the internationally significant shortages can be considered low (9 and 4). The reason for this may originate from the lack of completely developed data collection and database structures in the field of shortage reporting. If we look at the result of surveys and the scientific literature, there is a greater number of oncology shortage drugs in Europe and United States as well [38, 136, 316, 319]. The authors believe that their findings illustrate a global phenomenon as the comparison of key findings of our study based on national shortage list were comparable with the search results based on internationally significant shortages.

It is highly likely that anyone searching online for drugs in shortage will encounter a suspect seller, even when only searching for product information rather than with the primary intention of buying a product. It should be emphasized and communicated toward patients, healthcare professionals and policy makers that not only shortages but also the online sales of oncology drugs that are in short supply pose a global problem as shown in our study. It represents a high risk to the patient care as these products are not available through the closed drug supply chain, but are obtainable over the Internet.

A gray market of shortage oncology drugs has been identified by the current study. It seems that the limited access to pharmaceuticals within the traditional supply-chain is a challenge for healthcare while being just another opportunity for illegitimate online sellers.

A multidisciplinary approach - including law enforcement, regulatory agencies, manufacturers, and customs - is required to combat both drug shortage issues and the illegal Internet trade of medications. The problems and challenges can only be resolved with harmonized actions at international, national and local institutional levels [43, 64, 80, 234, 321, 322].

2. Strengths and limitations of analyzing the online accessibility of oncology shortage drugs

The main strengths of our study include: up-to-date information regarding the joint threat of oncologic drug shortages and illegal Internet pharmacies, deeper insight into the temporality and relationship of these two threats and their possible effects on healthcare systems compared to previous studies [155, 160, 256]. A representative number of eleven drug shortage databases and internationally significant drug shortages were identified and their Internet availability was assessed. Also an inadequate function of the NABP online verification page was discovered.

This study also has limitations which need to be pointed out. The main limitation is that the complete risk based safety mapping [258] of online pharmaceutical market was not carried out, as the medications were not purchased. Actual purchases of oncology products would have provided a more in depth analysis and could have pointed out further patient and medication safety risks. Evaluation of the transportation, storage, packaging, product and patient information leaflet contents, and the analysis of chemical and microbiological quality would have added further useful data. It should be noted that test purchase of oncology drugs raises several legal, ethical and safety issues. Among numerous factors, unfortunately geographic location and language of search terms can affect search engine results. The research group aimed to perform standardized searches and exclude different sources of bias as described in Methods. Regional differences originating from geographic location and language can be minimized if English terms are used during searches and first five search engine result pages (fifty results) are all evaluated. Accordingly, regardless of geographical location most visited online pharmacy websites can be identified representing European setting.

The authors had to face a methodological limitation as the quality of shortage information presented in the databases is highly variable and unfortunately difficult to assess [323]. However, the authors think that currently the best method to describe this global phenomenon and tendencies is based on the assessment shortage databases [324-326].

Conclusion

There are numerous drugs which are liable for illegal trade. Somatropin was chosen for our study as it is a relatively innovative product and beside its approved indications several unauthorized off-label and illegal uses have been published previously. Our results clearly illustrate that prescription only biologic drugs are widely available on the Internet and can be easily accessed by anyone. However numerous patient safety concerns are raised based on our study results (e.g.: access without prescription and compromised product quality).

Most online vendors did not require a valid medical prescription before dispensing. Limited or even no medical information was provided for customers and patients. Additionally, none of the websites requested any health information during the ordering process or before purchases. Our result support the fact that online medications are not necessarily cheaper as price including shipping fees was similar for one sample, while significantly higher for the other two samples. All three purchased somatropin samples arrived within a relatively short time and products seemed to be authentic by visual examination.

Although biological drugs may require special precautions for storage and administration none of the samples in our study meet the necessary criteria. The lack of the necessary product information provided by the sellers and appropriate language package leaflet instruction negatively influences proper and effective use of the products. Necessary administration devices were not supplied with the medications and storage temperatures were not guaranteed during handling and shipping.

In accordance with the results of the CZE-UV and ESI-MS measurements, all the online purchased growth hormone products contained somatropin (22125 Da), however, in significantly ($p < 0.001$) lower concentration than indicated. Additionally, unknown protein content was also detected for sample B (22229 Da and 22321 Da). Identification of these compounds would require peptide mapping experiments. These results suggest that the online ordered products contained the same active ingredient but also that these preparations had undergone significant degradation most likely due to inadequate storage and/or delivery conditions. Presence of these unknown peptide components doubt safe use of the product. Beside the concerns raised by the internet availability of biopharmaceuticals, healthcare systems, institutions and patients are facing new challenges like the increasing number of shortage drugs [33, 42, 318, 320, 324, 327, 328, 329, 330, 331] and the possibilities of purchasing out-of-stock medicines outside the traditional drug-supply-chain [56].

Currently international legislation and national authorities cannot guarantee continuous drug supply in several therapeutic areas affected by shortages and also the effective measures assuring safe internet sale of pharmaceuticals are still lacking. However, these problems are strongly related as the unavailability of medications, especially in the case of life saving therapies, can be a driving factor to procure pharmaceuticals from online vendors [80, 318]. Health institutions, clinicians and pharmacists may not be aware that patients can buy drugs from uncertain and illegitimate sources and these products are likely to influence the success of therapies [58]. The most vulnerable group is the patients as they are unable to weigh the potential benefits and actual dangers of using medicines from illegitimate sources. To avoid the penetration of illegal, substandard and falsified products a holistic approach is needed in combining international and national preventive measures, local institutional policies and public awareness campaigns [57].

Summary and novel findings

1. **A Risk based safety mapping of the online somatropin market was carried out:**
    - Growth homone products are available and marketed directly to patients:
        - 26 relevant search engine results and 17 internet vendors were identified and the products advertised to patients correlate with the national market share of somatropin products.
    - Definite patient safety risks were identified concerning online pharmacies selling somatropin products, because:
        - 94% of the vendors did not require valid medical prescription before dispensing these prescription only products,
        - 35% of the vendors aimed to facilitate purchases by marketing cheap prices and accessibility,
        - 82,4% of the online pharmacies did not display any postal address or phone number,
        - 70% displayed no medical information on the websites and healthcare professional was not accessible in 100% of internet pharmacies
        - None of the vendors were classified as approved or legitimate according to the LegitScript verification database.
        - Neither (0%) of the obtained somatropin (2 Genotropin products and one Omnitrope sample) products had any national (Hungarian) or English written information enclosed.
    - Definite medication safety risk was identified:
        - All products seemed to be authentic by visual examination of the packaging and ampules. However, all online samples had significantly ($p < 0.001$) lower somatropin concentration than indicated on the obtained products (35,10%, 52,50%, 53,22%) and unknown protein content was also detected in one sample.
2. **National and international oncology shortage drugs were identified and pattern of oncology shortage drugs was introduced:**
    - Following the analysis of eleven drug shortage databases, thirty seven active pharmaceutical ingredients (20% of 178 L01 ATC) were identified in 2014 and 2016.
    - The total number of documented shortage events (active pharmaceutical ingredient on a shortage list) were nearly the same in 2014 (n=61) and 2016 (n=60) and represent a wide range of fourth level chemical ATC subgroups.
    - Nine oncologic drugs that were in shortage globally in 2014 (bleomycin, carboplatin, carmustine, cisplatin, fluorouracil, gemcitabine, irinotecan, methotrexate, mitomycin) and four (bleomycin, carboplatin, cisplatin, etoposide) in 2016.

3. **Shortage oncology drugs are available and marketed directly to patients without no limitation and it is an international phenomenon threatening patient safety:**
    - All evaluated oncology drugs (100%) affected by shortages were available on the Internet in 2014 and 2016,
    - 74 and 79 Internet pharmacies were identified in the two years that were offering oncology shortage drugs to individuals,
    - The main evaluated parameters showed similarity for national and international shortage products (relevant links and websites within first 50 search engine results, number of shortage oncology drugs identified per pharmacy, prescription requirement, legitimacy).
    - There was generally no limitation by the majority (91.9% in 2014 and 97.45% in 2016) of the Internet pharmacies on the amount of medication that could be ordered.
    - Definite patient safety risks were identified:
        - 87,4% of the vendors in 2014 and 73,4% of the vendors in 2016 did not require valid medical prescription before dispensing these prescription only products,
        - 79,7% of the online pharmacies in 2014 and 72,2% of the online pharmacies in 2016 did not display any postal address or phone number,
        - Healthcare professional were accessible in only 9,5% and 8,9% of the vendors in 2014 and 2016,
        - None of the vendors were classified as approved or legitimate according to the LegitScript and VIPPS verification database.
4. **An important limitation of the VIPPS verification website was documented.**
    - The online tool was not able to identify explicit illegal websites that are otherwise listed among “Not Recommended Sites” by the NABP itself.

Further perspectives

Future perspectives of the research team include the continuous development of the Risk based safety mapping of online pharmaceutical market. We would like to identify additional high risk products, active pharmaceutical ingredients and illegitimate vendors to evaluate patient and medication safety risk. For this our aim is to cooperate with the Institutes and Departments from the Faculty of Pharmacy, Faculty of Medicine and Clinical Center. As our Department is working together with the National Board Against Counterfeiting's workgroup against counterfeit medicine (*Hamisítás Elleni Nemzeti Testület Gyógyszerhamisítás elleni munkacsoportja*) therapeutic areas highly affected by counterfeits in Hungary can also be identified (e.g.: participation in operation PANGEA regarding tramadol products in 2017.). Products and active ingredients that are in our focus of attention are the followings: oxytocin, antibiotics, quercetin, tramadol, benzodiazepines, eye drops treating glaucoma.

To quantify the real risk of illegal online internet sale of medicines and to provide valuable data about Hungarian citizens a Hungarian survey questionnaire was developed with 28 questions regarding online medicine purchase, online medicine purchase experiences and attitude, internet use, health state and medications. Data were collected directly from Hungarian citizens (n=1055) from Southern Transdanubian region who use outpatient health service for chronic or acute conditions. With the analyzation of data further vendors and products that reach patients can be identified. Preliminary data suggest that reasonable number of patients (25%) will purchase medications on the Internet in the near future and respondents who use the internet more and purchase goods online will more likely to buy medications online. Further, younger age and higher educational level will determine the medication purchase behavior.

The research group incorporated the identified and evaluated illegitimate online pharmacies (n=100) and the legal online pharmacies operating in Hungary (n=100) in an online available database prototype that can help consumers to differentiate between legal and illegal ones and to quantify the risk of hazard with a fast 5 question online tool. Our aim is to continue the development of this database prototype and include more internet vendors and refine the risk assessment.

We would also like to test and develop new rapid identification tools aiming falsified medications and illegal internet pharmacies: Thin Layer Chromatography, mobile application for consumers and health care professionals to analyze medicine authenticity or by using network research methods to crawl and identify networks of illegal internet pharmacy websites.

With the communication of our results to the public and the policy makers we would like to educate consumers/patients and health care workers about the health risk associated with the online purchase of pharmaceuticals, implement preventive measure in the Hungarian drug supply chain at community and hospital-clinical pharmacy level, and ultimately to make the internet pharmacy market a safer place.

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Supplementary information

Table S1: The query of the drug shortage databases for L01 ATC in 2014 and 2016

	Drug shortage information sources	Hungary		Germany		Belgium		France		Italy		The Netherlands		EMA		FDA		ASHP		Canada		Australia	
No.	**Acitve Pharmaceutical Ingredient (WHO ATC) (Total L01 ATC API n=178)**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**	**2014**	**2016**
1	amsacrine				x								x										
2	arsenic trioxide	x	x					x										x					
3	asparaginase				x																		
4	**bleomycin**	x	x							x		x	x				x	x	x				
5	bosutinib											x											
6	busulfan											x											
7	capecitabine		x			x	x				x												
8	**carboplatin**	x	x			x				x	x							x	x	x			
9	**carmustine**	x						x	x									x		x	x		
10	chlormethine								x														
11	cisplatin	x	x							x			x					x	x				
12	clofarabine											x											
13	cytarabine		x															x	x	x			
14	dacarbazine		x																				
15	dactinomycin												x										
16	dasatinib																				x		
17	daunorubicin																x						

18	decitabine											x											
19	docetaxel	x	x				x			x	x				x								
20	doxorubicin		x													x	x	x	x	x			
21	epirubicin	x									x									x			
22	etoposide	x	x		x																		x
23	fludarabine										x												x
24	**fluorouracil**	x								x								x					
25	**gemcitabine**	x	x							x										x			
26	**irinotecan**	x	x			x	x			x								x		x			
27	melphalan				x		x		x														
28	**methotrexate**	x	x			x												x					
29	**mitomycin**	x	x	x				x										x		x		x	
30	oxaliplatin	x	x			x				x													
31	paclitaxel		x							x	x		x										
32	procarbazine				x																		
33	temozolomide		x							x													
34	thiotepa								x														
35	topotecan	x	x		x															x			
36	vincristine										x										x		
37	vinorelbine	x	x																	x			

APIs used to conduct online search (n=22)

Internationally significant shortages in 2014 (n=9)

Internationally significant shortages in 2016 (n=4)

National drug shortages (Hungary) n=16 (2014) and n=19 (2016)

Table S2: The identified internet pharmacies selling oncology shortage drugs in 2014.

No.	URL	L01 ATC search APIs on the website	Is it possible to buy the products (Yes=1; No=0)	Contact informations (0=none, 1=partial, 2=street name and number; telephone number)	Is prescription required? (Yes=1; No=0)	Doctor/Pharmacist available? (0=none; 1=medical doctor; 2=pharmacist; 3=both)	Shipping to Europe (Yes=1; No=0)	Selling without prescription POM is a marketing message present? (Yes=1; No=0)	Selling to professionals as well? (Yes=1; No=0)	Is there limit in the order? (Yes=1; No=0)	LegitScript verification (0=not in database; 1=Rogue; 2= unapproved)	vipps.nabp.net (0=not in database; 1=not recommended; 2 =other)
1	allchemiststore.com	1	1	1	0	3	1	0	0	1	0	0
2	angelbiogenics.in	1	1	1	0	0	1	0	0	0	0	0
3	anthronomics.com	1	1	0	0	0	1	0	0	0	0	0
4	anticanceraid.co	2	0	1	0	0	0	0	0	0	0	0
5	anticancermedsrx.com	7	1	1	0	0	1	0	0	1	1	0
6	anticancersuppliers.com	1	1	1	0	0	1	0	0	0	0	0
7	besthealthcare365.com	1	1	1	0	0	1	0	0	0	1	0
8	buckadaypharmacy.com	2	1	1	0	0	1	0	0	1	2	1
9	buy-canadian-drugs-net	1	1	1	1	0	1	0	0	0	2	1
10	buycancerpills.com	2	1	1	0	0	1	0	0	0	1	0
11	buy-pharma.com	6	1	1	1	0	1	0	0	1	1	1
12	canadadrugpharmacy.com	0	1	1	1	0	1	0	0	0	2	1
13	canadadrugs.com	1	1	1	1	0	0	0	0	0	2	1
14	canadapharmacyonline.com	1	1	1	1	2	1	0	0	0	2	1
15	canadian-discount-pharmacies-com	1	1	1	1	0	1	0	0	0	2	0
16	canadian-pharmacies-online.net	1	1	1	1	0	1	0	0	0	2	0
17	canamericaglobal.com	2	1	1	0	0	0	0	0	1	2	1
18	cancercurepharmacy.com	12	1	1	0	2	1	0	0	0	0	1
19	cancermedicine.co.in	2	1	1	0	0	1	0	0	0	1	0
20	cancertumourmedicines.com	1	1	1	0	0	1	0	0	0	0	0
21	chemistdirect.co.uk	1	1	1	1	3	1	0	0	0	0	0
22	chimedsupply.com	1	1	1	0	0	0	0	1	0	0	0
23	community-rx-online-com	1	1	1	1	2	1	0	0	1	0	0
24	drugpillstore.com	1	1	1	0	0	1	0	0	1	1	0
25	drugsdropship.net	1	1	1	0	0	0	0	0	0	0	0
26	drugshoponline.com	1	1	0	0	0	0	0	0	0	1	0
27	drugssquare.com	7	0	0	1	0	1	0	0	0	1	0
28	dvijaypharma.in	2	1	1	0	0	1	0	0	0	0	0
29	edmedicinemart.com	1	1	1	0	0	1	0	0	0	0	0
30	edmedicinestore.com	1	1	1	0	0	1	0	0	0	0	0
31	exportersindia.com	1	1	1	0	0	1	0	0	0	0	0
32	expressbuypharma.com	1	0	1	1	0	1	0	0	0	1	0
33	expresscheapgeneric.com	10	0	1	1	0	1	0	0	0	1	0
34	fastdrugshop.com	1	1	1	0	0	1	0	0	0	0	0
35	firstgenericsmart.be	1	1	1	0	0	1	0	0	0	0	0
36	flavorx.com	1	1	0	0	0	1	0	0	0	0	0
37	genericanticancer.com	0	1	0	0	0	0	0	0	0	1	0
38	globaldiscountdrugs.com	4	0	1	0	2	1	0	0	0	1	1
39	goldenmds24.com	1	1	0	0	0	1	0	0	0	1	0
40	goldpharma.sc	1	0	0	0	0	0	0	0	0	0	1

No.	URL	L01 ATC search APIs on the website	Is it possible to buy the products (Yes=1; No=0)	Contact informations (0=none, 1=partial, 2=street name and number; telephone number)	Is prescription required? (Yes=1; No=0)	Doctor/Pharmacist available? (0=none; 1=medical doctor; 2=pharmacist; 3=both)	Shipping to Europe (Yes=1; No=0)	Selling without prescription POM is a marketing message present? (Yes=1; No=0)	Selling to professionals as well? (Yes=1; No=0)	Is there limit in the order? (Yes=1; No=0)	LegitScript verification (0=not in database; 1=Rogue; 2= unapproved)	vipps.nabp.net (0=not in database; 1=not recommended; 2 =other)
41	greaterlondonpharmacy.com	1	1	0	0	0	1	0	0	0	1	0
42	indiamart.com	3	1	1	0	0	1	0	0	0	0	0
43	internationaldrugmart.com	7	0	1	0	2	1	0	1	0	1	1
44	kiwidrug.com	1	1	1	1	0	0	0	0	0	1	1
45	lancerhealthcare.com	1	1	1	0	0	1	0	0	0	0	0
46	magiccuringtrade.com	1	1	0	0	0	1	0	0	0	0	0
47	medcentercanada.com	1	1	1	0	0	1	0	0	0	2	1
48	medicareremediesindia.com	3	1	1	0	0	1	0	0	0	0	0
49	medications.com	1	1	0	0	0	1	0	0	0	2	1
50	medicinedropshipper.com	1	1	1	0	0	1	0	0	0	0	0
51	medicines2u.com	1	1	1	0	1	1	0	0	0	2	0
52	medidart.com	4	0	1	1	0	1	0	0	0	2	0
53	mooremedical.com	1	1	1	1	0	1	0	0	0	2	0
54	mybiosource.com	0	0	1	0	0	1	0	1	0	0	0
55	nexuslife.in	1	1	1	0	0	1	0	0	0	0	0
56	northdrugstore.com	0	1	1	1	0	1	0	0	0	2	1
57	northwestpharmacy.com	0	1	1	1	0	0	0	0	0	2	1
58	olx.ph	1	1	0	0	0	1	0	0	1	0	0
59	openmedshop.com	1	1	1	0	0	1	0	0	0	1	0
60	ourmeds.org	2	1	0	0	0	1	0	0	0	1	0
61	panthermeds.com	4	1	0	1	0	1	0	0	0	2	0
62	pfytonremedies.com	1	1	1	0	0	1	0	0	0	0	0
63	pharmacy2u.co.uk	8	1	1	0	1	1	0	0	0	2	0
64	pharmacyescrow.org	1	0	1	0	0	1	0	0	0	1	0
65	pharmacy-network.vu	1	1	1	0	2	1	1	0	1	0	0
66	pillsbill.us	0	1	0	0	0	1	0	1	0	1	0
67	safetorontoshop.com	1	1	1	0	0	1	0	0	0	1	0
68	saliuspharma.in	3	1	1	0	0	1	0	0	0	0	0
69	adv-care.com	4	0	1	0	2	1	0	0	0	2	1
70	shabbirmedicalhall.in	1	1	1	0	0	1	0	0	0	1	0
71	shyampharma.com	1	1	1	0	0	1	0	0	0	0	0
72	smartrxoutlet.com	1	1	0	0	0	1	0	0	0	0	0
73	topdrugmart.com	1	1	1	0	0	1	0	0	1	1	0
74	yourtableteshop.com	1	1	1	0	0	1	0	0	0	1	0

Table S3: The identified internet pharmacies selling oncology shortage drugs in 2016.

No.	URL	L01 ATC search APIs on the website	Is it possible to buy the products (Yes=1; No=0)	Contact informations (0=none, 1=partial, 2=street name and number; telephone number)	Is prescription required? (Yes=1; No=0)	Doctor/Pharmacist available? (0=none; 1=medical doctor; 2=pharmacist; 3=both)	Shipping to Europe (Yes=1; No=0)	Selling without prescription POM is a marketing message present? (Yes=1; No=0)	Selling to professionals as well? (Yes=1; No=0)	Is there limit in the order? (Yes=1; No=0)	LegitScript verification (0=not in database; 1=Rogue; 2= unapproved)	vipps.nabp.net (0=not in database; 1=not recommended; 2 =other)
1	internationaldrugmart.com	7	1	2	0	2	1	0	0	1	1	1
2	edmedicinestore.com	1	1	2	0	0	1	0	0	0	0	0
3	pro-agra.com	1	1	2	0	0	1	0	0	0	0	0
4	indiamart.com	1	1	2	0	0	1	0	0	0	0	0
5	actizapharmacy.in	7	1	2	0	0	1	0	0	0	0	0
6	ishaanpharma.com	1	1	2	0	0	1	0	0	0	0	0
7	cancercurepharmacy.com	10	1	2	0	2	1	0	0	0	2	1
8	onlinemedsus.com	4	1	2	0	2	1	0	0	0	1	0
9	pharmawebcanada.to	12	1	1	1	0	1	0	1	0	1	1
10	anticancermedsrx.com	13	1	0	0	0	1	0	0	0	1	0
11	canada2u.net	1	1	1	1	0	1	0	1	0	1	1
12	cheap-generic.co	11	1	1	0	0	1	0	0	0	1	0
13	buypharma1.com	7	1	1	0	0	1	0	0	0	1	0
14	drugssquare.com	7	1	1	1	0	1	0	1	0	1	0
15	buy-modafinil-uk.com	3	1	1	0	0	1	0	0	0	1	0
16	saverxcanada.to	2	1	1	1	0	1	0	1	0	1	0
17	canadadrugs.com	3	1	2	1	0	1	0	0	0	1	1
18	urbanpharma.com	1	1	1	0	0	1	0	0	0	1	0
19	pharm-store.com	1	1	0	0	0	1	0	0	0	1	0
20	medplusmart.com	3	1	1	0	0	1	0	0	0	0	0
21	planetdrugsdirect.com	1	1	1	1	0	1	0	0	0	1	1
22	dropshipmd.com	2	1	0	0	0	1	0	0	0	1	0
23	medicair.co.za	1	1	0	0	0	1	0	0	0	1	0
24	canadianpharmacymeds.com	1	1	1	1	0	1	0	0	0	1	0
25	allchemiststore.net	3	1	1	1	0	1	0	0	0	0	0
26	superbgenerics.com	1	1	1	0	0	1	0	0	0	1	0
27	pharmacymarketonline.com	1	1	1	0	0	1	0	0	0	1	1
28	chemistdirect.co.uk	1	1	0	1	0	1	0	0	0	2	0
29	canadapharmacyonline.com	1	1	1	1	0	1	0	0	0	2	1
30	cancerdrugs.supply	1	1	1	0	0	1	0	0	0	1	0
31	online-pharmacy-one.org	1	1	1	0	0	1	1	0	0	1	0
32	medcentercanada.com	1	1	1	0	0	1	0	0	0	1	1
33	http://secure.adv-care.com	3	1	2	0	2	1	0	0	0	2	1
34	genericmds.com	2	1	0	0	0	1	0	0	0	1	1
35	buygenericmd.com	1	1	0	0	0	1	0	0	0	1	0
36	exportersindia.com	1	1	2	0	0	1	0	0	0	0	0
37	topdrugmart.co	1	1	0	0	0	1	0	0	0	1	0
38	buymeds247online.com	1	1	0	0	0	1	0	0	0	1	0
39	pharmacysell.net	1	1	0	0	0	1	0	0	0	1	0
40	bestbuymedsonline.com	1	1	0	0	0	1	0	0	0	0	0

No.	URL	L01 ATC search APIs on the website	Is it possible to buy the products (Yes=1; No=0)	Contact informations (0=none, 1=partial, 2=street name and number; telephone number)	Is prescription required? (Yes=1; No=0)	Doctor/Pharmacist available? (0=none; 1=medical doctor; 2=pharmacist; 3=both)	Shipping to Europe (Yes=1; No=0)	Selling without prescription POM is a marketing message present? (Yes=1; No=0)	Selling to professionals as well? (Yes=1; No=0)	Is there limit in the order? (Yes=1; No=0)	LegitScript verification (0=not in database; 1=Rogue; 2= unapproved)	vipps.nabp.net (0=not in database; 1=not recommended; 2 =other)
41	yourmeds247.com	1	1	0	0	0	1	0	0	0	1	0
42	globaldiscountdrugs.com	2	1	2	0	2	1	0	0	1	1	1
43	anticanceraid.co	3	0	2	0	0	1	0	0	0	2	0
44	canada-edrugs.to	1	1	1	1	0	1	0	1	0	1	0
45	buy-pharma.co	2	1	1	0	0	1	0	0	0	0	1
46	specialitiespharma.com	2	1	2	0	0	1	0	0	0	0	0
47	indianpharmanetwork.co.in	1	1	2	0	0	1	0	0	0	0	0
48	medidart.com	2	1	2	0	0	1	0	0	0	0	0
49	77canadapharmacy.com	1	1	1	0	0	1	0	0	0	1	1
50	canamericaglobal.com	1	1	1	0	0	1	0	0	0	1	1
51	medicinesdelivery.com	1	1	1	0	0	1	0	0	0	1	0
52	commoner.org.uk	1	1	1	0	0	1	0	0	0	0	0
53	procanadadrugs.com	1	1	1	0	0	1	0	0	0	2	1
54	northpharmacyrx.com	1	1	0	1	1	1	0	0	0	1	0
55	easy.md	1	1	2	0	0	1	0	0	0	1	1
56	brandmedicines.com	1	1	1	0	0	1	0	0	0	1	0
57	buckadaypharmacy.com	2	1	1	1	0	1	0	0	0	1	1
58	hongkongdropshipper.com	2	1	0	0	0	1	0	0	0	1	0
59	canadadrugsonline.com	1	1	1	1	0	1	0	0	0	2	1
60	npdpharmacy.net	1	1	0	0	0	1	0	0	0	1	0
61	ipharmacylist.com	1	1	0	0	0	1	0	0	0	1	1
62	allgenericpharmacy.com	2	1	1	0	0	1	0	0	0	0	0
63	alishech-vmc.net	1	1	0	0	0	1	0	0	0	0	0
64	rxusa.com	1	1	2	0	0	1	0	0	0	2	1
65	onlineshoppharmacy.com	1	1	0	1	0	1	0	0	0	1	0
66	freedom-pharmacy.bz	1	1	0	0	0	1	0	0	0	1	0
67	universaldrugstore.com	1	1	1	1	0	1	0	0	0	2	1
68	safemeds4all.com	1	1	1	1	0	1	0	0	0	1	0
69	realhealthshop.com	1	1	1	0	0	1	0	0	0	0	0
70	northdrugstore.com	1	1	1	1	0	1	0	0	0	2	1
71	cheapodrugs.com	1	1	2	1	0	1	0	0	0	1	1
72	genericworldpharm.com	1	1	2	0	0	1	0	0	0	0	0
73	magnusonlinepharmacy.com	1	1	1	0	0	1	0	0	0	1	0
74	usmedicinestore.com	1	1	0	0	0	1	0	0	0	0	0
75	canadadrugpharmacy.com	1	1	1	1	0	1	0	0	0	1	1
76	genericseldenafil.com	1	1	0	0	0	1	0	0	0	1	0
77	bestpricerx.com	1	1	1	1	0	1	0	0	0	2	1
78	buyanticancermedicine.com	1	1	2	0	0	1	0	0	0	0	0
79	pharmacy-network.vu	0	2	1	1	0	1	0	0	0	0	0