



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Illicit erectile dysfunction products

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A decade of trends and a 2007-2010 product update



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Colophon

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Abstract

Illicit erectile dysfunction products in the Netherlands A decade of trends and a 2007-2010 product update

Illicit erectile dysfunction (ED) products often contain experimental medicines. The acute health risks of using such illicit ED products, however, appear to be relatively low – at least to date. Less health damage has been reported than expected based on the presumed use of these products, although their long-term effects on human health are unknown.

This report was compiled from the records of five national institutes in the Netherlands and is the third RIVM report to be published on illicit ED products. The investigated products were all confiscated outside the official distribution system.

Illicit

Illicit ED products are illegally produced or distributed without the necessary licences. There are three licensed ED products available on the Dutch market (Viagra®, Cialis® and Levitra®). All need to be prescribed by a physician. The use of illicit ED products has increased dramatically during the last decade, most likely due to the ease of purchasing via the Internet.

Risks

Risks that have been identified are overdosing, adverse combination(s) with alcohol or drugs and long-term use. Adulterated food supplements containing experimental medicines (analogues), counterfeit generics and ED products mixed with antidepressants are considered to represent the greatest health risks.

Research

This report describes the product characteristics and presents the chemical analysis data of 538 illicit ED products (containing PDE5 inhibitors) confiscated in the period 2007–2010. These products can be classified as counterfeit medicines (17%), illicit generics (unapproved medicines) (69%) and adulterated food supplements (13%). Most ED products contain an effective amount of the active substance, although many are fraudulently mislabelled in terms of the active drug substance and dose. The results of this study show that the composition of illicit ED products is usually unreliable.

Surveillance

Marketing surveillance of medicines is well organised in The Netherlands, but it does need to be improved for food supplements as current regulations and laws governing the composition of such products are too limited. According to the RIVM, improved measures aimed at safeguarding the veracity of food supplements are desirable. Although there appears to be a low incidence of health damage attributable to the use of ED products, it remains necessary to monitor these products for trends in new active drug substances and long-term health risks. It is also important to investigate user behaviour.

Keywords:

Counterfeit medicine, Adulterated food supplements, Analogues of PDE5 inhibitors, Health risk analysis, Trend monitoring.

Rapport in het kort

Illegale erectiemiddelen in Nederland Analyses van producten (2007-2010) en een decennium van trends

Illegale erectiemiddelen bevatten vaak experimentele geneesmiddelen. Toch lijken de acute gezondheidsrisico's van illegale erectiemiddelen tot nu toe betrekkelijk klein. Er wordt echter minder gezondheidsschade geregistreerd dan op basis van het gebruik wordt verwacht. De risico's op lange termijn zijn onbekend.

Het onderzoek is uitgevoerd op basis van gegevens die vijf Nederlandse instituten hebben verzameld. Dit is het derde rapport dat het RIVM over illegale erectiemiddelen heeft uitgebracht. De onderzochte middelen zijn buiten het officiële distributiekanaal in beslag genomen.

Illegaal

Illegale erectiemiddelen zijn middelen die niet op een legale manier zijn geproduceerd of waarvoor niet de noodzakelijke vergunningen zijn verkregen. In Nederland zijn drie legale erectiemiddelen (Viagra[®], Cialis[®], Levitra[®]) verkrijgbaar op voorschrift van een arts. In de afgelopen tien jaar is het gebruik van illegale erectiemiddelen sterk toegenomen, vooral doordat ze via internet eenvoudig kunnen worden gekocht.

Risico's

De geïdentificeerde risico's zijn: overdosering, het combineren met alcohol of drugs, en langdurig gebruik. De gezondheidsrisico's zijn het grootst bij vervalste voedingssupplementen die experimentele geneesmiddelen bevatten, vervalste geneesmiddelen, en illegale erectiemiddelen waaraan antidepressiva zijn toegevoegd.

Onderzoek

Voor het onderzoek zijn de productkenmerken en de samenstelling beschreven van 538 illegale erectiemiddelen die tussen 2007 en 2010 in beslag zijn genomen. Deze middelen bevatten erectiebevorderende geneesmiddelen (PDE5-remmers). Het betreft vervalste geneesmiddelen (17%), illegale generieke geneesmiddelen (69%) en vervalste voedingssupplementen (13%). In de meeste producten zit een werkzame hoeveelheid, hoewel de etiketten daarover veelal opzettelijk onjuiste of onvolledige informatie bevatten. De resultaten laten ook zien dat illegale erectiemiddelen in hun samenstelling meestal onbetrouwbaar zijn.

Toezicht

Het toezicht op geneesmiddelen is in Nederland goed gereguleerd, maar laat bij voedingssupplementen te wensen over. Het RIVM vindt dat meer toezicht op de samenstelling van voedingssupplementen gewenst is. Momenteel is de wet- en regelgeving op de samenstelling daarvan beperkt. Ook blijft het noodzakelijk om, ondanks de geringe signalering van gezondheidsschade, ontwikkelingen op het gebied van nieuwe werkzame stoffen en gezondheidsschade op de lange termijn te volgen. Ook is het van belang om het gedrag van de gebruiker te onderzoeken.

Trefwoorden:

Vervalste geneesmiddelen, Vervalste voedingssupplementen, PDE5-remmers (analoga), Gezondheidsrisico's, Trendanalyse.

Contents

Summary—9

1 Introduction—11

2 Illicit ED product update 2007-2010—13

- 2.1 Methods—13
- 2.2 Results and discussion—13
 - 2.2.1 The database of illicit ED products 2007-2010—13
 - 2.2.2 Drug substances detected—14
 - 2.2.3 Subcategories—15
 - 2.2.4 Health risks related to the illicit ED products in the database—16

3 Analogues of approved PDE5 inhibitors—19

- 3.1 Introduction—19
- 3.2 Methods—19
- 3.3 Results and discussion—19
 - 3.3.1 New analogues—19
 - 3.3.2 Health risks—20
 - 3.3.3 The origin of analogues—20
 - 3.3.4 Patents disclose the drug development process—21
 - 3.3.5 Libidfit (acetildenafil)—21

4 Health risks of illicit ED products—23

- 4.1 Introduction—23
- 4.2 Methods—23
- 4.3 Results and discussion—23
 - 4.3.1 Health risks of prescribed ED medicine—23
 - 4.3.2 Literature—24
 - 4.3.3 Cases of health damage in the Netherlands—26
 - 4.3.4 General consideration—26

5 Discussion and conclusions—29

- 5.1 Products and drug substances over 2000-2010—29
- 5.2 Analogues of PDE5 inhibitors between 2000-2010—31
- 5.3 Health risks between 2000-2010—32
- 5.4 Conclusions—33
- 5.5 Recommendations—33

Appendix 1 The flow of samples—35

Appendix 2 Listings—37

Appendix 3 Analogues of sildenafil—47

Appendix 4 Analogues of tadalafil—51

Appendix 5 Analogues of vardenafil—53

Appendix 6 The molecular genealogy of sildenafil—55

Appendix 7 Drug substances in illicit ED products 2000-2010—57

References—67

Summary

This is the third RIVM report on illicit erectile dysfunction (ED) products confiscated outside the official distribution system in the Netherlands. The current report covers the period 2007-2010, complementing a total survey period of ten years. It describes the product characteristics and chemical analysis results, the obscure designer drugs commonly referred to as 'analogues', health risks and trends observed over the past decade.

Illicit ED products

The chemical analysis data and product characteristics of 538 illicit ED products were reviewed. This showed four types of products (see table below). Despite some indications being found for the presence of counterfeited illicit generics, this could not be confirmed due to a lack of reliable reference material.

Counterfeit Viagra [®] , Cialis [®] and Levitra [®]	17%
Illicit generics (unapproved medicines)	69%
Illicit other (e.g., premixed bulk powder)	1%
Illicit food supplements with an active drug substance	13%

The illicit ED products were also categorised for the accuracy of their label claim in relation to the drug substance and dose. This showed that most counterfeits and illicit food supplements were fraudulently mislabelled. The majority of the illicit ED products could not be categorised because the declaration was unknown or the declared dose had not been verified. Nearly half of the illicit generics that could be categorised were fraudulently mislabelled. The predominant defects were labels falsely indicating the presence of only natural ingredients, a too low dose and the fraudulent substitution of tadalafil for sildenafil. Very high dosages of the approved drug substances were only observed incidentally. Illicit ED products sold as medicines predominantly contain sildenafil (81%) or tadalafil (15%). Illicit ED products sold as food supplements predominantly contain analogues (61%). Vardenafil is rarely detected in illicit ED products.

Analogues

The number of different analogues identified in illicit ED products worldwide has increased from 4 in 2004 to more than 42 in 2010 and is continuing to grow. Analogues, in principle, exert the same pharmacological effect but are different in potency, side-effects and toxicity. Nearly all of the analogues currently identified are the intellectual property of the legitimate pharmaceutical industry and have previously been disclosed in patent literature. Because patent literature is publicly accessible on the Internet, selecting suitable analogues is like 'cherry-picking' for criminals.

Health risks

Extrapolating from the literature, it is estimated that at least a third of the ED medicines in the Netherlands are obtained from outside the official distribution system. This translates into 150,000 purchases of illicit ED medicines in 2009, not including illicit ED products sold as food supplements. Pharmacovigilance data on 300,000 prescriptions shows that relatively few, but potentially severe, adverse drug reactions are recorded for the intended user group (12 cases per year). Literature was consulted on the user group of illicit ED products in order to assess the health risks. This literature showed that these products are regularly used both by healthy young males and elderly males. Healthy young users have a low risk of acute health damage but risk factors are the concomitant use of alcohol or drugs

(marihuana specifically) and probably impatience, resulting in multiple dosing. Males above 50 years of age are in the high risk category because the contra-indications are more common for their age group.

Sixteen possible cases of health damage due to illicit ED products were identified in the database of the National Poisons Information Centre between 2007-2010. The victims were young users that experienced mild and transient cardiovascular events. No cases of serious health damage could be identified.

Trends

The percentage of illicit generics and food supplements described in our reports has increased considerably over the past decade (2000-2010). Since 2004 the use of non-PDE5 inhibitors has decreased considerably and the prevalence of both the counterfeit brands and the drug substances is fairly constant. Currently, PDE5 inhibitors are identified in 98% of the illicit ED products; sildenafil, tadalafil and analogues are identified most frequently.

The doses of sildenafil and tadalafil between 2000-2010 have generally remained low to normal and pose no great health risk to the healthy recreational user. However, considering the scale of use, it is becoming important to study consumer behaviour and to monitor serious and specific health complaints (e.g., eye-disorders due to PDE6 inhibition). The illicit ED products of future concern are the counterfeited illicit generics (low quality), products with analogues and products with an antidepressant (SSRI-type) and a PDE5 inhibitor.

Literature shows that the recreational use of ED drugs has grown enormously. The illegal market is driven by the huge demand for PDE5 inhibitors by non-ED patients. By providing low quality but efficacious ED drugs, the manufacturers seem to be aiming at returning customers. This trend was also noticed for illicit weight-loss medicines in 2008.¹ The upcoming release of approved generics on the EU market is expected to bring changes to the market in illicit ED products: refined counterfeit generics and counterfeit drug substance (API).

Conclusions

The potential public health risk posed by fraudulent labelling has specifically increased for adulterated food supplements.

At present, the short-term health risks associated with the use of illicit ED products in the Netherlands appear to be limited and largely related to user behaviour. The long-term toxicological effects and the risks of long-term exposure are unknown yet very relevant, considering the scale of use.

The technical quality of illicit ED products is inherently subject to change.

Recommendations

1. Public warnings on fraudulently labelled food supplements could be intensified.
2. Future monitoring of illicit ED products could focus on obscure drug substances (e.g., analogues, polymorphs, SSRIs), and counterfeit (illicit) generics.
3. The ministry of Health is advised to set up a monitoring system to investigate the scale of use of illicit ED products and to gauge the health damage caused by illicit ED products.
4. The ministry of Health is advised to investigate user behaviour and user motives in relation to the use of ED drugs by non-ED patients and provide an adequate response to the high demand.

1 Introduction

The 10th anniversary of the introduction of Viagra® marks a decade of growing abuse of illicit erectile dysfunction (ED) products. It was recently estimated that for every two legitimate prescriptions of an ED drug product in Europe, an additional third was purchased outside the official distribution system. This translates into an astonishing 6 million purchases of ED drug products outside the official distribution system in Europe per year.² For the Netherlands, this would mean that in addition to the 300,000 annual prescriptions, an estimated additional 150,000 purchases are made outside the official distribution system. The number of adulterated food supplements with ED drugs would still have to be added to that figure. In view of the scale of use and to protect public health, the health authorities in the Netherlands have a key interest in monitoring illicit ED products and their associated health risks.

Our Institute, the National Institute for Public Health and the Environment (RIVM), performs chemical analyses on samples that are seized by the Health Care Inspectorate (IGZ) and the new Food and Commodity Authority (nVWA). In addition, we publish our results in an aggregated manner in RIVM reports, in which we try to detect trends in illicit medicinal products.

Our first report was published in 2005, covering the period 2000-2004.³ In that report, a classification of illicit medicines was introduced. Essential in that classification was that the presentation of the illicit medicine (e.g., packaging, leaflets) was the cornerstone for classification and not the actual content of the medicines. This classification was instrumental in assessing the results in terms of risks to public health and, in particular, in the allocation of responsibilities. For instance, a user taking a recognisable illicit medicinal product can be held accountable for the consequences. This first report recommended that the health authorities should concentrate on combating refined counterfeits (visually indistinguishable from authentic) and increase public awareness of the risks of illicit ED products. A limitation of that report was that it was based solely on suspect ED medicines analysed by RIVM.

Our second report was published in 2007, covering the period 2005-2006.⁴ In that report, suspect ED products were also included that had been analysed by the Dutch Customs Laboratory and by the Dutch Forensics Institute (NFI).¹ These datasets were merged into one database to draw a more representative picture of the fraudulent medicines in the Netherlands. The results showed a larger share of illicit generics, the perfecting of counterfeit packaging material and an increase from 3 to 13 illicit analogues of sildenafil, tadalafil and vardenafil. Health risks had increased from the perspective of the user being deceived.

This is the third report on illicit ED products in the Netherlands, covering the period 2007-2010. This third report attempts to describe the actual health damage due to illicit ED products in the Netherlands. In addition, special attention is given to the fast-growing number of structural analogues of sildenafil, tadalafil and vardenafil. The second chapter describes the product update using the chemical analytical data and product characteristics of suspect ED medicines contributed by the RIVM, the Dutch Customs Laboratory (DL) and the Dutch Forensics Institute (NFI). A new

¹ The roles of the contributing laboratories in analysing suspect ED medicines is described in Appendix 1.

contributing party is the laboratory of the Royal Dutch Association for the Advancement of Pharmacy (LNA), with data on suspect samples provided by public pharmacists.

The third chapter of this report describes the further growth to over 42 illicit analogues of sildenafil, tadalafil and vardenafil ('designer drugs') that have been detected in illicit ED medicines over the period 2000-2010. Because of their challenging legal status, the common origin of the analogues is argued, illustrated by the drug development process and patent literature. The question of how to combat analogues is discussed by describing an example of a successful court case, by considering the role of the pharmaceutical industry and the need for a general solution.

The fourth chapter of this report addresses the health damage due to illicit ED products. Signs of actual health damage were assessed by a survey of international literature (1999-present) and, for the Netherlands, by consulting the National Poisons Information Centre and the National Pharmacovigilance Centre Lareb.

The fifth chapter is a general discussion of the trends observed when the 2007-2010 data is put into perspective with the two earlier reports. It discusses the type of counterfeits and the drug substances – including analogues – identified in the period 2000-2010. Trends in new drug substances and formulations are described that call for an adaptation of screening methods. The report closes with conclusions and recommendations.

2 Illicit ED product update 2007-2010

2.1 Methods

The database of illicit ED products in this report was compiled from the records of the National Institute for Public Health and the Environment (RIVM), the Netherlands Forensic Institute (NFI), the Customs Laboratory (DL) and the Laboratory of Dutch Pharmacists (LNA) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP). Each of the participating laboratories analyses medicines on a case-by-case basis, serving their own objectives and mission (Appendix 1). As the laboratories did not generate data for the purpose of producing this report, there are differences in the recorded parameters. This survey is not the result of coherent sampling; however, with the participation of multiple laboratories the authors aim to draw the best representative picture available.

The illicit ED products in this chapter were retrieved from the laboratory records by searching on product names, medical claims, appearance and drug substance. This approach resulted in the retrieval of 'positive' samples, i.e., products claiming to contain a drug substance and products in which the chemical analysis showed the presence of a drug substance. False negative samples could not be retrieved (e.g., unfamiliar product name with a non-ED drug substance). The retrieved illicit ED products were categorised based on the data recorded (e.g., visual appearance, product claim, chemical analysis). Contrary to the earlier reports, illicit food supplements were distinguished from unapproved medicines because they are not recognisable as medicinal products to the user. Therefore, the category 'Imitation' used in earlier reports was split into 'Illicit food supplement' and 'Illicit generic'.

2.2 Results and discussion

2.2.1 *The database of illicit ED products 2007-2010*

The database comprised a total of 538 illicit ED products (see Appendix 2). Table 1 shows the type of illicit ED products in the database. Figure 1 shows the distribution of illicit ED products submitted by the different laboratories.

Table 1 Illicit ED products in the database

Medicines	Counterfeit Viagra, Cialis and Levitra
	Illicit generics (unapproved medicines) ²
	Illicit other (e.g., premixed bulk powder)
Food supplements	Illicit food supplements with an active drug substance

Figure 2 shows the distribution of the 538 illicit ED products over the main categories. The majority of the data was on products that were visually recognisable as medicines. Counterfeit Viagra, Cialis and Levitra represent 17% of the illicit ED products. Illicit generics, such as 'Kamagra', account for the largest share of the database with 69%. Possible counterfeit Kamagra products were first noticed in 2007 and have been detected regularly ever since. Due to the absence of reliable reference material, counterfeiting could not be confirmed and these samples are placed under illicit generics. Illicit other medicines accounted for 1% and illicit food supplements for 13%.

