Chromatography in the detection and characterisation of illegal pharmaceutical preparations

Eric Deconinck[1,*], Pierre-Yves Sacré[1,2], Patricia Courselle[1], Jacques De Beer[1]

[1]Division of food, medicines and consumer safety, Section Medicinal Products, Scientific Institute of Public Health (WIV-ISP), J. Wytmansstraat 14, B-1050 Brussels, Belgium

[2]Analytical Chemistry Laboratory, CIRM, University of Liège, Avenue de l'Hôpital 1, B36, B-4000 Liège, Belgium

Abstract:

Counterfeit and illegal pharmaceutical products are an increasing worldwide problem and constitute a major challenge for analytical laboratories to detect and characterize them. Spectroscopic techniques as infrared spectroscopy and Raman spectroscopy were always the first methods of choice to detect counterfeits and illegal preparations, but due to the evolution in the products seized and the necessity of risk assessment, chromatographic methods are becoming more important in this domain. This review intends to give a general overview of the techniques described in literature to characterize counterfeit and illegal pharmaceutical preparations, focussing on the role of chromatographic techniques, with different detection tools.

Keywords: counterfeit medicines, detection, characterisation, chromatography

*corresponding author: Eric.Deconinck@wiv-isp.be

Tel. +32 2 642 51 36

Fax. +32 2 642 53 27

1. Introduction

Counterfeiting of medicinal products is a problem that exists since centuries. During the first century of our era, Pedanius Dioscorides, a Greek physician, warned already about the dangers of adulterated drugs [1]. Since then many crises of falsification of medicines have been documented [2]. Most of these crises implicated falsified herbal medicines and resulted in many lethal accidents, due to a lack of efficacy and/or toxicity of the adulterated drugs.

In modern times the counterfeiting of drugs is a growing problem for already several years, especially since the extension of the internet. It is estimated that counterfeit drugs represent 7% of the worldwide pharmaceutical market [3,4]. Africa, South East Asia and many countries in Latin America are the most affected areas, where the World Health Organisation estimates that more than 30% of the medicines on sale are counterfeited [5]. The industrialized countries (USA, EU, Australia, Canada, Japan and New-Zealand) have approximately 1% of their pharmaceutical market affected despite the effective regulatory systems and market controls.

According to data of the Pharmaceutical Security Institute (PSI), the international trade of counterfeit medicines is in permanent growth [6]. Figure 1 shows the total number of reports of counterfeiting over the past nine years, revealing a permanent increase of the number of cases. Many factors may explain this growth, among others: the lack of effective enforcement agencies in developing countries and the lack of a harmonised legal framework to define pharmaceutical crime and the penalties to apply. There is more and more evidence that the trade in counterfeit drugs is linked to international organised crime, since the trade of counterfeit drugs is more lucrative than the trade in narcotics and the criminal penalties for pharmaceutical counterfeiting are less severe [7,8]. The growth concerning the counterfeiting of medicines is also shown by the evolution of the number of cases opened by the FDA's office of criminal investigations (Figure 2) [9].

The World Health Organisation (WHO) first cited the counterfeiting of medicines in 1985 at the conference of experts on the rational use of drugs in Nairobi. In 1988, a World Health Assembly Resolution (41.16) recommended to "initiate programmes for the prevention and detection of export, import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations" [10]. This led to the launch of many international initiatives among which the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT) started by the WHO in 2006. In parallel, the major pharmaceutical companies established the PSI in 2002. On the European level the European Alliance for Access to Safe Medicines (EAASM) was created [11]. This is a pan-european patient safety initiative committed to promoting the exclusion of counterfeit and substandard medicines from the supply chain. The European Parliament and the Council of Europe created recently an amendment to the European directive 2001/83/EC [12] on the community code relating to medicinal products for human use, describing the policy of the European Union towards counterfeit and substandard medicines. On the 26th of October 2011 Europe launched the Medicrime convention which was held in Moscow, Russia. Medicrime is the first international instrument for the criminalisation of counterfeiting of medical products and similar crimes in order to protect public health [13].

The WHO [14] defines a counterfeit drug as: "one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without the active ingredients, with insufficient active ingredient or with fake packaging." Next to this definition the WHO also defines a substandard medicine (also called, out of specification (OOS) products) as: "a genuine medicine produced by manufacturers authorized by the National Medical Regulatory Authority which do not meet the quality specifications set for them by national standards". By

definition the latter group of medicines should not be present on the market. If they are, a problem occurred with the controls of the legitimate supply chain or there have been unscrupulous activities and reselling of medicines to be destroyed [10].

The European parliament recently adopted a definition of "falsified medicines" that is a compromise between the counterfeit and substandard medicines definition of the WHO: "A falsified medicinal product is any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, name, composition in respect of any of its components including excipients and strength; and/or (b) its source, including the manufacturer, country of manufacturing, country of origin, marketing authorization holder; and/or (c) its history, including the records and documents relating to the distribution channels used [15]."

US law defines counterfeit drugs "as these sold under a product name without proper authorization. Counterfeiting can apply to both brand name and generic products, where the identity of the source is deliberately and fraudulently mislabelled in a way that suggests it is the authentic approved product. Counterfeit products may include products without the active ingredient, with an insufficient quantity of the active ingredient, with the wrong active ingredient, or with fake packaging [4]."

Due to the fact that the above mentioned definitions are quite general and not always adapted to the situation encountered on the European and the other markets of the industrialised world, the Dutch National Institute for Public Health and the Environment (RIVM) proposed a classification (table 1) distinguishing counterfeits, which appearance corresponds to the one of the genuine products, and imitations, which do not [16]. Most of these imitations originate from Asian countries, who do not recognize European and American patents and represent the majority of illegal pharmaceutical preparations analysed in the Official Medicines Control

Laboratories (OMCL) recognised by the European Directorate For Quality of Medicines (EDQM).

A recent study funded by Pfizer estimates the West-European illicit trade of medicines at € 10.5 billions. This study states that one out of five Europeans has bought a prescription only medicine from an illegal source. Most of these bought their medicines on the internet. According to a WHO estimation, more than 50% of the medicines bought from websites disclosing their identity are counterfeited [17,18].

Even if pharmaceutical counterfeiting is a global problem, the categories of adulterated drugs and the risks associated vary according to the region considered.

In developing countries the "anti-infective" drugs are the most counterfeited [19]. This represents a serious public health problem, since most of the population buy their medicines in the street at low prices. These products are often counterfeited or substandard medicines with less or no therapeutic activity. When treating diseases associated with a high untreated mortality such as malaria, pneumonia, meningitis, AIDS, typhoid and tuberculosis with inefficient drugs, mortality and morbidity increase. Moreover, the use of subtherapeutic amounts of active ingredients increases the risk of developing microbial resistance. In this case, even genuine drugs could become inefficient [10].

In industrialised countries the main therapeutic categories counterfeited are "lifestyle" drugs (weight loss drugs and potency enhancement drugs). The risks associated with these drugs are mostly due to the presence of toxic compounds or impurities, too high amounts of active ingredients, presence of unexpected active ingredients or new unknown designer molecules and wrong, missing or inadequate information concerning the use of the drug [20]. Other categories such as antineoplastic drugs or cardiovascular counterfeited drugs have also been detected [21]. The fact that counterfeit medicines may enter the legal supply chain represents a major risk for public health. Moreover, besides potential adverse effects, the patients may

loose trust in medicines even if they are sold in pharmacy and so damage their trust in the health care systems, the health care professional, the pharmaceutical industry and the Drug Regulatory Authorities [22].

Another problem besides counterfeiting is the adulteration of herbal products. In the developed countries people buy herbal alternatives for the treatment of obesity or erectile dysfunction disorders via internet, believing that there is no risk for their health. Though, several studies detected synthetic drugs as adulterants in the herbal formulations, representing huge risks for public health [23,24]. When purchasing counterfeit drugs, the patient can be held partially responsible for the health risk he is willing to take, but this is not the case for adulterated herbal remedies. These products are fraudulently labelled and there is no way for the patient of knowing he is taking preparations representing high risks for his health.

The national and international authorities have to be supported with data about the falsified samples from laboratory analysis. Therefore several laboratories throughout the world specialised themselves in the detection and analysis of counterfeit medicines. More knowledge about the samples can lead to a better fight against counterfeiting and a growing awareness of the risks by the patients.

Several reviews have already been published in the domain of counterfeit medicines and illegal pharmaceutical preparations. Most of them focus on a specific technique e.g. Nuclear Magnetic Resonance (NMR) [25] or on a specific type of counterfeited products e.g. PDE-5 inhibitors [26]. A few, more general reviews were published [4,27], in which the different techniques that could be applied in the analysis of counterfeit medicines were shortly discussed together with some applications. This review intends to give an updated overview of the techniques and approaches used in the detection and characterisation of counterfeit medicines and illegal pharmaceutical preparations, with a focus on the role of chromatography and the chromatographic approaches described in literature. To our

knowledge no reviews were published in this domain focussing on chromatography. Though chromatographic and hyphenated techniques have high potential in the analysis and characterisation of counterfeit medicines and illegal pharmaceutical preparations, since they allow not only the detection and quantification of active ingredients but can also give a complete image of the composition of the sample. This characteristics made chromatography the number one technique for risk evaluations of illegal preparations.

2. Analytical approaches

The fight against the counterfeiting of medicines resulted in numerous articles where several analytical techniques have already been used for the detection of counterfeit medicines. These techniques are separated in two main groups: chromatographic and spectroscopic techniques.

2.1. Spectroscopic approaches: a brief overview

Spectroscopic techniques are often preferred to chromatography for the identification of counterfeit drugs because of the fact that they are fast, need less (or no) sample preparation and some of them are non destructive. Fourier-transformed Infrared spectroscopy (FT-IR) [28-31], