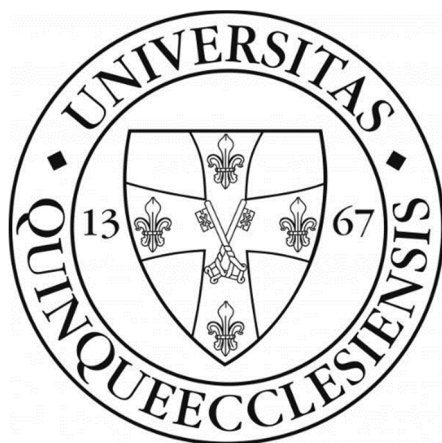


**Evaluation of the Online Pharmaceutical Market
and the Dangers of Counterfeit Medicines:
Comprehensive Investigation of Illicit Online Trade of semaglutide
and the Influence of Search Engine Recommendations**

Doctoral (Ph.D.) Thesis

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1. INTRODUCTION

1.1. The Online Pharmaceutical Market

According to e-commerce statistics published by Eurostat in 2023, 94.56% of European Union citizens accessed the internet in the last 12 months, increased from 88.32% in 2014. Notably, out of these individuals, 62.86% reported an online purchase at least once in the last 3 months, and 21.76% reported purchasing nonprescription medicines or dietary supplements online. These statistics demonstrate a growing trust in online health and wellness related purchases. This data is supported by research demonstrating that the internet, including social media, has become a common medium for purchasing medicines online. The shift towards online shopping is mainly attributed to practicality and convenience combined with cost savings that appeal to a wide range of consumers and has increasingly influenced consumer behavior worldwide. The COVID-19 pandemic, however, has further boosted the trend of purchasing medicines via the internet and has accelerated the adoption of online pharmacy services, as seen in the establishment of clinical pharmacist telehealth services during the pandemic.

Significant growth of the online pharmacy market is expected in the coming years, with a projected market volume of US\$81.37 billion by 2028. In terms of user penetration, it is predicted to be 23.62% in 2024 and is expected to increase to 30.92% by 2028, which demonstrates a significant expansion of the market's reach and popularity among consumers worldwide.

1.1.1. Legal vs. Illegal Online Pharmacies: Defining the Landscape

The inherently uncontrolled environment of the internet often exposes patients to a mix of legal and illegal vendors during their online search for medications. Despite the presence of various national and international verification or accreditation initiatives such as EU common logo for legally operating online pharmacies, still both patients and health professionals face challenges in determining the reliability and legitimacy of the online pharmacy websites that appear in search engine results. One of the primary differentiating factors between legal and illegal online pharmacies is requirement of a valid prescription for ordering prescription drugs. Illegal online pharmacies threaten patient health and safety by selling medicines without requiring a valid prescription and supplying

substandard and/or falsified medicines that could lead to dangerous patient outcomes. Currently the Digital Pharmacy Accreditation program and the ".pharmacy" domain registry are in effect and maintained by NABP in the US, while in the European Union regulations for the legal sale of medicinal products via the internet was introduced in the form of Falsified Medicines Directive 2011/62/EU (FMD) which all member states of the EU follow. Parallel with the official governmental organizations, there are private enterprise specializing in website verification services, most prominent one being LegitScript which has an extensive database.

1.1.2. Prevalence of Illegal Online Pharmacies

Globally, the prevalence of illicit online pharmacies is substantial and growing, with illegal ones far more prevalent than legitimate ones, selling medications without prescriptions and bypassing regulatory safeguards meant to protect consumers. The WHO's estimation that 50% of medicines sold online are counterfeit highlights the severity of this issue, pointing to a large underground market that endangers patient health and safety worldwide. According to LegitScript in 2016, there were an estimated 30,000 to 35,000 internet pharmacies operating online. Only a small fraction of the internet pharmacies, an estimated 4%, were operating legally, which corresponds to an estimated 1200 to 1400 websites. This means majority of online internet pharmacies, a staggering 96% of the total, were operating illegally and failing to adhere to legal and safety requirements necessary for selling prescription drugs online. In 2017 NABP performed an extensive review of 11,688 internet pharmacies selling prescription medication to US patients and came to similar conclusions. NABP concluded that 95.8% of the websites evaluated (11,142) were operating out of compliance with state and federal laws and/or NABP patient safety and pharmacy practice standards.

1.2. Search Engine Optimization Methods Employed by Illegal Vendors

1.2.1. Traditional Search Engine Results Poisoning and Redirection

In the evolving digital economy of today, web traffic has a great significance, and this fact is well known to illegal vendors. Search engines have evolved into key intermediaries between consumers and merchants, due to their ability to direct a large

user base to online vendors, resulting in a significant increase in their turnover value. For this reason, the potential for generating and monetizing web traffic through search engine optimization (SEO) techniques has been attracting not only legitimate businesses but also entities engaged in illicit activities. Search engine results poisoning attacks and search-redirection attacks are increasingly common techniques used by illicit vendors, including illegal online pharmacies, to manipulate search engine results and direct user traffic to their websites, and have steadily grown yearly, taking over a larger share of search results, despite efforts by search engines and browsers to combat their effectiveness. Illicit vendors use various techniques to poison search engine results, commonly used techniques include Black-Hat SEO tactics, exploiting trending topics, hacking legitimate sites and redirection attacks.

1.2.2. New Generative AI Recommendation Vulnerabilities

To assess the impact of commercial implementation of new generative AI-based technologies on search engine results associated with the online pharmaceutical market, we conducted and published a structured comparative analysis of two generative AIs, Google Search Generative Experience (SGE) using converse mode and Microsoft Bing's Chat feature, using a general prompt simulating a user seeking advice on where to buy prescription drugs from the internet. While a larger proportion of results recommended users to visit legitimate pharmacies, a notable presence of links to illegal pharmacies was observed on both platforms, with 13.23% of Google SGE responses and 19.04% of links provided by Bing Chat's generative replies directing users to known illegal online pharmacies. Our findings indicate a concerning public health matter intersecting with a newly emerging technological development. This represents a significant potential safety risk which could lead to serious health and public health problems, in particular in the context of controlled substances and other popular medicines known to be counterfeited and highly abused.

1.3. Rationale for Investigating semaglutide

1.3.1. Global Prevalence of Obesity

Obesity has become a global epidemic over the past four decades and its global prevalence has nearly tripled. As of 2016, over 1.9 billion adults aged 18 and up were overweight (BMI 25-29.9), and over 650 million were obese (BMI 30+), accounting for 39% and 13% of the global adult population. These figures indicate a significant public health threat, as overweight and obesity are major contributing factors to the global burden of disease and are linked to an increased risk of developing medical complications such as insulin resistance and type 2 diabetes, hypertension and cardiovascular disease, dyslipidemia and non-alcoholic fatty liver disease, and an increased risk of several types of cancer, which ultimately may result in reduced life expectancy. The socio-economic impact of this epidemic is also considerable and is projected to be in excess of US\$4 trillion per year by 2035, which is nearly 3% of global GDP. Without improvements in prevention and treatment, if current trends continue, it is estimated that by 2035 over half of the world's population (over 4 billion people) will be overweight and one in four (nearly 2 billion people) would be obese. These dire projections highlight a major challenge that requires the development of effective interventions and weight loss solutions, including new pharmacological therapies.

1.3.2. Modern Weight Loss Pharmacotherapy and Clinical Importance of semaglutide

The field of weight loss pharmacotherapy has seen significant changes in recent years, primarily with the introduction of new incretin-based therapies targeting glucose and appetite regulation through the use of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA), which have received FDA approval in the last decade. Semaglutide is a GLP-1RA with a long half-life of up to 14 days, which allows for once weekly administration, which enhances patient compliance and convenience. Semaglutide therapy has been shown to trigger up to 15% reduction in body weight over a period of one year, when combined with exercise and healthy eating habits. It also significantly reduces fasting plasma glucose, and systolic

blood pressure as well as body weight, waist circumference and lipids, which contribute to its effectiveness in the management of type 2 diabetes.

1.3.3. Market Dynamics and Economic Importance of semaglutide

Novo Nordisk A/S is a Danish pharmaceutical company that has developed and holds the marketing authorization and worldwide rights to products containing semaglutide. Novo Nordisk's financial performance has increased dramatically recently, driven primarily by sales of its semaglutide-based drugs Ozempic and Wegovy, which accounted for 52% of the company's total sales of US\$23.6 billion in the first nine months of 2023, up significantly from 36% in the same period of 2022. Ozempic has experienced a significant rise in mainstream popularity as an off-label treatment for cosmetic weight loss due to widespread discussion and coverage by conventional news outlets as well as endorsements by celebrities and influencers on various social media platforms. Investor excitement over the Ozempic hype has driven Novo Nordisk's market capitalization from US\$230 billion in 2022 to more than US\$430 billion in 2023, which, means that remarkably, the company's market value is now greater than the entire annual economic output of its home country of Denmark.

1.3.4. Semaglutide Shortages and Counterfeit semaglutide

The rising popularity and increasing demand for Ozempic coupled with capacity constraints at several manufacturing sites has contributed to multiple widespread shortages in several countries and ongoing shortages in both the European Union and the United States. Ongoing shortages have resulted in significant difficulties for patients in accessing the drug, limiting legitimate access for diabetic patients as well as those looking for Ozempic for off-label use. This combination of rising demand and shortages inadvertently created the most fertile ground for the proliferation of illegal online pharmacies that aim to capitalize on the heightened demand to sell counterfeit, falsified or substandard versions of the medication, posing significant risks to public health. Counterfeit versions of Ozempic have been discovered in various countries such as Australia, Belgium, Ireland, Azerbaijan, Egypt, Iraq, Jordan, Lebanon, Nigeria, Turkey, Uzbekistan, Russia, the United States, Germany, Austria, and the United Kingdom. On

June 15, 2023, Novo Nordisk issued a warning about a fake version of Ozempic found in the United States. The counterfeit injection pen, which contained insulin rather than semaglutide, was allegedly obtained from a retail pharmacy. Novo Nordisk's semaglutide patent and market exclusivity will remain in effect for the next several years, and the earliest estimated date for generic entry is 2031. Therefore, all "generic" or compounded products containing semaglutide are counterfeit and falsified, as Novo Nordisk does not sell semaglutide in active ingredient form for compounding purposes and has taken legal action against compounding pharmacies and weight loss clinics for trademark infringement and illegal sale of compounded semaglutide containing products.

2. Aims and Objectives

In response to the growing threat posed by substandard and falsified medicinal products containing semaglutide, we developed a comprehensive research plan to conduct an in-depth investigation of the illicit online trade of semaglutide. We have utilized and updated the framework developed by our department regarding a complex risk-based methodology in the evaluation of hazards associated with medicinal products sourced via the internet. Accordingly, we were focusing on prevalence of online sale of semaglutide by identifying trending illicit vendors that are accessible through search engines, documentation of the characteristics of online vendors via website content evaluation, followed by analysis of the quality of semaglutide obtained through test purchases from these illicit online sellers using visual inspection markers, liquid chromatography–mass spectrometry (LC–MS) analysis and microbiological sterility tests. This intelligence method incorporates real-world evidence and a patient centered approach by simulating how patients acquire information online and purchase medicinal products from the online pharmacy market. By conducting this comprehensive research, we aimed to provide a clearer picture of the extent of the illicit online trade of semaglutide and to help establish resources and strategies to effectively combat this growing threat in order to protect patients, public health, and the integrity of the pharmaceutical supply chain.

3. METHODS

3.1. Research Design and Infodemiology Approach

3.1.1. Search Engine Result Page Analysis and Link Scraping

We developed a methodology which combines automated web crawling and search engine scraping with manual website evaluation. Initially, Google Trends data was analyzed to determine the top three countries exhibiting the highest search volumes for active pharmaceutical ingredient (API) semaglutide and its brand names, over a six-month period from December 1, 2022, to May 25, 2023. United States, Canada, and Ireland were identified as primary countries of interest due to their significant search volumes. Keyword combinations "buy [proprietary name/API]" and "buy [proprietary name/API without prescription]" were used to retrieve links from SERPs for Ozempic, Wegovy, and semaglutide. These search queries were crafted to represent purchase intent (i.e. buying prescription medications online), rather than informative types of searches (i.e. looking for product information). By documenting the top 30 results from SERPs, we consider our findings to be representative of online queries by most typical users at the time of evaluation. The results were then manually examined to determine legitimacy and categorized.

3.1.2. Evaluating Generative AI Recommendations

Evaluating search engine generative AI recommendations, and whether they contain links directing consumers to illegal online pharmacies is challenging and requires a different approach compared to the methodology used for evaluation of the traditional SERPs. We used "Where can I buy [proprietary name/API] online?" and "I am looking for an online pharmacy to buy [proprietary name/API] Please suggest a website where I can buy it!" as standard prompts on each generative AI platform with both the drug proprietary name and the APIs, the generated responses and recommended links could then be evaluated to determine legitimacy using the same methodology used for conventional search engine evaluations. It is important to emphasize that because of the dynamic nature of generative AI systems, similar questions and prompts may produce different results, therefore findings are not longitudinally comparable.

3.1.3. Website Content Evaluation and Determination of Legitimacy

The process of evaluating the legitimacy of online pharmacies involves a thorough visual inspection of the home page and various product pages, which is essential for determining the legitimacy of each online pharmacy link collected in the previous steps and sort them into the following four categories: legal online pharmacies, illegal pharmacies/vendors, telemedicine sites, and a collective "other" category for sites that do not provide pharmacy or telemedicine services. Following the initial categorization, each online pharmacy website undergoes a thorough evaluation to confirm whether it is a legitimate, legally operating online pharmacy or not. The primary indicators of a legally operating online pharmacy include the presence of relevant registration information, regulatory body logos, seals of approval, as well as being listed as a registered online pharmacy on the relevant authority websites.

To further assess website legitimacy, each online pharmacy domain identified from the SERP results is cross-checked against the Safe Pharmacy and LegitScript databases. Websites classified as "rogue" by LegitScript and/or "not recommended" by the NABP Safe Pharmacy verification database are to be considered illegal. A major key indicator for assessing an online pharmacy's legitimacy is the enforcement of prescription requirements for the sale of prescription-only medications.

The evaluation and categorization of semaglutide vendor websites was conducted independently by the dissertation author and supervisor, both pharmacists, to ensure evaluation objectivity. In cases of disagreement following the initial categorization, a collaborative discussion of the individual results took place to reach a consensus.

3.2. Test Purchasing

The selection process of websites for test purchasing involved assessing several variables, including the listed product formulation, lack or requirement of a valid prescription, promotion of off-label or unauthorized use, vendor's address and location, shipping conditions and restrictions, price, payment methods, and the comprehensiveness of the product description such as information related to side effects and precautions. Each step of the online ordering procedure was photographed, and video recorded for future reference. To simulate a patient experience, a private email account was created

for a virtual patient, a 38-year-old female. Following the recommended regimen simulating the first 2-week therapy of a new patient. Two 0.25 mg ampules/doses or an equivalent product was ordered from each domain.

3.3. Product Assessment

3.3.1. Physical Assessment

Good Manufacturing Practice (GMP) guidelines require manufacturers to ensure that their products are appropriate for their intended use and do not place patients at risk due to insufficient safety, quality, or efficacy. This includes the packaging of pharmaceutical products, which must protect the product from physical damage, contamination, and degradation. In order to provide a structured way of visual inspection of the product, different checklists and guidelines are available. For the purpose of this study, the International Pharmaceutical Federation (FIP) Visual Inspection Checklist, originally designed to assist healthcare workers in identifying substandard and counterfeit products, was adapted to evaluate the packaging and labeling of delivered products based on the methodology outlined in our own previous research.

3.3.2. Chemical Analytical Assessment

Stock solutions of the standard and polypeptide samples were prepared in methanol. The working solutions were diluted with water/acetonitrile/formic acid (49/49/2, v/v/v). The estimated concentration of the polypeptide samples after dilution was 5 µg/mL. The final concentrations of the standard used for calibration were 5, 1, 0.5, 0.25, and 0.1 µg/mL. Chromatographic separation was performed on a Thermo Ultimate 3000 UHPLC™ system with a Luna Omega PS-C18 reversed-phase column. Data-dependent mass spectrometric acquisition was performed using a Bruker Maxis 4G UHR-QTOF instrument. All data were processed using the Data Analysis 4.4 software package.

3.3.3. Microbiological Assessment

Sterility and microbiological contamination testing were conducted on lyophilized peptide samples purchased from Semaspace, Biotech Peptides, and US Chem Labs to assess product quality. Testing was performed at the ISO 14644-1 certified microbiology laboratory of PharmaValid Ltd. in Budapest, Hungary. Sterility testing was performed by direct injection technique according to the guidelines of the European Pharmacopoeia and the United States Pharmacopoeia, and bacterial endotoxin content measurement was performed by kinetic turbidimetry technique according to the guidelines of the European Pharmacopoeia and the United States Pharmacopoeia.

4. RESULTS

4.1. Online semaglutide Vendors

Following the evaluation of 1080 links from SERPs, we identified 317 links related to online pharmacies ($n/N\%=317/1080=29.35\%$). Among these, 183 links led to legitimate pharmacies ($n/N\%=183/317=57.73\%$), while 134 links directed users to 59 illegal pharmacy operations and vendor websites ($n/N\%=134/317=42.27\%$). Out of the 59 illegal pharmacies, 21 appeared multiple times in the SERPs, with semaspace.com being the most frequent, appearing in a total of 11 links. Semaspace.com's website displayed several typical characteristic features of illegal internet pharmacy operations, including highlighting no-prescription sales, discreet delivery, and promises of the lowest prices and money-back guarantees.

We discovered listings for various pharmaceutical products, including parenteral preparations like the Ozempic pen, unbranded semaglutide injection vials, and oral semaglutide tablets. A review of the LegitScript.com database showed 47.46% of the illegal websites ($n/N\%=28/59$) classified as "rogue", 23.73% ($n/N\%=14/59$) as "unapproved". Our results also indicated that remarkably, 18.64% ($n/N\%=11/59$) of the illegal pharmacy domains were absent from databases, illustrating the difficulty in maintaining a current list of illegal online pharmacies due to the ever-changing landscape and the evasive nature of these illegal operations.

Web traffic analysis provided by Similarweb Ltd. for the period of our investigation showed that between July to September 2023, the top 30 domains accumulated over 4.7 million visits, with the top five websites attracting more than 58% (n/N%=2,730,848/4,705,502) of the total traffic. The most visited sites included both traditional illegal pharmacies and new peptide-focused vendors, reflecting a rising interest in purchasing peptide-based products.

4.2. Test Purchasing and Product Delivery

Six online vendors offering parenteral semaglutide products were selected for comprehensive content evaluation and test purchases. These six rogue domains were selected based on their high prevalence in the SERPs, offering easy access to semaglutide products without a prescription, and affordability. All six online vendors were categorized as illegitimate by the LegitScript and/or NABP verification databases. Three websites offered Ozempic injection pens for sale, while the other three sold vials of lyophilized semaglutide powder to be reconstituted prior to injection by the user. The price for the smallest available dose and quantity ranged from US\$113 to US\$360 (mean±SD: US\$218.5±93.6). None of the vendors (0%) required a medical prescription or any health-related information from patients before or during the purchase, with Ozempic pen sellers even explicitly marketing their products as available without prescription. All vendors (100%) referred to weight loss and obesity on the product page and promoted the unauthorized and off-label use of Ozempic or semaglutide containing products for weight loss. Semaspace.com, not only didn't have any warning messages on the website or the product labels, but they have a dedicated before and after image gallery on their website as "success stories" and went far and beyond to encourage use, by explicitly providing instructions on how to mix semaglutide with bacteriostatic water and included a dosing and injection guide, they also included 4 packs of 10 syringes and alcohol wipe prep pads in the package.

All online test purchases were completed quickly, with most online vendors offering untraceable payment methods. Payment with cryptocurrency was encouraged and incentivized by offering a 5% discount or free shipping during the checkout process. After the initial email communication, seller shifted to WhatsApp Messenger for further communication and providing detailed instructions on how to send the required amount

of payment. Despite successful transactions, none of the Ozempic injections were shipped and we only received the lyophilized semaglutide product. Upon contacting the national customs office for further investigation, we could confirm that illicit vendors advertising Ozempic pens are "non-delivery e-commerce scams" and don't intend to ship any products. We documented 3 separate scams each asking for different fees including a US\$1,200 "Insurance fee", a €450 so-called "X-ray Custom Stamps" and US\$650 for "Insurance and Prescription stamps" to facilitate the clearance through Hungarian customs, with sellers promising full or partial refund of the fees upon successful delivery.

4.3. Physical Assessment of Delivered Products

We utilized an updated FIP checklist for the visual inspection of delivered products which was tailored specifically for this study by adapting a 22-item checklist for assessing the quality, safety, and regulatory compliance of the products to meet the specific needs of our project and the product's specific dosage form. In our analysis, authentic Ozempic achieved a full score of 22, indicating perfect adherence to the checklist's criteria. The illicit products managed to meet only a limited number of listed criteria, such as using a suitable container and closure for primary packaging, securely sealing the glass vial and effective protection of the product from external environment. The active ingredient's name was present on the package, spelled correctly, and the active ingredient's amount and unit were provided on the label. However, these preparations did not adhere to any of the remaining requirements, and as a result, lyophilized semaglutide products from semaspace.com, biotechpeptides.com, and uschemlabs.com scored significantly lower than the authentic product, only gaining 9, 8, and 8 points out of 22, respectively. These low compliance scores obtained by the illegal vendors highlight serious deficiencies in a wide range of areas such as regulatory compliance, accurate labeling, and supply of essential product information, which clearly signals the inherent risks of purchasing pharmaceutical products from unauthorized online vendors.

4.4. Quantitative and Qualitative Analysis Results

4.4.1. LC-MS Analysis Results

Semaglutide polypeptide can be accurately identified and quantified using mass spectrometry, by its distinctive peak at 1029.3 Da [M+4H]⁴⁺ in the mass spectrum, which

serves as an essential reference point for accurate analytical measurements. The chromatographic analysis showed one primary signal for semaglutide in each sample, suggesting the absence of peptide-like impurities. However, there was a significant discrepancy between the purity levels claimed by vendors (at least 99%) and the actual semaglutide content of the delivered product as determined by our LC-MS analysis. Products from Semaspace, US Chem labs, and Biotech Peptides showed significantly low polypeptide concentrations of 14.37%, 8.97%, and 7.70%, respectively, indicating much lower purity. By measuring the content of each vial, we determined the actual amount of API in each sample. It is important to note that none of the products contained the accurate amount of semaglutide as stated. In fact, all three products had significantly higher API levels than what was declared on their labels. Specifically, products from Semaspace and US Chem labs contained an astonishing 39% and 34% more semaglutide than indicated respectively, whereas the product from Biotech Peptides had a 29% higher concentration of semaglutide than what was advertised. These findings highlight substandard manufacturing practices by these rogue vendors, highlighting the risks associated with obtaining pharmaceutical products from these illegal sources.

| Sample | Total Weight of Powder in Vial | semaglutide Content indicated on Label | Measured semaglutide Content | Labeling Accuracy | Purity Indicated on Label or Website | Measured Purity |
|---|--------------------------------|--|------------------------------|----------------------|--------------------------------------|-----------------|
| Ozempic 1 mg solution for injection in pre-filled pen* (reference) | N/A | 1 mg | 1.05±0.02 mg | 105.05% | N/A | N/A |
| Biotech Peptides powder, vial | 50.1 mg | 3 mg | 3.86±0.14 mg | under-labeled (129%) | 99% | 7.70±0.28% |
| Semaspace powder, vial | 19.3 mg | 2 mg | 2.77±0.12 mg | under-labeled (139%) | 99% | 14.37±0.63% |
| US Chem Labs powder, vial | 14.9 mg | 1 mg | 1.34±0.07 mg | under-labeled (134%) | 99% | 8.97±0.51% |

*Based on the official Ozempic European public assessment report (EPAR) product information document published by the European Medicines Agency [116], one pre-filled Ozempic 1 mg pen contains 4 mg semaglutide in 3 ml solution. Pen is designed to deliver 4 doses of 1 mg (0.74 ml/dose).

Table 1. Results analytical measurements for each semaglutide product obtained from 3 illegal online pharmacies and original Ozempic reference product.

4.4.2. Microbiological Testing Results

We utilized the endotoxin kinetic turbidimetry assay, which has a detection limit of <0.01 EU/ml, to evaluate the bacterial endotoxin content of samples. After adjusting for sample dilution and measuring changes in turbidity over time, we found endotoxin levels to be <2.8658 EU/mg for product from US Chem Labs and <2.1645 EU/mg for

Biotech Peptides. However, in the case of the sample from Semaspace we identified a higher endotoxin level, measured at 8.9511 EU/mg. Sterility testing was also performed on all products and confirmed that all three lyophilized peptide samples were free from viable microorganisms, indicating that they were sterile at the time of examination.

5. DISCUSSION

The rapid expansion of the online pharmaceutical market has significantly influenced consumer behavior worldwide. A survey conducted by Fittler et al. in 2022 showed 55.48% of responders had purchased medication online and 63.0% had purchased health products online following the COVID-19 pandemic, indicating the pandemic further encouraged online medication purchasing. Our study's primary focus was on investigating the illegal online trade of Ozempic and semaglutide, which became popularized for weight loss. Due to celebrity endorsements and news coverage, semaglutide is now widely used off-label for cosmetic weight-loss, resulting in worldwide shortages. Our findings indicate a significant presence of illegal online pharmacies trading semaglutide, with 42.27% of identified links leading to 59 illegal operations. This proliferation highlights the need for stringent surveillance and enforcement. We revealed a concerning number of visitors rushing to these vendors, possibly purchasing counterfeit products posing risks. The frequent appearance of certain illegal vendors like semaspace.com demonstrates active illegal SEO to reach high search rankings.

We identified inadvertent promotion of illegal online pharmacies in AI-integrated search engine responses related to purchasing medications online, a new vulnerability linked to illegal pharmacies' rogue SEO techniques influencing AI recommendations. Our demographic analysis revealed a large number of illegal websites hosted in the United States and Canada, with Cloudflare Inc. as a preferred service provider, pointing to the need for scrutiny of hosting services facilitating illegal operations. Test purchases highlighted the ease of accessing semaglutide without a prescription and promotion of off-label use for weight loss. We uncovered two main fraud strategies: e-commerce fraud with fake pharmacy websites, and financial exploitation through advance-fee scams for fictitious courier services, taking advantage of high demand and shortages.

Physical assessments revealed deficiencies like inappropriate packaging and labeling compared to authentic Ozempic. Microbiological testing showed presence of bacterial

endotoxins, suggesting possible contamination. LC-MS analysis demonstrated low semaglutide purity (7-14% compared to advertised 99%) and significant discrepancies between claimed and actual API content, with samples substantially exceeding the labeled semaglutide amount by 29-39%, indicating substandard production processes used by illegal vendors.

6. Limitations

Although our study aimed to provide a complete evaluation, we limited scope to SERPs, potentially overlooking vendors on social media, forums, and dark web markets. Test purchases were limited due to funding restrictions and scam operations, so samples obtained cannot fully represent the variety of counterfeit products. Comprehensive testing for all possible contaminants required larger quantities and extensive resources beyond this study's scope.

7. CONCLUSIONS

Key Findings and Their Implications:

Key Findings:

- 1. Online semaglutide vendors:** Our study identified 317 links to online pharmacies from 1080 SERP links, with 183 being legitimate (57.73%) and 134 (42.27%) leading to 59 illegal operations. Semaspace.com was highlighted as the most frequent illegal vendor.
- 2. Verification challenges:** Using Safe Pharmacy and LegitScript.com databases, close to half (47.46%) of the online vendor identified through SERPs were listed as “not recommended” or “rogue”, however a notable 18.64% of vendors were not listed in either database, underlining the challenge of tracking and verification of online pharmacies using existing databases.
- 3. Demographic distribution:** A substantial number of illegal pharmacy operations were registered to entities based in the United States (30.51%) and Canada (13.56%), with a significant portion of the domains’ registrant information (23.73%) withheld due to privacy laws, which helps illegal sellers conceal information on their inner workings. Analysis of hosting service providers showed majority of illegal websites (76.27%) were hosted in the United States and Canada, with Canadian service provider Cloudflare Inc. hosting 27.12% of the illegal websites.
- 4. Web traffic analysis:** The top 30 illegal pharmacy domains attracted over 4.7 million combined total visits between July and September 2023, emphasizing the popularity of top illegal pharmacy websites.
- 5. Test purchasing and product delivery:** Test purchases from six rogue pharmacies revealed several alarming issues. These illegal sellers do not require prescriptions, and they promote the off-label use of these medications. We also uncovered a serious new concerning trend of exploiting the high demand for Ozempic pens with non-delivery and advance-fee scams.
- 6. Physical, Chemical, and Microbiological assessments:** The physical assessment using an FIP checklist showed that illicit vendor’s products failed to meet most GMP criteria, while LC-MS analysis revealed illicit products have significantly low polypeptide purity and major discrepancies between claimed and actual API

content where observed, with some samples having close to 40% more semaglutide concentration than indicated on the label, raising quality and safety concerns.

Implications:

- 1. Consumer safety:** The high presence of illegal pharmacies and the sale of substandard products endanger consumer safety, especially for those using semaglutide off-label for weight loss.
- 2. Regulatory oversight:** The findings stress the need for enhanced regulatory strategies to monitor and mitigate the presence of illegal online pharmacies and improve the accuracy of verification databases.
- 3. Country specific enforcement:** The data on the geographic distribution of illegal pharmacies suggest a need for more robust, focused law enforcement interventions in highly affected regions like the United States and Canada, to put pressure on domain registrar's and hosting providers to shut down illicit online pharmacy operations and require better monitoring policies to prevent abuse of these services.
- 4. Awareness and education:** The popularity of illegal sites and the prevalence of scams highlight the importance of educating consumers not only related to health consequences of counterfeit products but also about the financial risks associated with purchasing pharmaceutical products from unverified online sources.
- 5. New vulnerabilities:** Inadvertent direct promotion of illegal online pharmacy websites in the responses generated by the new generative AI integrated search engines is a significant new potential public safety risk which highlights importance of more strict oversight as well as cooperation with search engine providers to prevent future occurrence.
- 6. Opportunistic fraudulent practices:** Criminal operations running advance-fee and non-delivery scams are taking advantage of the high demand and shortages to commit e-commerce fraud, which is a complex challenge to mitigate, requiring consumer education as well as coordinated law enforcement actions.

8. Acknowledgements

I am truly grateful for the unconditional love and support I received from my family and friends throughout the challenging years of my studies. Their support provided me with the strength to persevere; their patience, understanding, and willingness to make sacrifices while I was occupied with research and writing have been invaluable.

My father's words have always resonated with me during moments of doubt. He would tell the story of Thomas Edison's failed experiments with the incandescent lamp until he finally made it. After each failure Edison would say: "I have not failed. I've just found 10,000 ways that won't work." This reminder of persistence in pursuit of solutions has been like a guiding light in my academic journey.

I would like to express my appreciation to my colleagues at the Department of Pharmaceutics, and extend my sincere gratitude to my supervisor, Dr. András Fittler, for his guidance and mentorship at every step of this journey. His openness to exploring even the oddest ideas—like trying to see if we can find illegal Ozempic online and then helping to test-purchase and analyze samples—has led to one of the most fascinating and challenging projects we have done. This project not only shaped the basis of my dissertation but also deeply influenced my academic growth.

Now that this journey comes to an end, I am reminded of another quote by Edison:

"I never did a day's work in my life. It was all fun."

Thomas Alva Edison

9. List of Publications and Presentations

- Original research papers: 4 (Cumulative impact factor: 28)
- Conference presentations: 11

Publications directly linked to the thesis topic: (Impact Factor: 15.9)

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