² In the 2000-2010 period Viagra, Cialis and Levitra were under patent protection in the Netherlands and generics were not allowed to be dispensed.

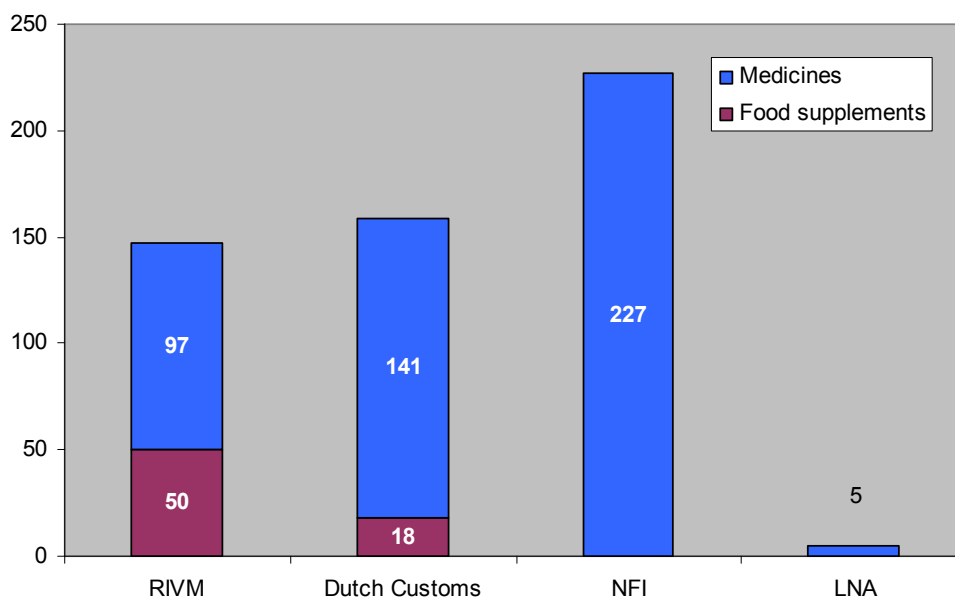


Figure 1 Illicit ED products contributed per laboratory 2007-2010.

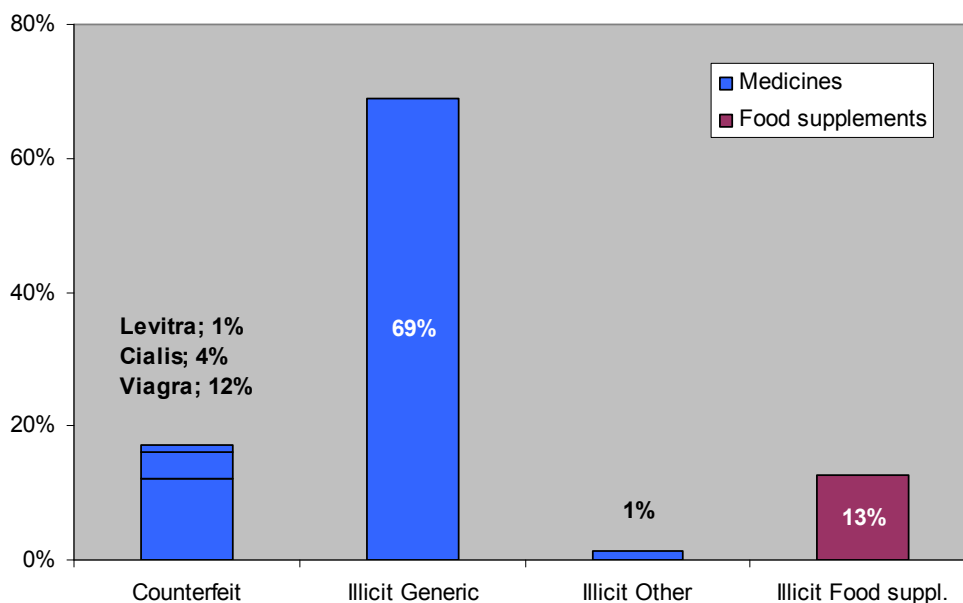


Figure 2 Distribution over the main categories 2007-2010.

2.2.2 Drug substances detected

Counterfeits and illicit generics predominantly contain sildenafil (81%), followed by tadalafil (15%) (Fig. 3). Vardenafil is rarely detected in illicit ED medicines. On one occasion, a counterfeit Cialis contained trans-tadalafil, which is the wrong optical isomer.⁵ For the first time, Viagra tablets in a single blister pack were found to have a very different composition: 2 placebo tablets and 2 tablets with 100 mg sildenafil. Normally, composites of several tablets are prepared to determine the average dose, which in this case would have given the wrong dose. However, the

differences were recognised beforehand by Near Infrared Spectrometry (NIRS) and the dose was determined for the individual tablets.

Illicit food supplements predominantly contain analogues (61%) followed by 'other' drug substances (17%). Analogues are molecules that are structurally similar to sildenafil, tadalafil or vardenafil but have not been evaluated for safety or efficacy. The category 'other' drug substances comprises amphetamine, icariine and yohimbine and the muscle relaxant carisoprodol.

On several occasions sildenafil was identified in a tablet by RIVM using a validated chromatographic technique, yet the NIR spectroscopy tested negative for sildenafil citrate. This is attributed to the use of other salts or polymorphs.

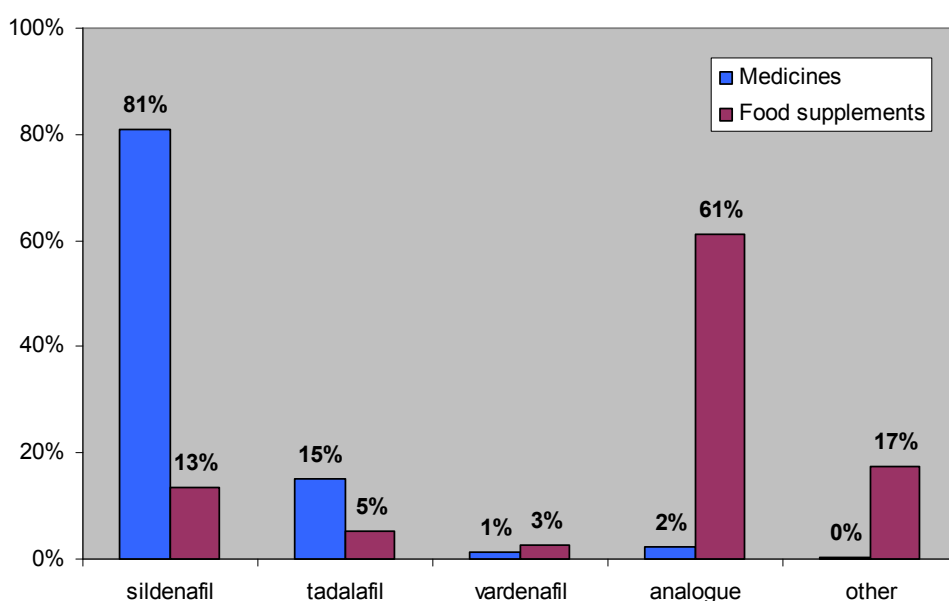


Figure 3 Distribution of drug substances identified in illicit medicines and illicit food supplements.

2.2.3

Subcategories

Illicit ED products were placed into subcategories depending on the accuracy of the label claim in relation to drug substance and dose (Table 2). The subcategory 'professional' used in earlier reports was renamed 'accurate' to place less emphasis on the intended craftsmanship. For example, tablets containing 50% of the declared dose may very well be produced deliberately to double production and still maintain an effective dose. In order to focus on the mislabelling, the relevant subcategories used previously (non-professional, mixed, fraudulent and placebo) were merged into the subcategory 'fraudulent'.

Figure 4 shows that 60% (n = 55) of the counterfeits in the database were fraudulently labelled with respect to drug substance and dose. The predominant defects included a too low dose of sildenafil in counterfeit Viagra and the use of sildenafil in counterfeit Cialis instead of tadalafil.

Among the counterfeits 12% (n = 11) was categorised as 'accurate' and 28% (n = 26) was categorised as unknown (dosage had not been determined).

Among the illicit generics 60% (n = 223) lacked information on either the declaration or dosage. The illicit generics with a known declaration and dosage were almost equally distributed over the subcategories 'accurate' and 'fraudulent'. Their predominant defects in illicit generics were the same as observed for the counterfeits. Very high dosages were observed incidentally and only for fraudulent

illicit generics. On one occasion, tablets contained an undeclared 171 mg sildenafil plus 24 mg tadalafil per tablet.

Among the illicit food supplements 94% (n = 64) was categorised as fraudulent. The majority of these contained undeclared analogues in efficacious quantities. Some 6% (n = 4) of the illicit food supplements was categorised as 'other' because the declared dosage was not verified (all yohimbine).

Table 2 Subcategories of illicit ED product and examples

Subcategory	Criteria
Accurate	Correct drug substance and dose*
Fraudulent	Wrong drug substance or dose
Other	Not categorised due to missing data

*A dose within 90-110% of the declared amount is considered a correct dose; a dose outside that range is considered a wrong dose.

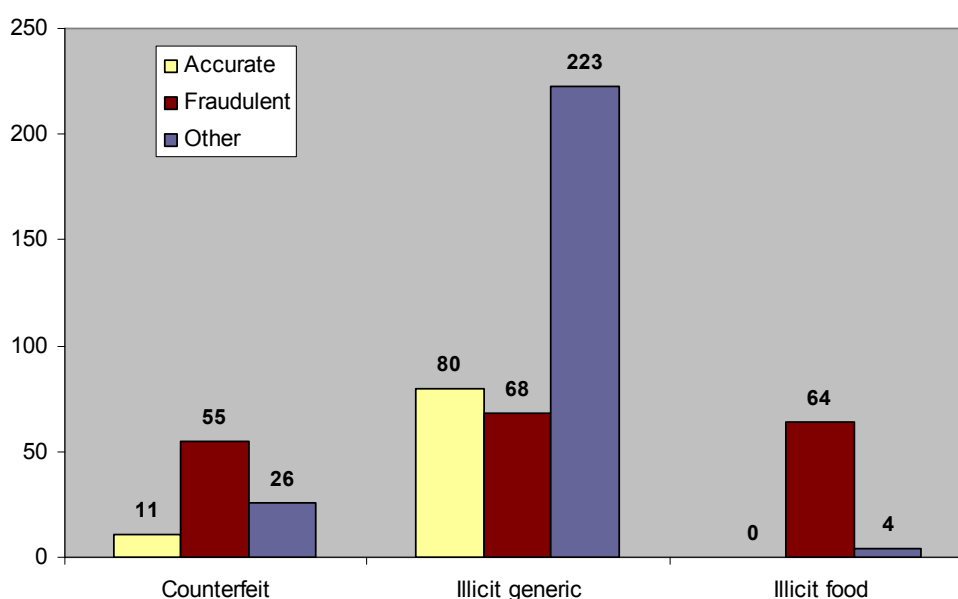


Figure 4 Distribution of the illicit ED products with respect to the accuracy of the label claim (drug substance and dose).

2.2.4 Health risks related to the illicit ED products in the database

Counterfeits and illicit generics in the database were clearly recognisable as medicines. As it is presumed that today's consumers are aware of the inherent health risks posed by medicines obtained from outside the official distribution channel, they can subsequently be held co-responsible for the consequences to their health.

Counterfeits and illicit generics generally contain effective amounts of sildenafil and tadalafil. Because most doses are within the normal range, the acute health risks related to these two drug substances are well charted (assuming pharmaceutical quality). The occurrence of fraudulently low doses does not elevate the health risk as it does not leave a serious illness untreated. The fraudulent use of sildenafil instead of tadalafil and of their mixtures is also expected to have little impact on health risks. Clinical studies show little difference in health risks between treatment

with Viagra (sildenafil), Cialis (tadalafil) and Levitra (vardenafil).^{6,7} The health risks are elevated for products with fraudulently high doses, but these cases are rare. The majority of the illicit food supplements in the database were fraudulently mislabelled, as the drug substance was not declared on the label. Therefore, users are deceived and cannot be held accountable for the health damage caused. Fraudulent illicit food supplements primarily contained analogues. Their health risks as PDE5 inhibitors are normally extrapolated from sildenafil, tadalafil and vardenafil but their kinetics and toxicology remain uncharted. Their obscurity and their undeclared presence pose a considerable health risk. Analogues will be discussed specifically in the next chapter.

The expected long-term health risks for illicit medicines relate to their questionable purity and production hygiene. Assuming that manufacturers avoid using expensive pharmaceutical quality ingredients and quality control, all sorts of impurities can be expected and indeed are found regularly. In approved medicines the level of impurities is strictly limited, as these may, in time, cause health damage (e.g., genotoxins may cause cancer). Illicit ED products may contain reagents, solvents and metals that could slowly cause health damage. The long-term health-risks are especially relevant for the counterfeit generics, which can only be profitable when they are of the lowest possible quality.

It should be noted that the formulation may have a large impact on health risks. For example, the approved sildenafil citrate is moderately soluble in water⁸, hence more rapidly soluble salts (or polymorphs) may boost the uptake and cause adverse effects (e.g., cardiovascular), which are not normally expected at that dose. The NIR authenticity test at RIVM in combination with LC-DAD-MS analysis confirmed the presence of unknown salt forms and polymorphs but we did not investigate their pharmacokinetic consequences.

3 Analogues of approved PDE5 inhibitors

3.1 Introduction

In our previous two reports on illicit ED products we showed an increasing number of analogues of sildenafil, tadalafil and vardenafil.^{3,4} An analogue is a drug substance that is structurally and functionally similar to a registered drug substance. The analogues described in these reports are not drug substances registered at the EMA or FDA and have no known safety or efficacy profiles. Despite this, analogues are extensively used in illicit ED products marketed as food supplements.

Several new analogues are present in the database of illicit ED products 2007-2010. In this chapter an update is given on the analogues currently known around the world and their intellectual origin, health risks, status as a medicine and future implications are described.

3.2 Methods

Scientific literature was gathered through bibliographic search engines on the Internet, using keywords and molecular structures (Pubmed, Winspirs and WIPO). In addition, information was used that was shared by medicines agencies and customs around the world.

3.3 Results and discussion

3.3.1 New analogues

The number of different analogues identified in illicit ED products worldwide has increased from 4 in 2004 to >42 in 2010 (Table 3) and is continuing to grow. In appendices 3, 4, and 5 a referenced overview is given of all the drug substances, including analogues, identified in illicit ED products in the period 2000-2010.

Table 3 The growth in number of analogues detected in fraudulent medicines

Year	Analogues	Source
2004	3	1 st RIVM report on illicit ED medicine Analogues of sildenafil
2006	13	2 nd RIVM report on illicit ED medicine Analogues of sildenafil, tadalafil and vardenafil
2010	42	This report, see also appendices 3, 4, and 5

One of the new analogues is nitroso-prodenafil, which was first characterised by RIVM in collaboration with Health Canada in a product from the Czech market.⁹ Since then its identification has been reported in Estonia, Singapore and the US. Nitroso-prodenafil is a combination of aildenafil and a nitrosamine that may act as nitrogen monoxide (NO) donor; a combination that could cause a severe drop in blood pressure.¹⁰ Although it is unknown how much NO can be usefully generated, the amount present is 3-fold the amount present in a 10 mg dose of isorbide nitrate. Aildenafil is an analogue of sildenafil, which is being developed as an ED drug in China.¹¹⁻¹³

3.3.2 Health risks

Health risks for analogues are usually extrapolated from the approved PDE5 inhibitors (sildenafil, tadalafil and vardenafil) and then relate solely to their PDE5 inhibitory function. Although the PDE5 inhibiting properties of analogues are obvious, their kinetics, toxicology and other pharmacological properties are uncharted. Specific health risks have only been established for a few analogues (Table 4).

Table 4 Specific health risks for three analogues

Analogue	Reason	Risk
Acetildenafil	Non-selective PDE5 / PDE-6 inhibitor	Additional risk of visual disturbances ¹⁴⁻¹⁶ , ataxia ¹⁷
Amino-tadalafil	Free Hydrazide	Highly reactive chemical group ^{4,18,19}
Nitroso-prodenafil	Combines a prodrug of aildenafil and a nitrosamine	Potentially dangerous combination of a PDE5 inhibitor and a source of NO. ⁹ Many nitrosamines are carcinogenic.

3.3.3 The origin of analogues

Analogues are the by-products of the typical drug development process. Drug development is an iterative process of preparing and testing new molecules with ever better properties. Medicinal chemists determine which parts of the molecule are essential to its pharmacological activity (the active moiety) and which are not. The essential parts are conserved and the non-essential parts are varied to fine-tune secondary parameters. Therefore, analogues in principle exert the same pharmacological effect. However, they can be different in potency, side-effects and toxicity.

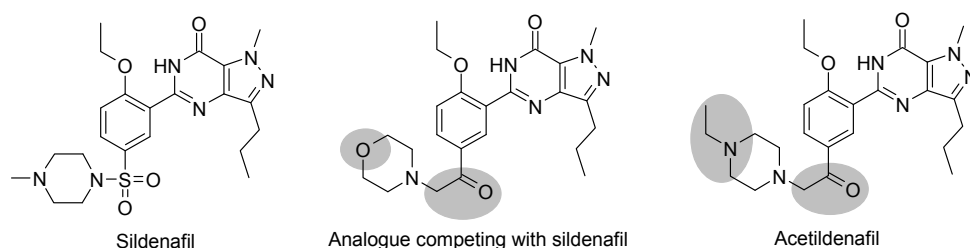


Figure 5 The competing analogues in the clinical development of Viagra (left and middle) and acetildenafil (right). The grey areas mark the structural differences with sildenafil in the non-essential part of the molecule. The active moiety in the three molecules is identical.

All of the analogues can be considered 'investigational drugs' from which eventually one or two analogues are selected for clinical development. Exactly which analogue is selected for development is determined by intellectual property rights, manufacturability and the expected benefit-risk ratio. Hundreds of pharmacologically active analogues will normally not be developed further. In the development of Viagra[®] two analogues were clinically evaluated (Fig. 5).²⁰ The one

that was finally selected later became known as sildenafil. The discarded analogue apparently had the same undesirable properties (PDE6 inhibition) as RIVM had shown for acetildenafil.^{4,20}

3.3.4 *Patents disclose the drug development process*

The intellectual property rights of a drug development process can be claimed by applying for a patent. Claims are supported with scientific evidence on the chemistry and preliminary pharmacology. Normally, such evidence is provided for some typical examples and the other analogues are claimed by structural and functional analogy. Therefore, patents and patent applications are a scientific blueprint of analogues that share a functional property (i.e., 'the treatment of impotence by PDE5 inhibition'). As patents and patent applications are publicly accessible, the entire drug discovery is also disclosed to criminals. Nearly all of the analogues identified in illicit ED products had been previously disclosed in patent literature. Appendix 6 describes the molecular genealogy of sildenafil using such patent information.

3.3.5 *Libidfit (acetildenafil)*

To prove that a food supplement adulterated with an analogue is in fact a medicine places the burden of evidence with the government. A successful example of fighting analogues is the Libidfit case in the Netherlands in 2007. Convinced by a Pfizer patent application²¹, dosage, *in vitro* pharmacological data¹⁵ and the libido enhancing claim of the product, the Court of Justice ruled that the product was a medicine.²² Conducting *in vitro* pharmacology on acetildenafil was deemed necessary because patent literature contained no pharmacological data on this specific type of analogue. The analogue evaluated against sildenafil in the clinical development of Viagra was unknown at the time.

4 Health risks of illicit ED products

4.1 Introduction

An investigation was carried out into the health risks of illicit ED products and the health damage caused by their use. As a point of reference, the adverse drug reactions (ADRs) for approved ED medicines were used as documented by the National Pharmacovigilance Centre Lareb. Lareb collects and analyses reports of suspected ADRs that are reported by health care professionals, patients and market authorisation holders. Each year Lareb receives about 7500 reports of ADRs. In 20% of these reports, a serious ADR is reported. It is presumed that Lareb primarily documents data on prescribed authentic ED medicines and not on counterfeits. No causality with counterfeits could be established. Therefore, the ADRs documented by Lareb are indicative of the health risks related to illicit ED products with PDE5 inhibitors. For further reference, public scientific literature was consulted for cases of actual health damage due to illicit ED products, user groups and the scale of use.

Pharmacovigilance focuses on the ADRs of registered medicines resulting from normal use. However, cases involving illicit generics or abnormal use (e.g., overdose, infants) may be documented by the National Poisons Information Centre (NVIC). NVIC documents information on suspected cases of poisoning voluntarily reported by physicians and informs them of the potential severity of the poisoning, possible symptoms and treatment options. The NVIC receives around 37,000 inquiries each year and these include inquiries about medicines and food supplements. Any case involving illicit ED products represents a case of health damage, as the patient required medical attention. Therefore, the NVIC was consulted to find cases of health damage due to illicit ED products.

The reporting of an ADR and the inquiry into a possible case of poisoning does not necessarily imply a causal relationship. The NVIC and Lareb do not investigate causality and do not perform any chemical analysis on the products involved.

4.2 Methods

Lareb was asked to provide a list of all ADR reports they had received for Viagra, Cialis and Levitra in the Netherlands since the market introduction. International scientific literature was searched for reports (using Pubmed and Scopus) on the scale of use, user groups and actual cases of health damage due to the use of illicit ED products.

To find possible cases of poisoning by illicit ED products, NVIC was provided with a list of terms to search their database. This list contained all the names of illicit medicines identified by the four laboratories from 2007-2010, chemical names and general search terms (e.g., ED, libido, virile, sex).

4.3 Results and discussion

4.3.1 *Health risks of prescribed ED medicine*

In the Netherlands ED medicines are prescribed approximately 300,000 times per year.²³ Lareb annually receives approximately 12 possible ADRs for Viagra and 4 for Cialis. Data on Levitra was not available. About 80% of the complaints documented by Lareb concern subjects between 50 and 80 years old, which is the

expected therapeutic age range for ED. Some 7% of the possible ADRs concerned females for whom ED medicines are not intended.

The most important of the possible ADRs and the numbers of reports are given in Table 5 by System Organ Class and by Preferred Term. These ADRs can also be expected to be the predominant ADRs due to illicit ED products PDE5 inhibitors in users over 50 years of age. However, it should be noted that the principle user group of illicit ED products may be younger and the ED products may be different. Therefore, less predominant ADRs were also considered for relevance.

Other such descriptors are eye disorders (14), drug ineffectiveness (2) and suicide attempts (2).²⁴ Eye-disorders are of interest because they are specifically expected for certain analogues (see Table 4). Drug ineffectiveness is of interest because this is expected for fraudulent counterfeits and generics. Suicide attempts are of interest because there are illicit generics that combine a PDE5 inhibitor with an antidepressant of the selective serotonin re-uptake inhibitor (SSRI) type to retard ejaculation. The use of SSRIs is associated with suicidal behaviour and the use of ED products is associated with patients on SSRIs to compensate for drug-induced ED.²⁵⁻²⁷

In general, health complaints are underreported, suggesting the 16 ADRs reported annually are an underestimate. One Viagra batch number was recorded by Lareb and this did not match any of the batch numbers for counterfeit Viagra recorded by RIVM since 2000.

Table 5 Possible ADRs for Viagra and Cialis in the Netherlands (1998-2008)

Description (number)	Descriptor	Number
System organ class (259)	General disorders	49
	Cardiac disorders	33
	Nervous system disorders	31
	Gastrointestinal disorders	28
Preferred term (301)	Death	31
	Myocardial infarction	17
	Headache	11
	Priapism	8

4.3.2 Literature

4.3.2.1 The scale of use of illicit ED products

The 10th anniversary of the Pfizer blockbuster drug Viagra[®] also marks a decade of a growing use of illicit ED products. It was recently estimated that on top of the 12 million prescriptions for ED medicines in Europe, an additional 6 million ED medicines were purchased outside the official distribution system.² When also accounting for adulterated food supplements, the unofficial market in Europe could amount to well over 50% of the legitimate market. A recent study conducted in Japan estimated the volume of the unofficial market in ED medicines at 250% of the legitimate market.²⁸ One report from Brazil stated that as much as 9% of a group of 167 male medical students with perfect erectile function³ (17-31 years) had repeatedly used ED products.²⁹ And in Germany, very high sewage discharges of PDE5 inhibitors were reported for a fitness centre implying a large-scale use of ED products by athletes.³⁰ Assuming the majority of the ED medicines outside the official distribution chain are illicit ED products, the scale of their use in relation to the pharmacovigilance data suggests that (serious) health damage could occur.

³ A proportion of the subjects declared to suffer from 'condom-related' erectile dysfunction.

4.3.2.2 Health damage due to illicit ED products

Three articles have been published in recent literature relating to actual health damage due to illicit ED products. The incidents were all connected to the presence of the anti-diabetic glibenclamide in the products. The two major incidents concern a serious outbreak of hypoglycaemia in Hong Kong³¹ and Singapore³² in 2008-2009. Over 200 victims were hospitalised and several died. Many of the victims were elderly and were presumably not recreational users. Several victims were repeatedly hospitalised with the same symptoms because they did not attribute their health complaints to the illicit ED products they were using. When the outbreak was well under way, it was discovered that glibenclamide was present in more than 7 different products in Asia. Potentially lethal doses of up to 30 times the normal dose were identified in counterfeits, illicit generics and food supplements. Several products were identified with both glibenclamide and sildenafil. The outbreak became apparent when an unusual number of comatose hypoglycaemic patients were admitted to one hospital in Hong Kong. Reanalysis of urine samples of previous similar cases showed that several cases had remained unrecognised. Only 35% of the victims for whom urinalysis was conclusive admitted to having used illicit ED products. Unexpectedly, in 2010 a new and isolated case was reported in Australia concerning counterfeit Cialis with glibenclamide that was imported from Asia.³³ In the Netherlands, no illicit ED products with glibenclamide were identified.

4.3.2.3 Users, their motives and risk factors

Although the pharmaceutical industry argues that there are still millions of 'secret' ED patients in Europe, it is common knowledge that ED products are used as recreational drugs to counteract the loss of libido due to the use of alcohol, drugs and fatigue.³⁴⁻⁴⁰ Other known user motives for non-ED patients are to counteract condom-related ED, to shorten the refraction time and as a form of sports doping.³⁰ Recurrent use may partially be rooted in the apparent rewarding properties of PDE5 inhibitors on the brain and fear of failure in non-ED patients when reverting to non-pharmaceutical sex.^{41,42}

The use of PDE5 inhibitors in the treatment of ED has serious contra-indications like recent myocardial infarction and the use of nitrates.^{16,43} Such contra-indications are normally associated with ED patients above 50 years of age, who are considered to be high-risk users.

Literature shows that members of the high-risk group, even with diagnosed ED, resort to using illicit ED medicines.^{2,31} However, literature also shows that illicit ED medicines are extensively used by low-risk users (healthy young men) for recreational purposes.^{30,34,36,38-40,44} In this age group, clinical studies have shown that ED drugs are generally well tolerated under controlled circumstances.⁴⁵ Risk factors identified in literature for health damage due to illicit ED products are their secretive use and the combination with alcohol, marihuana or other drugs.^{6,29,31,46-48} The NVIC data confirms that health damage is associated with the use of alcohol but also mentions multiple dosing. Multiple dosing could be the result of the false expectancy among many men that a PDE5 inhibitor should produce a spontaneous erection⁶ and that the effects of sildenafil and vardenafil are delayed when taken with (fatty) food.⁴⁵

A risk factor that should be addressed is the public perception of the official distribution system as a safety tool. This might answer the question why consumers apparently place such great trust in illicit generics (68% of the database samples).

4.3.3 Cases of health damage in the Netherlands

A list of possible cases of poisoning by illicit ED products was kindly provided by the National Poisons Information Centre (NVIC) (Table 6). NVIC recorded 16 cases of possible acute poisoning after exposure to 8 different products. The actual products causing the possible poisoning were not analysed in a laboratory. The list comprises 3 illicit generics and 5 different food supplements ingested by 4 infants (< 3 years) and 12 adult males and females (<50 years). In adults, the use of multiple doses and the concomitant use of alcohol were common. On one occasion, Libidoforte was used in a suicide attempt in conjunction with other medication. Victims mostly experienced transient cardiovascular events (which is in line with exposure to ED drugs) and vomiting.

In Table 6 the NVIC data is correlated to the chemical analytical data of products under that name present in the database of illicit ED products. Six of the eight products retrieved from the NVIC database were also present in the 2007-2010 database of illicit ED products: 2 *illicit generics* and 4 *food supplements*. The laboratories were unfamiliar with the products Tanagra and Sextra.

The *illicit generics* named 'Kamagra' and 'Sildenafil' are associated with sildenafil, which can be present at various dose levels per tablet. The *food supplements* in Table 6 are mainly associated with the presence of analogues. The history of the products shows that the manufacturers of adulterated food supplements regularly change the drug substance. Retrieval of the product from the victim and chemical analysis is the only way to know the actual drug substance. Due to the obscure safety profiles for analogues, it is uncertain whether all clinical symptoms match the associated active ingredient.

Table 6: Cases of health damage involving illicit ED products (2007-2010)

Case	Product involved	History on products with the same name (year of analysis)	
5 adults 3 infants	<i>Kamagra</i>	0-110 mg	Sildenafil (any year)
1 adult	<i>Sildenafil</i>	98 mg	Sildenafil (2009)
1 infant	<i>Tanagra</i>	-	-
1 adult	<u>Libidoforte</u>	65 mg	Hydroxy-homosildenafil (2008)
		n.d.	Sildenafil (2010)
1 adult	<u>Viafemme</u>	0.3 mg	Amino-tadalafil (2008)
		n.d.	Icariin (2010)
1 adult	<u>Libido Extreme</u>	n.d.	Noracetildenafil (2008)
		50 mg	Noracetildenafil (2010)
1 adult	<u>Sextra</u>	-	-
2 adults	<u>Yohimbine</u>	0-25 mg	Yohimbine (any year)

4.3.4 General consideration

Literature and the NVIC data have shown cases of health damage involving illicit ED products. Although the number of cases is limited and causality was not investigated, these cases are the first signs of actual health damage.

Examples of health damage due to illicit ED products were identified in the NVIC database using product descriptions. Historical laboratory data on these products suggest that they contained PDE5 inhibitors. The NVIC data shows that cardiovascular events occur among the users of illicit ED products under 50 years of age. This confirms that 'cardiac disorders' (Table 5) is a valid descriptor of health damage due to illicit ED products with PDE5 inhibitors for all age groups. Literature did not show examples of health damage due to PDE5 inhibitors but illustrates the

risks of the wrong drug substance being present in an illicit ED product. In addition, it also showed that the user group includes males in the high-risk user group.

Literature also shows that isolated incidents are hard to identify. A heart patient's death (high-risk group) may not trigger an investigation into the authenticity of the Viagra found in his room.⁴⁹ Furthermore, victims may be unwitting, uncooperative, or incapacitated³¹ and sexual partners unaware of the ED drugs.⁴⁸ The analogues of these ED-drugs and their metabolites are unknown to routine toxicology. Health damage by illicit ED products is therefore expected to be underreported to an even larger extent than for ED medicines that are legally prescribed.

Cardiovascular events and most of the other descriptors in Table 5 are unspecific for PDE5 inhibitors. In addition, illicit ED products might also contain other drug substances (e.g., analogues, SSRIs, glibenclamide) that cause different symptoms. Therefore, recognising cases by clinical symptoms is difficult. This underlines the importance of an appropriate toxicological screening (incl. analogues) and the thorough examination of all the medicines and food supplements used by the patient.

Priapism and eye disorders are specific descriptors of PDE5 inhibitor-related adverse events which are expected to occur regularly. However, it is unclear whether these cases are recognised, pursued or documented. NVIC was not consulted over such cases.

In order to pick up the signals of health damage resulting from illicit ED products, health care professionals need to become aware of the scale of the phenomenon and use the descriptor list as a 'trigger'. In addition, health care professionals need to receive advice on what to do with the information.

5 Discussion and conclusions

5.1 Products and drug substances over 2000-2010

The three periods that are covered by RIVM reports (2000-2004, 2005-2006, and 2007-2010) describe about 120 illicit ED products per year. This annual number of products represents less than 1% of the ED products that literature suggests are annually used in the Netherlands outside the official distribution system.² Despite the small sample size, it is the only source of information on products outside the official distribution system.

In the first RIVM report, counterfeits accounted for 32% of all illicit ED products (Fig. 6) and consisted almost entirely of counterfeit Viagra (Fig. 7). Illicit imitations account for 68% of the samples.⁴ The prevalence of counterfeit Viagra over 2000-2004 was attributed to Viagra already being available on the official market before 2000 and Cialis and Levitra being introduced later in that period. Sildenafil was the most frequently identified drug substance (58%), followed by a large number of 'other' drug substances unrelated to PDE5 inhibitors (23%, e.g., clomifene, amphetamine) (Fig. 8). The first report anticipated a relative increase in Cialis and Levitra counterfeits as well as in the use of their drug substances in illicit ED products in general.

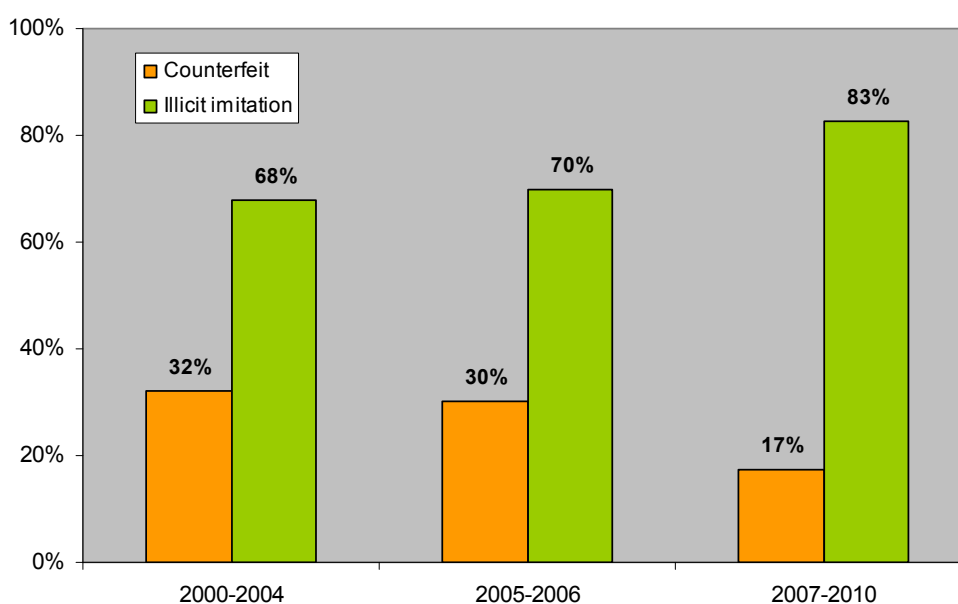


Figure 6 Distribution of illicit ED products over 2000-2010. Illicit imitations comprise illicit generics + illicit food supplements.

In the second RIVM report there was only a slight change in the percentage of counterfeits in the database. The anticipated increase in counterfeit Cialis (25%) and Levitra (6%) was observed. Sildenafil continued to be the most frequently identified drug substance (72%) and was now followed by tadalafil (18%). A relative increase was observed in the use of both sildenafil and tadalafil at the expense of 'other' drug substances. From that observation it was deduced that

⁴ In the 1st and 2nd reports illicit generics and illicit food supplements were taken together as 'imitations'. The data of the current report was adapted for comparison.

PDE5 inhibitors and specifically sildenafil, had become readily available on the unofficial market. In appendix 7 an overview is given of the most important drug substances identified in illicit ED products around the world between 2000-2010.

The third period covered by the current RIVM report shows a considerable decrease in counterfeits to 17% of all the illicit ED products in the database. This decrease may be explained by including data from the Dutch Forensics Institute (NFI), by effective enforcement or by consumers increasingly purchasing illicit generics.

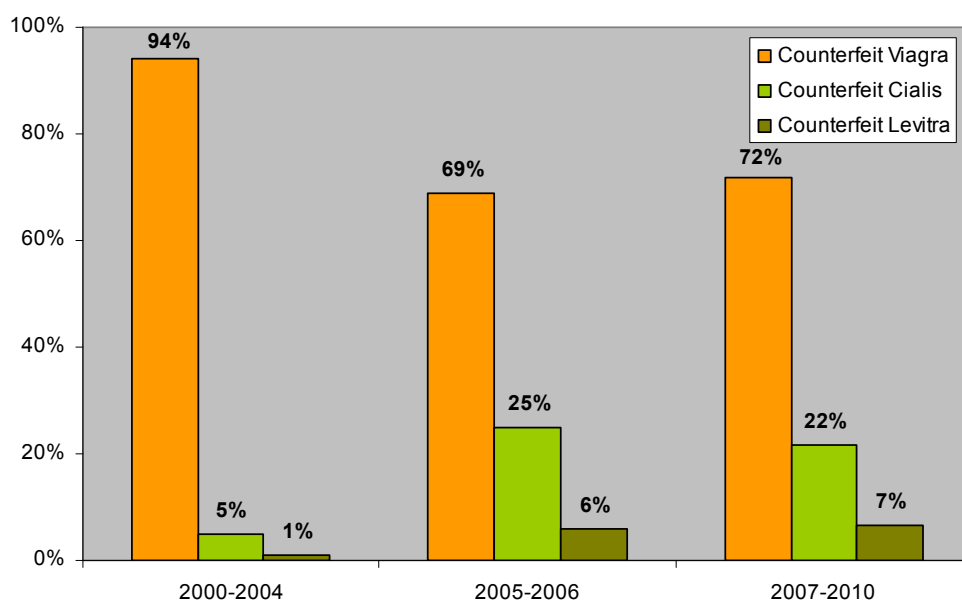


Figure 7 Distribution among the counterfeit brands over 2000-2010.

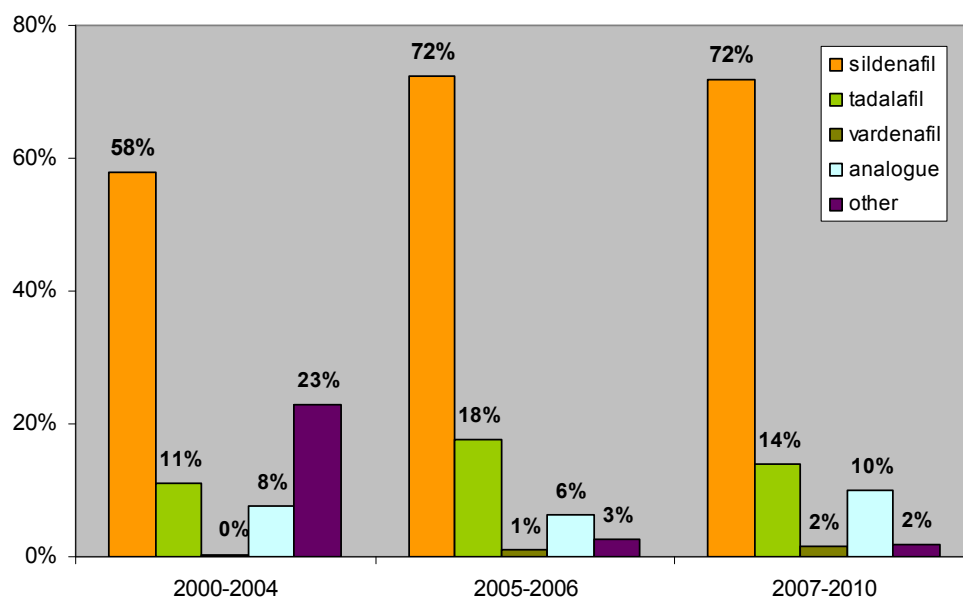


Figure 8 Distribution of drug substances in illicit ED products over 2000-2010.

The prevalence of sildenafil in the third period did not change (72%), contrary to that of tadalafil. The decrease in tadalafil was not expected and may be due to limited availability. Its synthesis requires piperonal, which is heavily monitored for it is also used in MDMA production (XTC). Replacing piperonal for another moiety does not produce very effective PDE5 inhibitors, which may be why analogues of that type were not observed.^{50,51} The reason for the limited occurrence of vardenafil is unclear.

The relative distribution among the counterfeits in the database is apparently stable after 2004. However, the ratio between the counterfeits in the database does not reflect the use of these brands in the official distribution system. In 2009 the Viagra/Cialis ratio in the official distribution system in the Netherlands²³ was 1.4, whereas in our databases it is 2.8 for 2005-2006 and 3.0 for 2007-2010.

5.2 Analogues of PDE5 inhibitors between 2000-2010

After the first analogue was identified in 2003, there was an explosive growth in the number of different analogues: from 3 to over 42 analogues in 2010. The analogue portfolio has gradually extended to more exotic and dangerous structures. About half of the known analogues are frequently identified in suspect food supplements in Europe; all of them were identified in Asia. The 'design' of new active analogues is easy for a medicinal chemist. The medicinal chemist will consult (patent) literature, use the active moiety of a molecule and attach it to any suitable reagent in non-critical positions. The theoretical options are numerous and will to some extent be determined by whatever reagents are available.

Some analogues, like amino-tadalafil, were synthesised for a specific reason. In the last synthesis step the poisonous hydrazine is used instead of methylamine to give a better conversion. Nitroso-prodenafil must also have been specifically designed as an aildenafil prodrug with dual action because of its complexity and dose. It does show that the manufacturers are highly educated and scrupulous.

Illicit ED products with analogues are marketed as food supplements to bypass the official route when developing a drug substance into a medicine. The concept of using analogues has become successful because of the time-consuming chemical analytical difficulties and the unclear judicial status of the products. This is why it has also spread to other food products (e.g., cannabinoids, weight-loss drugs).^{52,53} Fighting analogues is slow because the government has to argue their status as a medicine case-by-case. This approach may even trigger the development of new analogues and misleading indications (e.g., fertiliser)⁵. Therefore, combating analogues requires a swift and harmonised solution applicable to analogues in all therapeutic areas. The common denominator is that consumers are intentionally exposed to substances that can reasonably be expected to be investigational drugs, making them the subject of medical experiments.

In 2007, dosage became important to the definition of a medicine because of a ruling of the European Court of Justice. The court ruled that a food supplement with a sub-therapeutic dose of a natural prescription-only drug was not a medicine, ignoring clinical evidence of efficacy⁵⁴, the presence of other active ingredients⁵⁵, and reported ADRs for similar products.⁵⁶⁻⁵⁹ This ruling presented some hesitation in the prosecution of cases involving products with analogues because of their obscurity to science.

⁵ The cannabinoid analogue JWH-018 was promoted as a fertiliser but now is scheduled as a narcotic in several countries.

However, the relevance of a therapeutic dosage in a non-patient is questionable. In addition, one cannot safely extrapolate the risk/benefit ratio from a diagnosed patient to an undiagnosed member of the general public. Therefore, when determining the status of a product, far more importance should be placed on the pharmacological effect of a drug substance than the therapeutic effect it happens to be registered for (if any). Arguing that analogues are investigational drug substances that have a pharmacological effect is relatively easy.

5.3 Health risks between 2000-2010

The health risks of illicit ED products have changed over the past 10 years. Although the products are still totally unreliable, the extensive use of 'other' drug substances (e.g., clomifene) diminished after 2004. Since then, the use of the approved PDE5 inhibitors sildenafil and tadalafil dominate the drug substances identified. Because these PDE5 inhibitors, when taken responsibly, are relatively safe medicines, the health risks of illicit ED medicines in relation to the drug substance have decreased. The contrary is observed for illicit food supplements with analogues, where criminals now boldly create ingenious new analogues like nitroso-prodenafil.

New 'other' drug substances in the database and in literature were the muscle relaxant 'carisoprodol' and the antidepressant 'dapoxetine'.²⁷ Both of these drug substances exert a high health risk because a carisoprodol metabolite⁶⁰ is a known substance of abuse and dapoxetine^{25,61} has a questionable safety record. They are probably used in sex-related products to reduce stress and to delay ejaculation.^{6,48} Another antidepressant called flibanserin, which is intended for women, was identified in a food supplement in Asia in 2010 when it was officially still in phase III of clinical development.

Both dapoxetine and flibanserin are selective serotonin reuptake inhibitors (SSRIs). Clinical studies have shown a poor benefit-risk ratio for a sexual indication because they show the typical side-effects associated with SSRIs. The Internet offers ample opportunity to purchase medicines with a combination of sildenafil with an SSRI, which are not registered in the EU.²⁶

In earlier reports we described the trend from gross counterfeiting of tablets to refined counterfeiting of the total product (box, blister and leaflet). The major health risk associated with that trend was infiltration of the official supply chain. However, infiltration of the official distribution system may not be the primary goal of the criminals involved. Instead, as we also noted for illicit weight-loss drugs in 2008, they may be targeting a stable illicit market by aiming at returning customers. This would explain the low dose yet efficacious ED products in the database.

In the official distribution system patients would have a slight chance of a repeated exposure to counterfeit ED medicines. Therefore, the acute health risks are greater than the risks of long-term exposure. Provided that counterfeits contain relatively safe PDE5 inhibitors in low to normal doses, the health risks in the official distribution system are small.

However, outside the official distribution system returning customers will purchase unreliable products time after time. Even though the products in the database show a limited risk of acute health damage, repeated exposure increases the risk of purchasing a 'bad one' and of long-term health damage. Assuming criminals are continually attempting to maximise their profit margin, they will ignore the required quality requirements of the ingredients (e.g., the absence of impurities). Any causality between illicit ED products and, for example, cancer will be extremely

difficult to prove. In this respect the existence of counterfeit generics is worrying because of the expected low profit margin.

The level of exposure to illicit ED products changed between 2000-2010 from the occasional recreational user to widespread recreational use today. Extrapolating from literature to the European situation, there were an estimated 150,000 purchases of ED medicines outside the official distribution system in the Netherlands in 2009.^{2,23} Including adulterated food supplements, the illegal market is at least 50% of the size of the official market in the Netherlands. At that scale, (serious) health damage should be expected (see Table 5).

The upcoming market release of approved generics within the European market may bring some relief with respect to exposure to low-quality products. However, lower prices may also result in a lower quality of illicit ED products. Counterfeit generics and counterfeit drug substances will then become new threats.

5.4 Conclusions

The potential public health risk posed by fraudulent labelling has specifically increased for adulterated food supplements. These products secretly contain obscure drug substances that have no known safety or toxicology record. Their adverse effects could be mediated through mechanisms other than PDE5 inhibition.

The use of risky drug substances in illicit ED medicines has diminished drastically and nearly all medicines now contain low to normal doses of sildenafil or tadalafil. At present, the short-term health risks associated with the use of illicit ED products in the Netherlands appear to be limited and largely related to user behaviour (overdosing, concomitant use of alcohol and drugs). There is a lack of information on long-term health risks.

Despite the apparent infrequency of ADRs, the potential seriousness should not be underestimated. The pharmacovigilance data shows that serious ADRs are associated with the use of PDE5 inhibitors. Therefore, based on the current scale of consumption, it is likely that serious cases are already occurring.

The demand for ED products by non-ED patients is enormous and this is not expected to change in the future. Apparently, the user group considers these products to be a valuable addition to their quality-of-life and therefore worth the risk of purchasing from unreliable sources.

The technical quality of illicit ED products is inherently subject to change.

5.5 Recommendations

1. Public warnings about fraudulently labelled food supplements should be intensified.
2. Future monitoring of illicit ED products should focus on obscure drug substances (e.g., analogues, polymorphs, SSRIs) and counterfeit (illicit) generics.
3. The ministry of health should investigate the scale of use of illicit ED products and develop a monitoring system to gauge the health damage caused by illicit ED products.
4. The ministry of health should investigate user behaviour and user motives in relation to the use of ED drugs by non-ED patients and provide an adequate response to the high demand.

Appendix 1 The flow of samples

The samples analysed by the four laboratories were provided by the Netherlands Health Care Inspectorate (IGZ), the Food and Consumer Product Safety Authority (VWA), Dutch Customs, the police and public pharmacists. Suspect ED products were analysed case by case without the objective of random sampling. Suspect ED medicines were brought in for analysis following confiscation outside the official distribution chain. The samples were analysed using NIR, HPLC-DAD, HPLC-DAD-MS, ESI-(IT)-MS, and TLC techniques, depending on the laboratory. No attempts were made to collect information from the laboratories to verify the entire declared composition (e.g., botanical analysis).

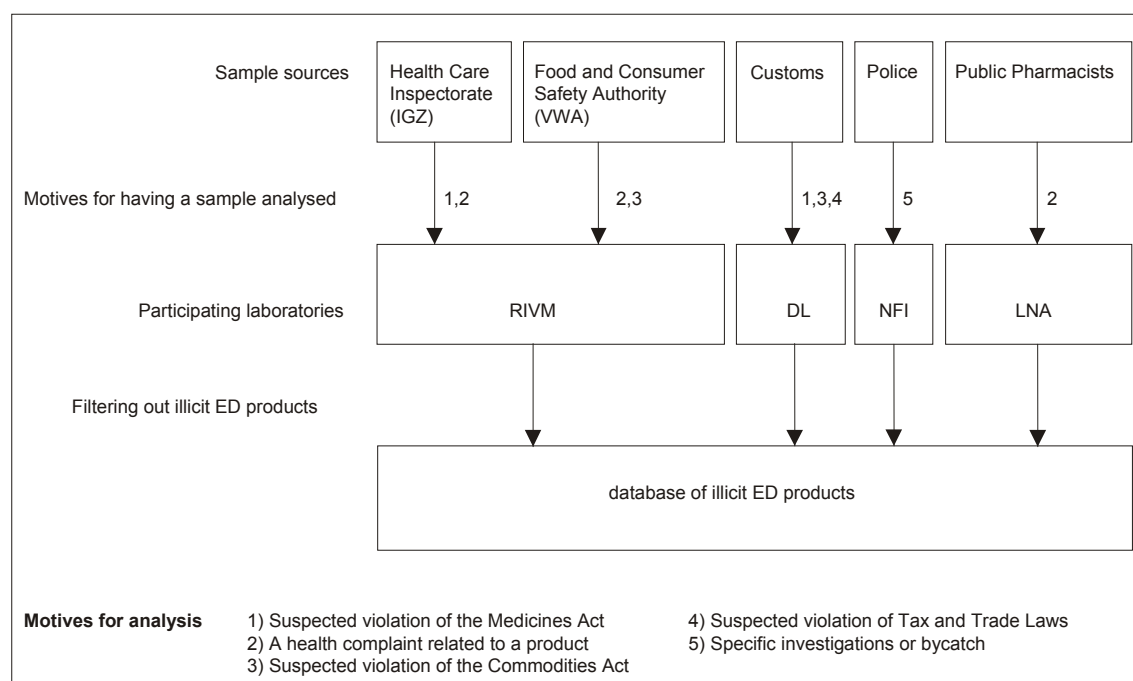


Figure 9 The flow of samples.

The laboratories were asked to search their own database for suspect ED products by searching on: 1) product names of ED drugs (e.g., Viagra, Cialis), 2) product claims (e.g., libido, erection) and 3) known drug substances used in libido-enhancing products (e.g., sildenafil, amino-tadalafil). Search terms 1 and 2 would retrieve erectogenic products containing any drug substance or no drug substance. Search term 3 was used to retrieve products for which the active erectogenic ingredient was entered into the laboratory database and had no searchable name or claim. The search terms would not retrieve 'false negatives': unfamiliar names/claim without drug substances or with drug substances with no known use in libido enhancing products. The datasets of suspect ED products provided to the database generally contained information on the product name, appearance, drug substance and dose.

Appendix 2 Listings

Lab: LNA	Illicit ED products		Laboratory findings			
Year	Product name	Embossing	API identified	Dose	Category	
2009	Cialis 50 mg	C50	sildenafil		Fraudulent	Counterfeit Cialis
	Cialis 20 mg	C20	tadalafil	<<10	Fraudulent	Counterfeit Cialis
	Viagra 50 mg		sildenafil	35	Fraudulent	Counterfeit Viagra
	Viagra 50 mg		sildenafil	45	Accurate	Counterfeit Viagra
2010	Kamagra	KGR100 / AP	sildenafil		Other	Illicit generic

Lab: RIVM	Illicit ED products		Laboratory findings			
Year	Product name	Embossing	API identified	Dose	Category	
2007	Viagra 100 mg		none	0	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	1.2	Fraudulent	Counterfeit Viagra
			vardeafil	10.7		
			homosildenafil	traces		
	Viagra 100 mg		vardeafil	10.4	Fraudulent	Counterfeit Viagra
			homosildenafil	traces		
	Cialis C20		sildenafil	24	Fraudulent	Counterfeit Cialis
			vardeafil	2.6		
			homosildenafil	3.9		
	Cialis C20		sildenafil	43	Fraudulent	Counterfeit Cialis
	Levitra 20		sildenafil	29.4	Fraudulent	Counterfeit Levitra
	Blue pill		–		Other	Illicit generic
	Viagra 100 mg		sildenafil	95	Accurate	Counterfeit Viagra
	Viagra 100 mg		sildenafil	66	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	60	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	94	Accurate	Counterfeit Viagra
	Viagra 100 mg		sildenafil	57	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	91	Accurate	Counterfeit Viagra
	Viagra 100 mg		sildenafil	85	Fraudulent	Counterfeit Viagra
	White capsules		thio-homosildenafil	56	Fraudulent	Illicit food
			homosildenafil	3		
	White capsules		thio-homosildenafil	53	Fraudulent	Illicit food
			homosildenafil	1		
	White capsules		thio-homosildenafil	57	Fraudulent	Illicit food
			homosildenafil	1		
	White capsules		thio-homosildenafil	56	Fraudulent	Illicit food
			homosildenafil	1		
	Erexer		sildenafil	50	Fraudulent	Illicit food
	E-rex		hydroxy-homosildenafil	72	Fraudulent	Illicit food
	VGR50		sildenafil	47	Accurate	Counterfeit Viagra
	Viagra 50 mg		sildenafil	34	Fraudulent	Counterfeit Viagra
	Nasutra		amino-tadalafil	9,3%		Illicit food
	Kamagra		sildenafil	94	Accurate	Illicit generic
	Kamagra		sildenafil	96	Accurate	Illicit generic
	Herb Vigour		tadalafil	50	Fraudulent	Illicit food
	Natural Vigour		vardeafil	34	Fraudulent	Illicit food
	China Vigour		nor-acetildenafil	70	Fraudulent	Illicit food
	Kamagra		sildenafil	101	Accurate	Illicit generic
	Sildenafil		sildenafil	97	Accurate	Illicit generic
	Viamax		piperidino-vardeafil	8	Fraudulent	Illicit food
	E-rex		hydroxy-homosildenafil	87	Fraudulent	Illicit food
	Red/White capsules		acetildenafil	36	Fraudulent	Illicit food
	Brown capsules		piperidino-vardeafil	2	Fraudulent	Illicit food
	Solution for spraying marihuana		thio-homosildenafil	–	Other	Illicit other
			homosildenafil	–		
2008	Qing Tian Zhu		thio-sildenafil	46	Fraudulent	Illicit generic
	Libido Extension		aidenafil	69	Fraudulent	Illicit food
	Libido XL		vardeafil	46	Fraudulent	Illicit food
	Kamagra oral jelly 100 mg		sildenafil	93	Accurate	Illicit generic
	Amoras		tadalafil	8,6	Fraudulent	Illicit food
	Viagra 100 mg		sildenafil	102	Accurate	Counterfeit Viagra
	Levitra 20 mg		sildenafil	11	Fraudulent	Counterfeit Levitra
			tadalafil	10		
	Viagra 100 mg		sildenafil	80	Fraudulent	Counterfeit Viagra
			hydroxy-homosildenafil	20		
	Viagra 100 mg		sildenafil	61	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	72	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	95	Accurate	Counterfeit Viagra
	V-mega		sildenafil	116	Fraudulent	Illicit generic
			tadalafil	25		
	V-max		sildenafil	21	Fraudulent	Illicit generic
	VigRX		sildenafil	42	Fraudulent	Illicit generic
	Levitra 20 mg		sildenafil	86	Fraudulent	Counterfeit Levitra
	Cialis 20 mg		tadalafil	14	Fraudulent	Counterfeit Cialis
			trans-tadalafil	4		
			sildenafil	traces		
	Viagra 100 mg		sildenafil	74	Fraudulent	Counterfeit Viagra
	Super Viagra		sildenafil	68	Fraudulent	Illicit generic
	Viagra 100 mg		sildenafil	91	Accurate	Counterfeit Viagra
	Vigour 300		sildenafil	171	Fraudulent	Illicit generic
			tadalafil	24		
	Kamagra 100 mg Oral Jelly		sildenafil	161	Fraudulent	Illicit generic
	Cialis 20 mg		sildenafil	58	Fraudulent	Counterfeit Cialis
	Cialis 20 mg		sildenafil	1	Fraudulent	Counterfeit Cialis
			tadalafil	11		
	Lovegra 100		sildenafil	97	Accurate	Illicit generic
	Kamagra 100 mg		sildenafil	93	Accurate	Illicit generic
	Viagra 100 mg		sildenafil	58	Fraudulent	Counterfeit Viagra
	Top Viril		thio-homosildenafil	29	Fraudulent	Illicit food
			homosildenafil	traces		
			hydroxy-homosildenafil	traces		
			yohimbine	traces		

Lab: RIVM	Illicit ED products		Laboratory findings			
Year	Product name	Embossing	API identified	Dose	Category	
2008	Golden Root Complex		hydroxy-homosildenafil	134	Fraudulent	Illicit food
	Golden Root Complex		hydroxy-homosildenafil	130	Fraudulent	Illicit food
	Golden Root Complex		hydroxy-homosildenafil	134	Fraudulent	Illicit food
	Armstrong		amino-tadalafil	53	Fraudulent	Illicit food
	Libidoforte		hydroxy-homosildenafil	65	Fraudulent	Illicit food
	Viafemme		amino-tadalafil	0.3	Fraudulent	Illicit food
			aildenafil	traces		
			hydroxy-homosildenafil	traces		
	Viafemme		amino-tadalafil	traces	Fraudulent	Illicit food
	Sensafem		yohimbine	n.d.	Other	Illicit food
	Sensafem		yohimbine	n.d.	Other	Illicit food
	Stimulust		nor-acetildenafil	n.d.	Fraudulent	Illicit food
	Libido Extreme		nor-acetildenafil	n.d.	Fraudulent	Illicit food
	ViaFemme		aildenafil	traces	Fraudulent	Illicit food
	ViaPower		aildenafil	46	Fraudulent	Illicit food
	ViaPower		aildenafil	49	Fraudulent	Illicit food
	ViaFemme		aildenafil	traces	Fraudulent	Illicit food
2009	Maxman		sildenafil	0.3	Fraudulent	Illicit generic
			tadalafil	6		
	Kamagra Oral Jelly 100 mg		sildenafil	99	Accurate	Illicit generic
	Strong		sildenafil	152	Fraudulent	Illicit food
	Kamagra 100 mg		sildenafil	98	Accurate	Illicit generic
	Viagra 100 mg		sildenafil	53	Fraudulent	Counterfeit Viagra
	Levitra 20 mg		sildenafil	41	Fraudulent	Counterfeit Levitra
	Cialis 20 mg		sildenafil	1	Fraudulent	Counterfeit Cialis
			tadalafil	12		
	Viagra 100 mg		sildenafil	58	Fraudulent	Counterfeit Viagra
	Cialis 20 mg		sildenafil	112	Fraudulent	Counterfeit Cialis
	Cialis 20 mg		sildenafil	119	Fraudulent	Counterfeit Cialis
	Kamagra Oral Jelly 100 mg		sildenafil	87	Fraudulent	Illicit generic
	Kamagra Oral Jelly 100 mg		sildenafil	99	Accurate	Illicit generic
	Epimedium		tadalafil	27	Fraudulent	Illicit food
	Kamagra 100 mg		sildenafil	92	Fraudulent	Illicit generic
	Viagra 100 mg		sildenafil	96	Fraudulent	Counterfeit Viagra
	Viagra 50 mg		sildenafil	51	Fraudulent	Counterfeit Viagra
	Sildenafil tablets 100 mg		sildenafil	98	Accurate	Illicit generic
	Bleu tablets		sildenafil	69	Other	Illicit generic
	Bleu tablets		sildenafil	65	Other	Illicit generic
	Durago-50		sildenafil	53	Accurate	Illicit generic
	Viagra 25 mg		sildenafil	24	Accurate	Counterfeit Viagra
	Tazalis-20 (tadalafil)		tadalafil	18	Accurate	Illicit generic
	Yellow tablets		sildenafil	50	Other	Illicit generic
	Tadalafil tablets		sildenafil	5	Fraudulent	Illicit generic
			tadalafil	0.4		
	Nizagara		sildenafil	108	Accurate	Illicit generic
	Nizagara		sildenafil	102	Accurate	Illicit generic
	Sagirra		noractildenafil	46	Fraudulent	Illicit food
	Viagra 100 mg		sildenafil	77	Fraudulent	Counterfeit Viagra
	Cialis 20 mg		sildenafil	48	Fraudulent	Counterfeit Cialis
	Cialis 20 mg		sildenafil	44	Fraudulent	Counterfeit Cialis
	Levitra 20 mg		sildenafil	19	Fraudulent	Counterfeit Levitra
	Viagra 50 mg		sildenafil	29	Fraudulent	Counterfeit Viagra
	Viagra 50 mg		sildenafil	31	Fraudulent	Counterfeit Viagra
	Sexlets		DHEA	2.4	Other	Illicit food
			yohimbine	0.3		
	Kamagra		sildenafil	92	Accurate	Illicit generic
				30-		
	Malegra Oral Jelly		sildenafil	100	Fraudulent	Illicit generic
	Tadora-20		tadalafil	18.5	Accurate	Illicit generic
	Kamagra		sildenafil	89	Fraudulent	Illicit generic
	Hawthorn		noractildenafil	47	Fraudulent	Illicit food
	Hawthorn		noractildenafil	52	Fraudulent	Illicit food
	Hawthorn		noractildenafil	52	Fraudulent	Illicit food
	Hawthorn		noractildenafil	44	Fraudulent	Illicit food
	Hawthorn		noractildenafil	42	Fraudulent	Illicit food
	Kamagra 100 mg		sildenafil	80	Fraudulent	Illicit generic
	Viapro		thio-aildenafil	46	Fraudulent	Illicit food
2010	Kamagra Oral Jelly		sildenafil	83	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	93	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	90	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	88	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	91	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	83	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	23	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	94	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	92	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	91	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	95	Accurate	Illicit generic
	Kamagra Oral Jelly		sildenafil	90	Fraudulent	Illicit generic
	Kamagra Oral Jelly		sildenafil	78	Fraudulent	Illicit generic
	Cialis 20 mg		sildenafil	36	Fraudulent	Counterfeit Cialis

Lab: RIVM	Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category
2010	Viagra 100 mg		sildenafil	<0.2	Fraudulent
				98.4	
	Viagra 50 mg		sildenafil	33	Fraudulent
				33	
	Man Power		Nitroso-prodenafil	108	Fraudulent
	Golden Root Complex		hydroxy-homosildenafil	70	Fraudulent
	Libido Extreme		noracetildenafil	50	Fraudulent
	Libido Naturel		aildenafil	39	Fraudulent
	Viapower		hydroxy-homosildenafil	73	Fraudulent
	Libidoforte		sildenafil	–	Fraudulent
	Cialis C50		sildenafil	46	Fraudulent
	Levitra 20		sildenafil	57	Fraudulent
	Rock Hard Weekend		Thio-aildenafil	82	Fraudulent
			aildenafil	traces	Fraudulent

Lab: Customs	Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category
2007	Virilina		yohimbine	–	Other Illicit food
	China vigour		noracetildenafil	–	Fraudulent Illicit food
	Herb vigour		tadalafil		Fraudulent Illicit food
	Witte capsules		tadalafil	1.5	Other Illicit generic
	Witte capsules		tadalafil	1.5	Other Illicit generic
	Kamagra oral jelly orange	Oral Jelly	sildenafil	32	Fraudulent Illicit generic
	Kamagra 100, pineapple	Oral jelly	sildenafil	55	Fraudulent Illicit generic
	Kamagra 100, orange	Oral jelly	sildenafil	65	Fraudulent Illicit generic
	Kamagra 100		sildenafil	85	Fraudulent Illicit generic
	Kamagra 100		sildenafil	88	Fraudulent Illicit generic
	Kamagra 100 gold		sildenafil	93	Accurate Illicit generic
	Kamagra 100 gold		sildenafil	93	Accurate Illicit generic
	Kamagra	Oral jelly	sildenafil	94	Accurate Illicit generic
	Kamagra 100		sildenafil	94	Accurate Illicit generic
				95, 98, and	
	Vega 100		sildenafil	109	Accurate Illicit generic
	Kamagra	Oral jelly	sildenafil	99	Other Illicit generic
	Kamagra	Oral jelly	sildenafil	100	Other Illicit generic
	Kamagra 100		sildenafil	100	Accurate Illicit generic
	Kamagra	Oral jelly	sildenafil	101	Other Illicit generic
	Kamagra 100		sildenafil	101	Accurate Illicit generic
	Kamagra 100 gold	Oral Jelly	sildenafil	102	Accurate Illicit generic
	Kamagra 100, pineapple	Oral jelly	sildenafil	102	Accurate Illicit generic
	Kamagra oral jelly/ sildenafil	Oral jelly	sildenafil	103	Other Illicit generic
	Kamagra sildenafil citrate		sildenafil	103	Other Illicit generic
	Kamagra oral jelly/ sildenafil	Oral jelly	sildenafil	103	Other Illicit generic
	Kamagra sildenafil citrate		sildenafil	104	Other Illicit generic
	Kamagra sildenafil citrate		sildenafil	105	Other Illicit generic
	Kamagra 100 Oral Jelly	Oral jelly	sildenafil	105	Accurate Illicit generic
	Kamagra 100 Oral Jelly, banana	Oral jelly	sildenafil	106	Accurate Illicit generic
	Kamagra sildenafil citrate		sildenafil	108	Other Illicit generic
	Kamagra oral jelly/ sildenafil	Oral jelly	sildenafil	109	Other Illicit generic
	Kamagra sildenafil citrate		sildenafil	110	Other Illicit generic
	Kamagra 100		sildenafil	110	Fraudulent Illicit generic
	Kamagra sildenafil citrate		sildenafil	111	Fraudulent Illicit generic
	Kamagra oral jelly/ sildenafil	Oral jelly	sildenafil	113	Fraudulent Illicit generic
	Kamagra 100, banana	Oral jelly	sildenafil	114	Fraudulent Illicit generic
	Coitus auxillery en potencia		Carisoprodol		Fraudulent Illicit food
2008	Viagra 100 mg		sildenafil	0	Fraudulent Counterfeit Viagra
	Kamagra oral jelly	Oral jelly	sildenafil	38	Fraudulent Illicit generic
	Kamagra oral jelly	Oral jelly	sildenafil	49	Fraudulent Illicit generic
	Cialis		sildenafil	74	Fraudulent Counterfeit Cialis
	Viagra		sildenafil	85	Fraudulent Counterfeit Viagra
	Buttons, Viagra tablets		sildenafil	87	Other Illicit generic
	Viagra		sildenafil	88	Accurate Counterfeit Viagra
	Viagra 100 mg		sildenafil	101	Accurate Counterfeit Viagra
	Viagra 100 mg		sildenafil	122	Fraudulent Counterfeit Viagra
	Viagra 100 mg		sildenafil	123	Fraudulent Counterfeit Viagra
	Stree Overlord		sildenafil	162	Fraudulent Illicit food
	Libido-extension		ildenafil	–	Fraudulent Illicit food
	Top Viril Men		yohimbine	–	Fraudulent Illicit food
			thiohomosildenafil		
2009	Vardenafil 20 mg		vardenafil	–	Fraudulent Illicit generic
	Vardenafil 10 mg		vardenafil	–	Fraudulent Illicit generic
	Vardenafil		vardenafil	–	Fraudulent Illicit generic
	Tazalis-10 (tadalafil)		tadalafil	8.1	Fraudulent Illicit generic
	Vardenafil (sild.)		vardenafil	–	Fraudulent Illicit generic
	Tadalafil		tadalafil	9.4	Other Illicit generic
	Tadalafil 10		tadalafil	9.6	Accurate Illicit generic
	Tadalafil		tadalafil	11.3	Other Illicit generic
	Tuf-20 (tadalafil)		tadalafil	12	Fraudulent Illicit generic
	Tadalafil 20 mg		tadalafil	15.8	Fraudulent Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	17.7	Fraudulent Illicit generic
	Tadalafil		tadalafil	17.7	Other Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	17.9	Accurate Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	18	Fraudulent Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	18	Fraudulent Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	18.2	Fraudulent Illicit generic
	Tadalafil 20		tadalafil	18.4	Fraudulent Illicit generic
	Tadalafil 20		tadalafil	18.5	Fraudulent Illicit generic
	Professional (tadalafil)		tadalafil	18.6	Accurate Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	18.7	Fraudulent Illicit generic
	Tadalafil tablet 20mg		tadalafil	18.7	Fraudulent Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	18.8	Accurate Illicit generic
	Tadora-20 (tadalafil)		tadalafil	18.9	Accurate Illicit generic
	TDFIL-20 (tadalafil)		tadalafil	19	Fraudulent Illicit generic
	Tadalafil 20 mg		tadalafil	19.1	Accurate Illicit generic
	Tadora (tadalafil)		tadalafil	19.2	Other Illicit generic
	Tadalafil 20		tadalafil	19.6	Accurate Illicit generic

Lab: Customs		Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category	
2009	Professional (tadalafil)		tadalafil	20.4	Other	Illicit generic
	Professional (tadalafil)		tadalafil	20.5	Other	Illicit generic
	Tadalafil		tadalafil	20.8	Other	Illicit generic
	Viamax		DHEA	–	Fraudulent	Illicit food
	Lovemate 700 mg		yohimbine	–	Fraudulent	Illicit food
	Libido forte		aildenafil	–	Fraudulent	Illicit food
	Libido Extreme Herbal Erection		noracetildenafil	–	Fraudulent	Illicit food
	Viagra 100 mg		sildenafil	17	Fraudulent	Counterfeit Viagra
	Tadalafil 20 mg		tadalafil	16	Fraudulent	Illicit generic
			sildenafil	4		
	Viagra 100 mg		sildenafil	17	Fraudulent	Counterfeit Viagra
	Nizagara (sildenafil)		sildenafil	23	Fraudulent	Illicit generic
	Super nizagara forte (sild.)		sildenafil	23	Fraudulent	Illicit generic
	Nizagara (sildenafil)		sildenafil	24	Fraudulent	Illicit generic
	Bull-100 (sildenafil)		sildenafil	40	Fraudulent	Illicit generic
	creams vitamins		sildenafil	48	Fraudulent	Illicit food
	Sildenafil		sildenafil	49	Other	Illicit generic
	Caverta 50		sildenafil	49	Accurate	Illicit generic
	Sildenafil		sildenafil	49	Other	Illicit generic
	Sildenafil tablets 50 mg		sildenafil	50	Accurate	Illicit generic
	Sildenafil		sildenafil	50	Other	Illicit generic
	Sildenafil tabl.		sildenafil	51	Other	Illicit generic
	Viagra 100 mg		sildenafil	52	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	58	Fraudulent	Counterfeit Viagra
	Viagra 100 mg		sildenafil	62	Fraudulent	Counterfeit Viagra
	Creams vitamins Peenagra		sildenafil	67	Fraudulent	Illicit food
	Kamagra-100 (sildenafil)		sildenafil	76	Fraudulent	Illicit generic
	White pink capsules		sildenafil	77	Fraudulent	Illicit generic
	Kamagra tablets 100 mg		sildenafil	91	Accurate	Illicit generic
	Vega 100		sildenafil	92	Accurate	Illicit generic
	Kamagra 100 mg		sildenafil	93	Accurate	Illicit generic
	Vega 100		sildenafil	93	Accurate	Illicit generic
	Manly (sildenafil)		sildenafil	94	Other	Illicit generic
	Kamagra 100 mg		sildenafil	94	Accurate	Illicit generic
	Lady-Era (sildenafil)		sildenafil	95	Other	Illicit generic
	Manly (sildenafil)		sildenafil	95	Other	Illicit generic
	Kamagra gold sildenafil citrate		sildenafil	95	Other	Illicit generic
	Sildenafil		sildenafil	96	Other	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	96	Accurate	Illicit generic
	Mygra-100 (sildenafil)		sildenafil	96	Accurate	Illicit generic
	Mygra-100 (sildenafil)		sildenafil	96	Accurate	Illicit generic
	Vega 100		sildenafil	96	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	97	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	97	Accurate	Illicit generic
	Mygra sildenafil		sildenafil	98	Other	Illicit generic
	Nizagara (sildenafil)		sildenafil	98	Other	Illicit generic
	Nizagara (sildenafil)		sildenafil	98	Other	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	98	Accurate	Illicit generic
	Kamagra 100 mg		sildenafil	98	Accurate	Illicit generic
	Kamagra 100 mg oral jelly	Oral jelly	sildenafil	98	Accurate	Illicit generic
	Kamagra oral jelly 7 flavors	Oral jelly	sildenafil	98	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	99	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	99	Accurate	Illicit generic
	Kamagra oral jelly 7 flavors	Oral jelly	sildenafil	99	Accurate	Illicit generic
	Kamagra tablets 100 mg		sildenafil	99	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	100	Accurate	Illicit generic
	Mygra 100 (sildenafil)		sildenafil	100	Accurate	Illicit generic
	Abra-100 (sildenafil)		sildenafil	101	Accurate	Illicit generic
	Kamagra 100 mg		sildenafil	101	Accurate	Illicit generic
	Libido Power		sildenafil	102	Fraudulent	Illicit generic
	Kamagra oral jelly 7 flavours	Oral jelly	sildenafil	105	Accurate	Illicit generic
	Kamagra oral jelly 100 mg	Oral jelly	sildenafil	106	Accurate	Illicit generic
	Kamagra 100 mg Oral jelly	Oral jelly	sildenafil	107	Accurate	Illicit generic
	Black dusters / black storm		sildenafil	–	Fraudulent	Illicit food
	Thoroughgoing craziness		sildenafil	–	Fraudulent	Illicit food
	The King		sildenafil	–	Fraudulent	Illicit food
	Black magic		thioaildenafil	–	Fraudulent	Illicit food
	Acai Elite		sildenafil	–	Fraudulent	Illicit food
2010	Tadalafil 20		tadalafil	17.7	Fraudulent	Illicit generic
	Tadalista-20		tadalafil	18.9	Fraudulent	Illicit generic
	Tadacip 20		tadalafil	19.6	Accurate	Illicit generic
	Kamagra 100		sildenafil	86	Fraudulent	Illicit generic
	Filagra soft-100		sildenafil	90	Fraudulent	Illicit generic
	Filagra soft-100		sildenafil	91	Accurate	Illicit generic
	Filagra-100		sildenafil	97	Accurate	Illicit generic
	Suhagra 100		sildenafil	99	Accurate	Illicit generic

Lab: Customs	Illicit ED products		Laboratory findings			
Year	Product name	Embossing	API identified	Dose	Category	
2010	Nizagra 100		sildenafil	102	Accurate	Illicit generic
	Sildenafil citrate 100		sildenafil	113	Fraudulent	Illicit generic

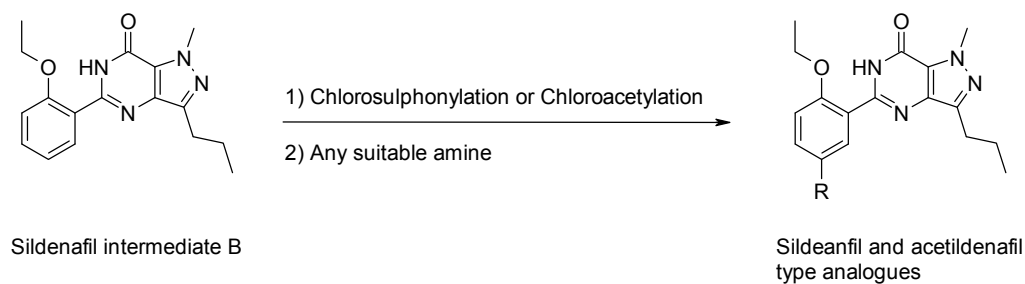
Lab / NFI	Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category
2007	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Blue scored tablets	50	sildenafil	Fraudulent	Illicit generic
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Blue tablet		sildenafil	Other	Illicit generic
	–	100	sildenafil	Fraudulent	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Cream powder		sildenafil	Other	Other
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Silagra-50		sildenafil	Other	Illicit generic
	Enthusia 100		sildenafil	Other	Illicit generic
	Enthusia 100		sildenafil	Other	Illicit generic
	Kamagra 100	Oral jelly	sildenafil	Other	Illicit generic
	Kamagra 100	Oral jelly	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green diamond shaped tablet		sildenafil	Fraudulent	Illicit generic
	Viagra		sildenafil	Other	Counterfeit Viagra
	Viagra		sildenafil	Other	Counterfeit Viagra
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green tablets		sildenafil	Other	Illicit generic
	Red diamond shaped tablet	50 / X	sildenafil	Other	Illicit generic
	Blue scored tablets	50	sildenafil	Fraudulent	Illicit generic
	Fiagra 50	FGR50 / Fiagra	sildenafil	Other	Illicit generic
	Fiagra 50	FGR50 / Fiagra	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Viagra	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Viagra	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Cialis		tadalafil	Other	Counterfeit Cialis
	Orange scored tablets		tadalafil	Other	Illicit generic
	Red tablet		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cialis	C20	tadalafil	Other	Counterfeit Cialis
	White tablets		tadalafil	Other	Illicit generic
	Cialis	C20	tadalafil	Other	Counterfeit Cialis
	White tablets	Taurus logo	tadalafil	Other	Illicit generic
			sildenafil		Illicit generic
			MDMA		Illicit generic
2008	Capsule with white powder		sildenafil	Fraudulent	Illicit generic
	Jar with liquid		sildenafil	Other	Other
	Kamagra	KGR100 / AP	sildenafil	Accurate	Illicit generic
	Blue tablets		sildenafil	Fraudulent	Illicit generic
	Blue tablets		sildenafil	Fraudulent	Illicit generic
	Viagra	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Vigora	100	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets	100	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets	100	sildenafil	Other	Illicit generic
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets		sildenafil	Other	Illicit generic
	Viagra	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Blue tablet (partial)		sildenafil	Other	Illicit generic
	Blue tablet (partial)		sildenafil	Other	Illicit generic
	Viagra	VGR50 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Blue diamond shaped tablets		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Cream powder		sildenafil	Other	Other
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Viagra	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Red triangular tablet		sildenafil	Other	Illicit generic
	Enthusia		sildenafil	Other	Illicit generic
	White tablets		sildenafil	Other	Illicit generic
	Kamagra 100	Oral jelly	sildenafil	Other	Illicit generic
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	Blue tablets		sildenafil	Other	Illicit generic
	Green tablet		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic

Lab / NFI	Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category
2008	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green tablet (partial)		sildenafil	Other	Illicit generic
	Kamagra 100		sildenafil	Other	Illicit generic
	Kamagra 100		sildenafil	Other	Illicit generic
	Kamagra 100		sildenafil	Other	Illicit generic
	Blue diamond shaped tablets		sildenafil	Other	Illicit generic
	Cilaa 20		tadalafil	Other	Illicit generic
	Orange tablets		tadalafil	Other	Illicit generic
	Orange tablets		tadalafil	Other	Illicit generic
	Cialis tablet (partial)	20	tadalafil	Other	Counterfeit Cialis
	White powder		tadalafil	Other	Illicit generic
2009	White tablets		tadalafil	Other	Illicit generic
	Blue tablets	VGR50 / Pfizer	tadalafil	Other	Counterfeit Viagra
	Blue tablet		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Red diamond shaped tablet	100	sildenafil	Other	Illicit generic
	Blue diamond shaped tablet	cupido 50	sildenafil	Other	Illicit generic
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	Cream powder		sildenafil	Other	Illicit other
	Red/purple triangular tablet (partial)		sildenafil	Other	Illicit generic
	Blue scored tablets		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
2009	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets	ASIA / 100	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets	Vega / 100	sildenafil	Other	Illicit generic
	Blue diamond shaped tablets		sildenafil	Other	Illicit generic
	Blue diamond shaped tablet	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Green tablet (partial)		sildenafil	Other	Illicit generic
	Green tablet	KGR / AP	sildenafil	Other	Illicit generic
	Blue tablet (partial)		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
2009	Orange diamond shaped tablet	KGR	sildenafil	Other	Illicit generic
	Kamagra	KGR / AP	sildenafil	Other	Illicit generic
	Green tablets	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Cream powder		tadalafil	Other	Illicit generic
	White tablets		tadalafil	Other	Illicit generic
	Orange almond shaped tablet		sildenafil	Other	Illicit generic
	Orange almond shaped tablet		sildenafil	Other	Illicit generic
	Blue scored tablets	Smile	sildenafil	Other	Illicit generic
	Blue scored tablets	Smile	sildenafil	Other	Illicit generic
	Light Blue scored tablets	Smile	sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
2009	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	Cream round convex tablets		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	Light Blue scored tablets	Smile	sildenafil	Other	Illicit generic
	Green Blue scored tablets	Smile	sildenafil	Other	Illicit generic
	Green diamond shaped tablets	AP	sildenafil	Other	Illicit generic
2009	White almond shaped tablet		tadalafil	Other	Illicit generic
	Viagra 100 mg	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green capsules Colorless liquid		tadalafil	Other	Illicit generic
	Blue diamond shaped tablets	KGR100 / AP	sildenafil	Other	Illicit generic
	White Green tablet (partial)		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	White diamond shaped tablets	VGR100 / Pfizer	sildenafil	Fraudulent	Counterfeit Viagra
	Green diamond shaped tablets	KGR / AP	sildenafil	Other	Illicit generic
	Green diamond shaped tablets	KGR / AP	sildenafil	Other	Illicit generic
2009	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green tablet (partial)		sildenafil	Other	Illicit generic
	White tablets		sildenafil	Other	Illicit generic
	Blue diamond shaped tablets	100	sildenafil	Other	Illicit generic
	Kamagra	Oral jelly	sildenafil	Other	Illicit generic
	Yellow substance sachet		sildenafil	Other	Illicit generic

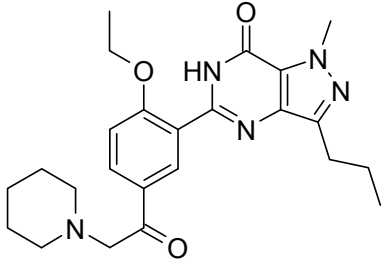
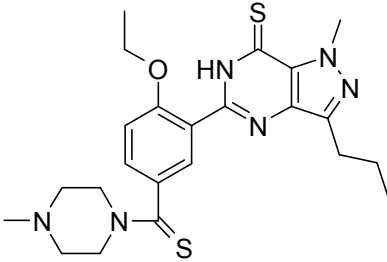
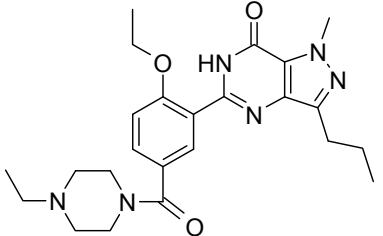
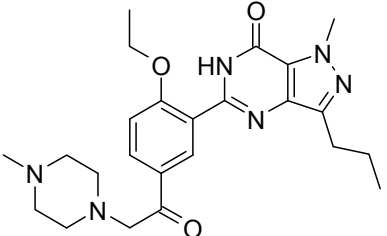
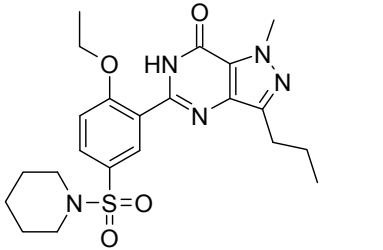
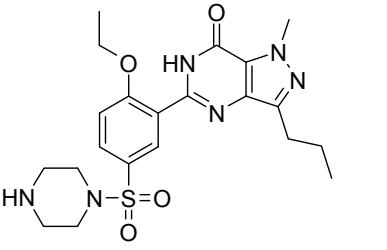
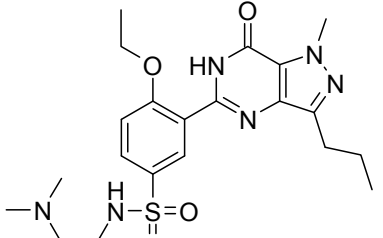
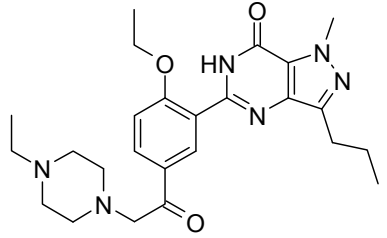
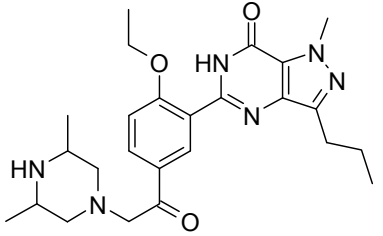
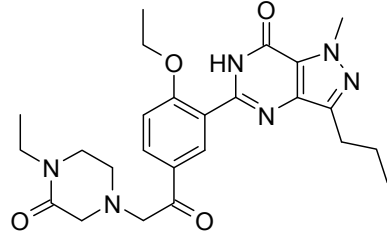
Lab / NFI	Illicit ED products		Laboratory findings		
Year	Product name	Embossing	API identified	Dose	Category
2009	Pink substance sachet		sildenafil	Other	Illicit generic
	Blue capsules brown powder		sildenafil derivate	Other	Illicit generic
	Kamagra	Oral jelly	sildenafil	Other	Illicit generic
	Yellow substance sachet		sildenafil	Other	Illicit generic
	Kamagra	Oral jelly	sildenafil	Other	Illicit generic
	Kamagra	Oral jelly	sildenafil	Other	Illicit generic
	Kamagra	Oral jelly	sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	Red viscous subst. sachet		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	White powder		sildenafil	Other	Illicit generic
	Yellow substance sachet		sildenafil	Other	Illicit generic
	Yellow substance sachet		sildenafil	Other	Illicit generic
	Red substance sachet		sildenafil	Other	Illicit generic
	White almond shaped tablet		tadalafil	Other	Illicit generic
	White powder		sildenafil derivate	Other	Illicit generic
	Viagra 100 mg		sildenafil	Other	Counterfeit Viagra
	Kamagra 100		sildenafil	Other	Illicit generic
	Yellow substance sachet		sildenafil	Other	Illicit generic
	Roze substance sachet		sildenafil	Other	Illicit generic
	Orange almond shaped tablet		tadalafil	Other	Illicit generic
	Blue tablet (partial)		sildenafil	Other	Illicit generic
	Blue tablets		sildenafil	Other	Illicit generic
	Red triangulair tablets		sildenafil	Other	Illicit generic
	Viagra 100 mg	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Green tablets (partial)		sildenafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Cream tablets		tadalafil	Other	Illicit generic
	Kamagra 100	KGR100 / AP	sildenafil	Other	Illicit generic
	Green diamond shaped tablet	KGR / AP	sildenafil	Other	Illicit generic
2010	Green diamond shaped tablet	KGR100 / AP	sildenafil	Other	Illicit generic
	Green tablet (partial)		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Blue scored tablet		sildenafil	Other	Illicit generic
	Kamagra 100	KGR100 / AP	sildenafil	Other	Illicit generic
	Yellow gel sachet		sildenafil	Other	Illicit generic
	Orange gel sachet		sildenafil	Other	Illicit generic
	Brown gel sachet		sildenafil	Other	Illicit generic
	Red gel sachet		sildenafil	Other	Illicit generic
	Viagra 100 mg	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Kamagra	KGR100 / AP	sildenafil	Other	Counterfeit Viagra
	Cialis 20 mg		tadalafil	Other	Counterfeit Cialis
	Cream powder (partial)		sildenafil base	Other	Illicit other
	Cream tablets		sildenafil	Other	Illicit generic
	Cream tablets		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green diamond shaped tablets	KGR / AP	sildenafil	Other	Illicit generic
	Eriacta-100		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Cialis 20 mg		sildenafil	Fraudulent	Counterfeit Cialis
	White tablets		sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green capsules		tadalafil	Other	Illicit generic
			sildenafil variants		
	Blue diamond shaped tablet	VGR100 / Pfizer	sildenafil	Other	Counterfeit Viagra
	Orange/Red tablets		tadalafil	Other	Illicit generic
	Pink hart shaped tablets		tadalafil	Other	Illicit generic
	Green tablet (partial)		sildenafil	Other	Illicit generic
	Green diamond shaped tablets	KGR100 / AP	sildenafil	Other	Illicit generic
	Kamagra	KGR100 / AP	sildenafil	Other	Illicit generic
	Green tablet (partial)	KGR100 / AP	sildenafil	Other	Illicit generic

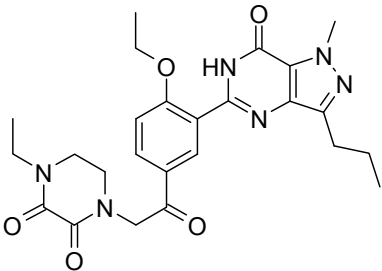
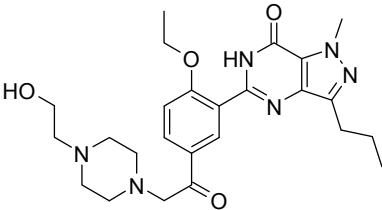
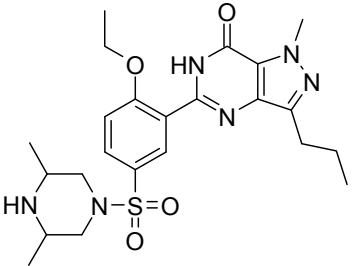
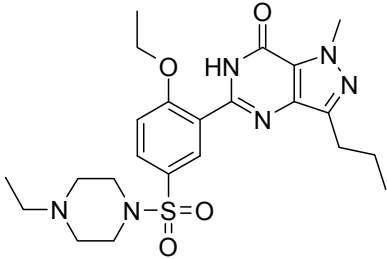
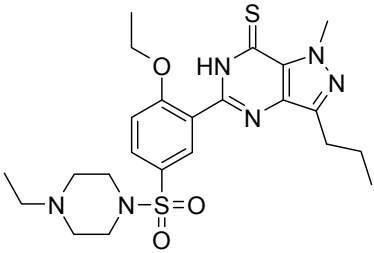
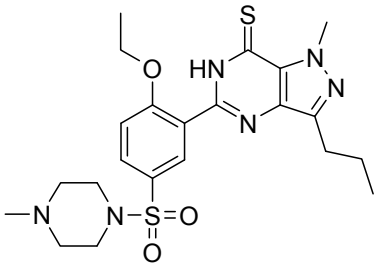
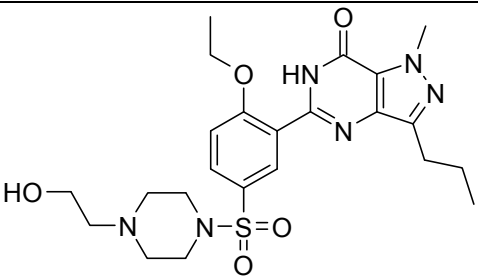
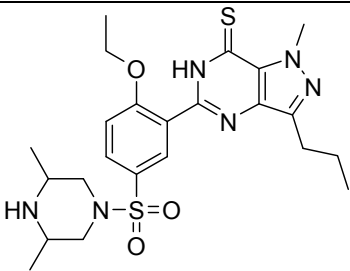
Appendix 3 Analogues of sildenafil

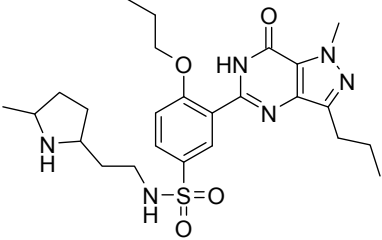
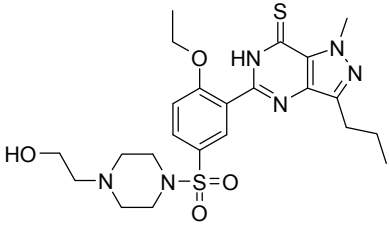
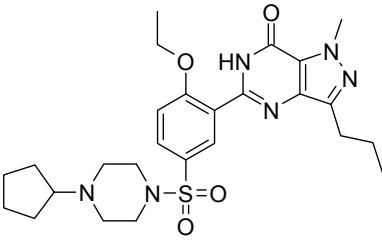
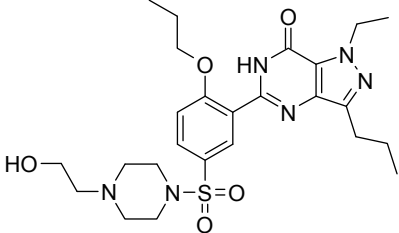
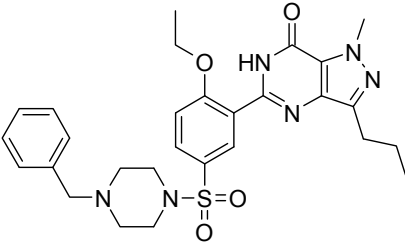
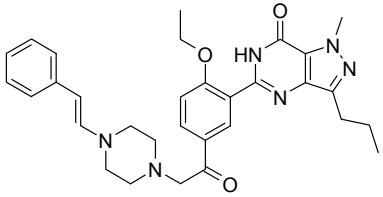
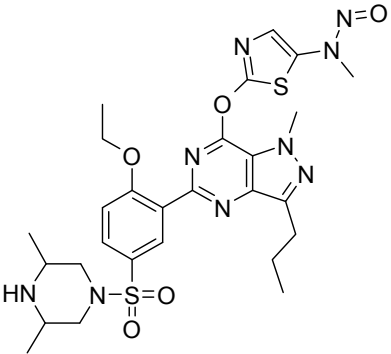
Principle synthetic route to sildenafil analogues used in drug development²¹. Thio-analogues^{62,63} are subsequently prepared by heating with P_2S_4 .



Analogues of sildenafil	
<p>Sildenafil</p>	Original API
<p>Nitrodenafil⁶⁴</p>	<p>Chlorodenafil⁶⁴</p>
<p>Hydroxychlorodenafil⁶⁴</p>	<p>Gendenafil</p>

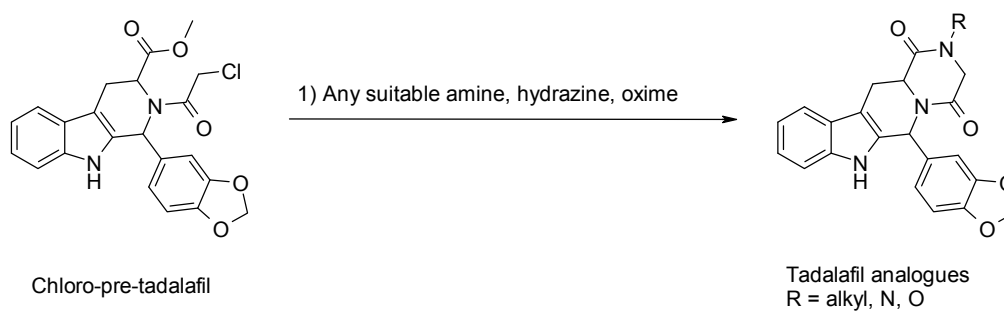
Analogues of sildenafil	
 <p>Piperidino acetildenafil⁶⁵ Piperidino hongdenafil</p>	 <p>Dithio-desmethyl-carbodenafil⁶⁶</p>
 <p>Carbodenafil</p>	 <p>Noracetildenafil^{67,68} Desmethylhongdenafil</p>
 <p>Norneosildenafil</p>	 <p>N-desmethylsildenafil</p>
 <p>Compound X⁶⁹</p>	 <p>Acetildenafil⁷⁰⁻⁷³ Hongdenafil</p>
 <p>Dimethylacetildenafil⁷⁴</p>	 <p>Oxohongdenafil⁶⁴</p>

Analogues of sildenafil	
 <p>Dioxo-acetildenafil Dioxo-hongdenafil</p>	 <p>Hydroxyacetildenafil^{65,75} Hydroxyhongdenafil⁷⁶</p>
 <p>Aildenafil¹¹ Dimethylsildenafil^{12,77,78}</p>	 <p>Homosildenafil^{72,79,80}</p>
 <p>Thio-homosildenafil^{62,70,81-83} Sulfohomosildenafil Homosildenafil thione</p>	 <p>KJH-1002^{62,81,82} Thiodenafil Thio-sildenafil Sulfosildenafil Sildenafil thione</p>
 <p>Hydroxy-homosildenafil Lodenafil^{70,72,84,85}</p>	 <p>Thio-aildenafil⁶³ Sulfodimethylsildenafil Dimethylsildenafil thione</p>

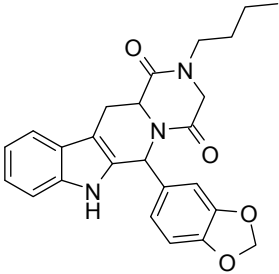
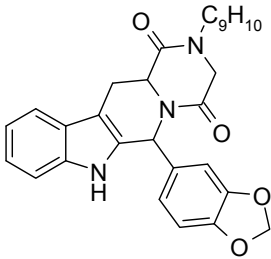
Analogues of sildenafil	
$\text{HHS}-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{HHS}$ <p>HHS = hydroxy-homosildenafil</p> <p>Lodenafilcarbonate^{84,85}</p>	 <p>Udenafil⁸⁶⁻⁸⁹</p>
 <p>Hydroxy-thio-homosildenafil^{90,91}</p>	 <p>Cyclopentynafil⁹²</p>
 <p>Mirodenafil</p>	 <p>Benzylsildenafil⁶⁴</p>
 <p>Cinnamylidenafil⁶⁴</p>	 <p>Nitroso-prodenafil</p>

Appendix 4 Analogues of tadalafil

Principle synthetic route to tadalafil analogues used in drug development⁹³:

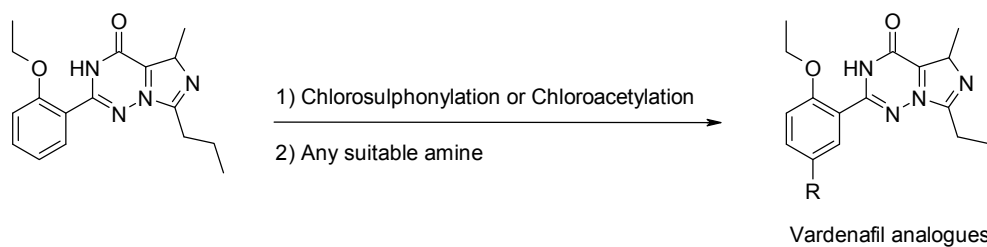


Analogues of tadalafil	
<p>Tadalafil⁹³</p>	Original API
<p>Trans-tadalafil⁵</p>	Nortadalafil
<p>Amino-tadalafil^{65,93-95}</p>	Chloropretadalafil⁹⁶

Analogues of tadalafil	
 <p>Chemical structure of Butyl-tadalafil, showing a tadalafil core with a butyl group attached to the nitrogen atom of the urea moiety.</p>	 <p>Chemical structure of N-Octyl-nortadalafil, showing a nortadalafil core with an octyl group attached to the nitrogen atom of the urea moiety.</p>
Butyl-tadalafil ⁹⁷	N-Octyl-nortadalafil ^{64,92}

Appendix 5 Analogues of vardenafil

Principle synthetic route to vardenafil analogues used in drug development^{98,99}:

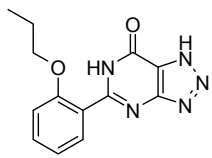
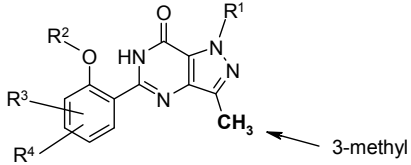
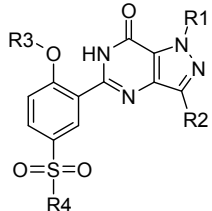
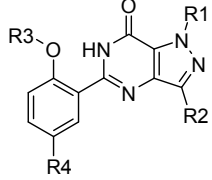


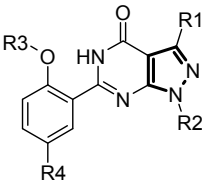
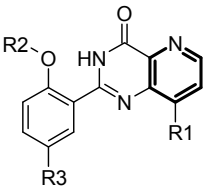
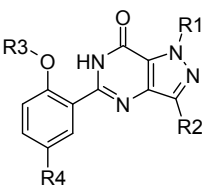
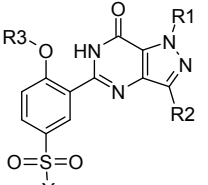
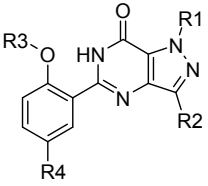
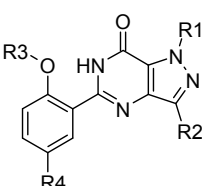
Analogues of Vardenafil	
<p>Vardenafil</p>	Original API
<p>Imadazosagatriazinone¹⁰⁰ Desulfovardenafil⁶⁴</p>	<p>Norneovardenafil⁶⁴</p>
<p>Hydroxyvardenafil⁷⁸</p>	<p>N-desethylvardenafil</p>
<p>Acetylvardenafil¹⁰¹</p>	<p>Piperidino vardenafil, Pseudo-vardenafil⁷⁶, Piperidenafil^{65,102}</p>

Appendix 6 The molecular genealogy of sildenafil

The discovery of sildenafil reverts to a compound called Zaprinast¹⁰³ that possessed moderate vasodilating properties. The Zaprinast molecular structure served as a template for the development of ED drugs of the sildenafil-type.

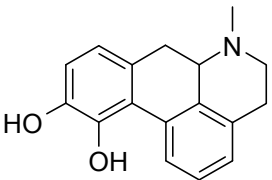
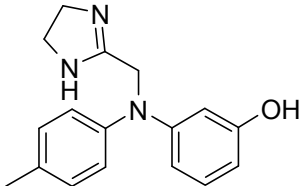
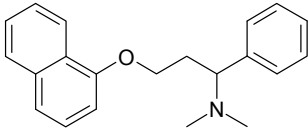
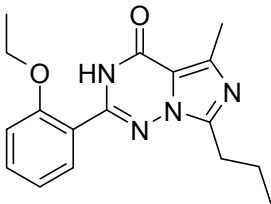
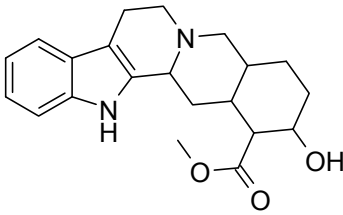
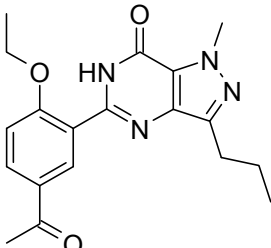
The table below shows the general molecular structures disclosed by patents and patent applications in the lead finding and lead optimisation phase, starting from 1986. In 1992 sildenafil and many of the currently known analogues were described for the first time as a potential treatment for angina. In 1994, a treatment for impotence was claimed for the first time for sildenafil, its analogues including the acetildenafil-type. The clinical candidates in the development of Viagra, sildenafil and the competing analogue described in chapter 3, are described in this patent. In 1998 and 1999 very specific claims are made for the synthesis of sildenafil and analogues and an indication. In 2002, a Korean institute patented thio-sildenafil which is essentially a copy of the Pfizer patent but with a C=O bond for a C=S bond. Thio-sildenafil and its thio-analogues are not registered as a medicine but are identified in adulterated food supplements regularly.

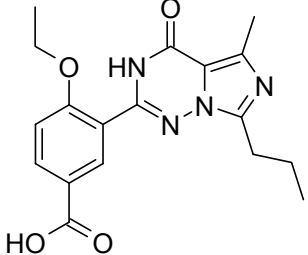
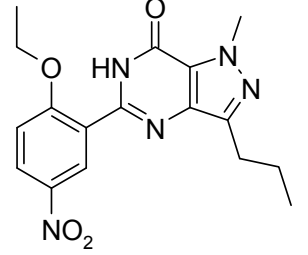
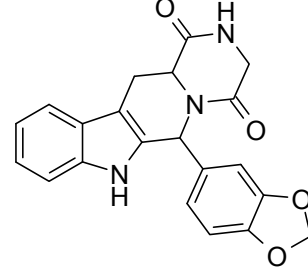
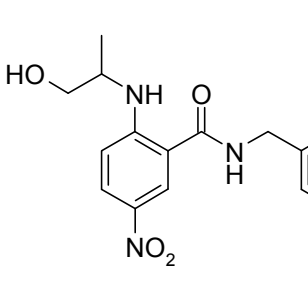
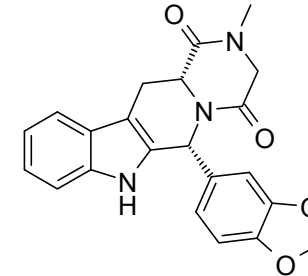
Year of publication	Structure	References and remarks
1976 1984	 Zaprinast	Chand, N., Eyre, P. ¹⁰⁴ Effects on blood vessels in smooth muscle Bowman, A., Drummond, A.H. ¹⁰⁵ Effects on the bovine penis
1986		Warner-Lambert Company EP0201188 General claim of treating vascular diseases by selective PDE inhibition
1992		Pfizer EP0463756 PDE inhibitors to treat angina (incl. Sildenafil)
1993		Pfizer EP0526004 PDE inhibitors to treat angina incl. Acetildenafil

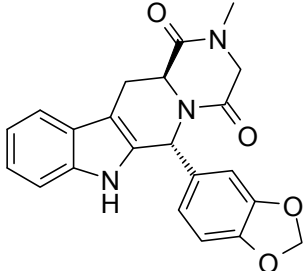
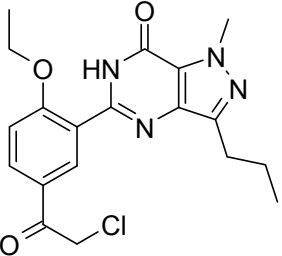
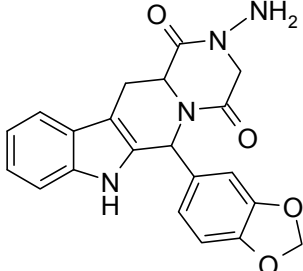
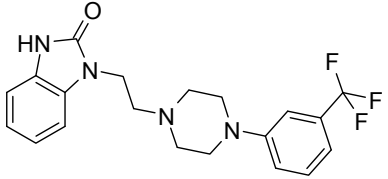
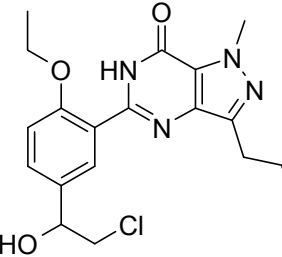
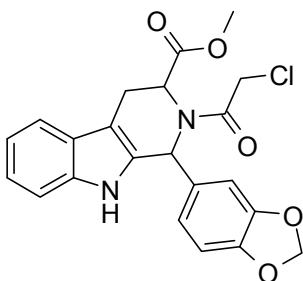
1993		<p>Pfizer WO 93/07149 PDE inhibitors to treat angina Different distribution of the N-atoms</p>
1994		<p>Pfizer WO 94/05661 PDE inhibitors to treat angina Pyridine derivative</p>
1994		<p>Pfizer WO 94/28902 PDE inhibitors to treat impotence Names specific analogues: e.g. sildenafil, hydroxy-homosildenafil ⁷⁰ and noracetildenafil ⁶⁷.</p>
1998		<p>Pfizer US5719283 Intermediates to prepare PDE-inhibitors (incl. acetildenafil intermediates)</p>
1999		<p>Pfizer EP0951908 Methode to treat impotence caused by spinal injury (incl. <u>Sildenafil and acetildenafil</u>).</p>
2002		<p>Korea Institute of Science WO 02/102802 Thiono analogues to treat impotence (copy-paste from Pfizer patent but with a sulphur for an oxygen)</p>

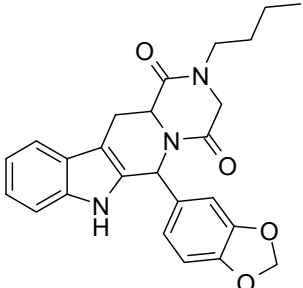
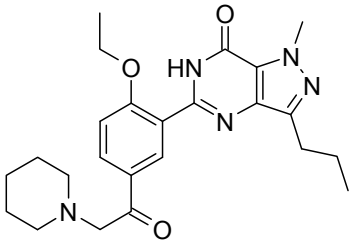
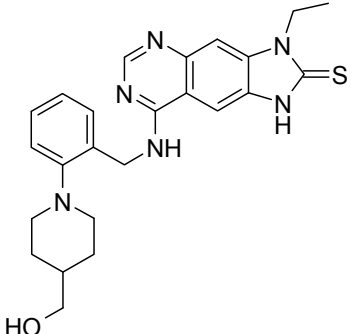
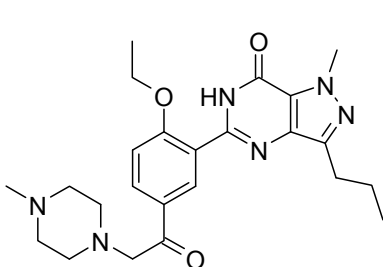
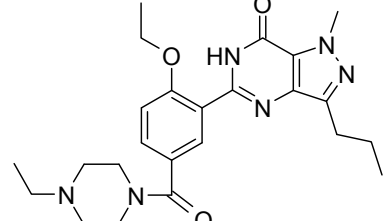
Appendix 7 Drug substances in illicit ED products 2000-2010

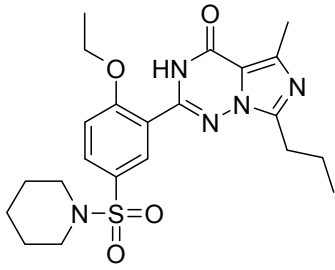
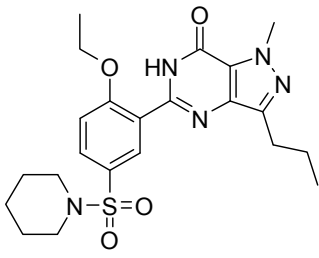
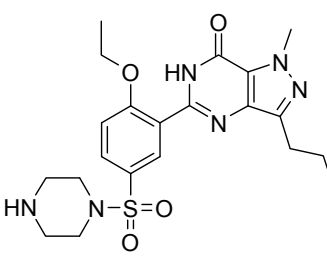
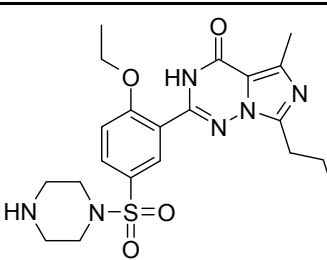
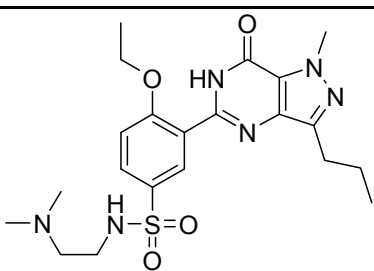
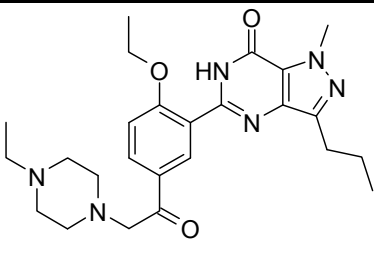
The table shows sildenafil, tadalafil, vardenafil, their analogues and other drug substances identified in illicit ED products throughout the world since 2000. The table is ordered by ascending molecular ion in ESI+ (MH^+). Several new analogues are about to be published and could not yet be included here.

[M+H] ⁺	Name	Structure	Formula
268	Apomorphine		C ₁₇ H ₁₇ NO ₂
282	Phentolamine		C ₁₇ H ₁₉ N ₃ O
306	Dapoxetine ²⁷		C ₂₁ H ₂₃ NO
313	Imadazosaga-triazinone ¹⁰⁰ Desulfovardenafil ⁶⁴		C ₁₇ H ₂₀ N ₄ O ₂
355	Yohimbine		C ₂₁ H ₂₆ N ₂ O ₃
355	Gendenafil		C ₁₉ H ₂₂ N ₄ O ₃

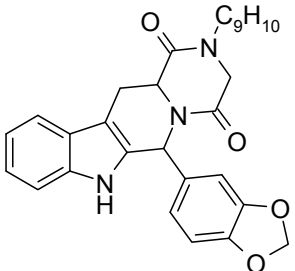
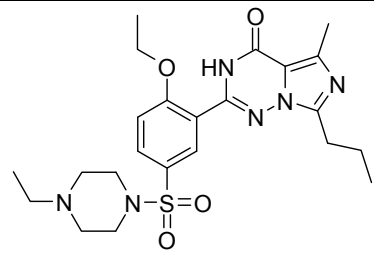
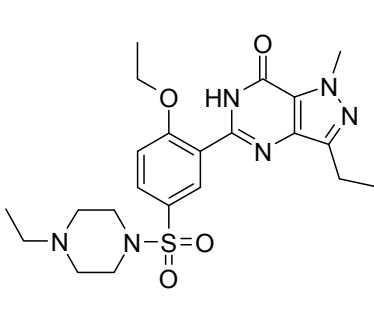
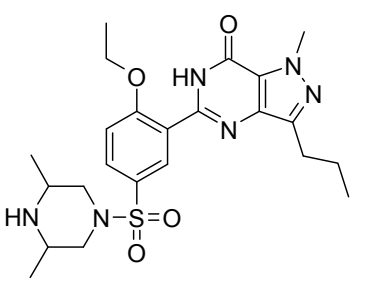
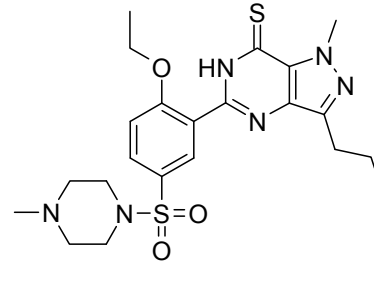
[M+H] ⁺	Name	Structure	Formula
357	Norneovardenafil ⁶⁴		C ₁₈ H ₂₀ N ₄ O ₄
358	Nitrodenafil ⁶⁴		C ₁₇ H ₁₉ N ₅ O ₄
376	Nortadalafil		C ₂₁ H ₁₇ N ₃ O ₄
390	Benzamidenafil FR 226807 Xanthoanthrafil ^{106,107}		C ₁₉ H ₂₃ N ₃ O ₆
390	Tadalafil ⁹³		C ₂₂ H ₁₉ N ₃ O ₄

[M+H] ⁺	Name	Structure	Formula
390	Trans-tadalafil ⁵		C ₂₂ H ₁₉ N ₃ O ₄
390	Chlorodenafil ⁶⁴		C ₁₉ H ₂₁ ClN ₄ O ₃
391	Amino-tadalafil ^{65,93-95}		C ₂₁ H ₁₈ N ₄ O ₄
391	Flibanserin BIMT-17 A female HSDD drug, not a PDE-5 inhibitor		C ₂₀ H ₂₁ F ₃ N ₄ O
392	Hydroxychlorodenafil ⁶⁴		C ₁₉ H ₂₃ ClN ₄ O ₃
427	Chloropretadalafil ⁹⁶		C ₂₂ H ₁₉ N ₂ O ₅ Cl

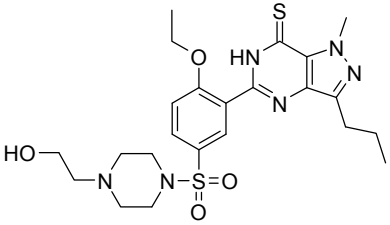
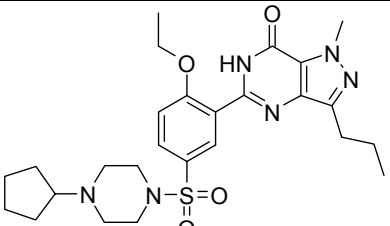
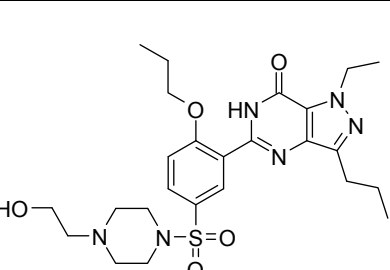
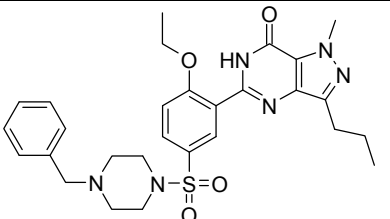
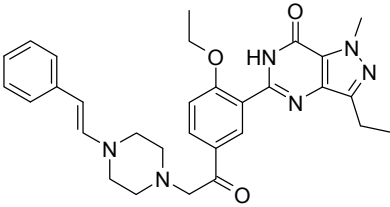
[M+H] ⁺	Name	Structure	Formula
432	Butyl-tadalafil ⁹⁷		C ₂₅ H ₂₆ N ₃ O ₄
438	Piperidino acetildenafil ⁶⁵ Piperidino hongdenafil		C ₂₄ H ₃₁ N ₅ O ₃
449	KF 31327 Thioquinapiperifil ¹⁰⁸		C ₂₄ H ₂₈ N ₆ OS
453	Noracetildenafil ^{67,68} Desmethyihongdenafil		C ₂₄ H ₃₂ N ₆ O ₃
453	Carbodenafil		C ₂₄ H ₃₂ N ₆ O ₃

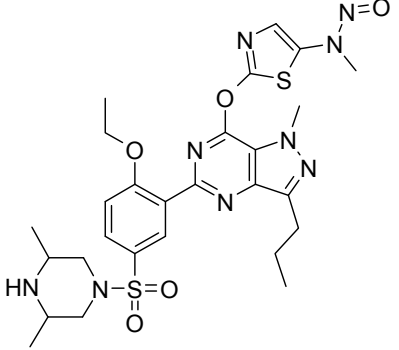
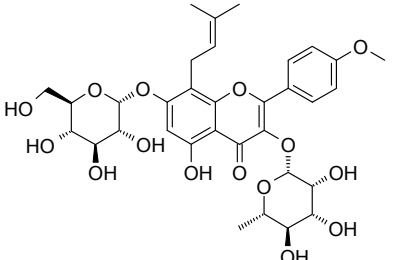
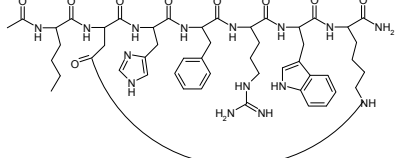
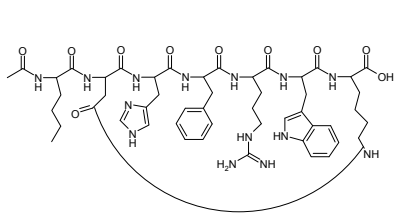
[M+H] ⁺	Name	Structure	Formula
460	Piperidino vardenafil Pseudovardenafil ⁷⁶ Piperidenafil ^{65,102}		C ₂₂ H ₂₉ N ₅ O ₄ S
460	Norneosildenafil		C ₂₂ H ₂₉ N ₅ O ₄ S
461	N-desmethylsildenafil		C ₂₁ H ₂₈ N ₆ O ₄ S
461	N-desethylvaridenafil		C ₂₁ H ₂₈ N ₆ O ₄ S
463	Compound X ⁶⁹		C ₂₁ H ₃₀ N ₆ O ₄ S
467	Acetildenafil ⁷⁰⁻⁷³ Hongdenafil		C ₂₅ H ₃₄ N ₆ O ₃

[M+H] ⁺	Name	Structure	Formula
467	Dimethylacetildenafil ⁷⁴		C ₂₅ H ₃₄ N ₆ O ₃
467	Acetylwardenafil ¹⁰¹		C ₂₅ H ₃₄ N ₆ O ₃
471	Dithio-desmethyl-carbodenafil ⁶⁶		C ₂₃ H ₃₀ N ₆ OS ₂
475	Sildenafil		C ₂₂ H ₃₀ N ₆ O ₄ S
481	Oxohongdenafil ⁶⁴		C ₂₅ H ₃₂ N ₆ O ₄
483	Hydroxyacetildenafil ^{65,75} Hydroxyhongdenafil ⁷⁶		C ₂₅ H ₃₄ N ₆ O ₄

[M+H] ⁺	Name	Structure	Formula
488	N-Octyl-nortadalafil ^{64,92}		C ₂₉ H ₃₃ N ₃ O ₄
489	Vardenafil		C ₂₃ H ₃₂ N ₆ O ₄ S
489	Homosildenafil ^{72,79,80}		C ₂₃ H ₃₂ N ₆ O ₄ S
489	Aildenafil ¹¹ Dimethylsildenafil ^{12,77,78}		C ₂₃ H ₃₂ N ₆ O ₄ S
491	KJH-1002 ^{62,81,82} Thiodenafil Thio-sildenafil Sulfosildenafil Sildenafil thione		C ₂₂ H ₃₀ O ₃ N ₆ S ₂

[M+H] ⁺	Name	Structure	Formula
495	Dioxo-hongdenafil Dioxo-acetildenafil		C ₂₅ H ₃₀ N ₆ O ₅
505	Thio-homosildenafil ^{62,70,81-83} Sulfohomosildenafil Homosildenafil thione		C ₂₃ H ₃₂ O ₃ N ₆ S ₂
505	Thio-aildenafil ⁶³ Sulfodimethylsildenafil Dimethylsildenafil thione		C ₂₃ H ₃₂ O ₃ N ₆ S ₂
505	Hydroxy-homosildenafil Lodenafil ^{70,72,84,85}		C ₂₃ H ₃₂ N ₆ O ₅ S
505	Hydroxyvardenafil ⁷⁸		C ₂₃ H ₃₂ N ₆ O ₅ S
517	Udenafil ⁸⁶⁻⁸⁹		C ₂₅ H ₃₆ N ₆ O ₄ S

[M+H] ⁺	Name	Structure	Formula
521	Hydroxy-thio-homosildenafil ^{90,91}		C ₂₃ H ₃₂ N ₆ O ₄ S ₂
529	Cyclopentynafil ⁹²		C ₂₆ H ₃₆ N ₆ O ₄ S
533	Mirodenafil		C ₂₆ H ₃₇ N ₆ O ₅ S
552	Benzylsildenafil ⁶⁴		C ₂₈ H ₃₄ N ₆ O ₄ S
556	Cinnamylidenafil ⁶⁴		C ₃₂ H ₃₈ N ₆ O ₃

[M+H] ⁺	Name	Structure	Formula
630	Nitroso-prodenafil		C ₂₇ H ₃₅ N ₉ O ₅ S ₂
677	Icariin		C ₃₃ H ₄₀ O ₁₅
1024	Melanotan II		C ₅₀ H ₆₉ N ₁₅ O ₉
1025	Bremelanotide		C ₅₀ H ₆₈ N ₁₄ O ₁₀
1035	Lodenafilcarbonate ^{84,85}	$\text{HHS}-\text{O}-\overset{\text{O}}{\parallel}-\text{O}-\text{HHS}$ <p>HHS = hydroxy-homosildenafil</p>	C ₄₇ H ₆₂ N ₁₂ O ₁₁ S ₂

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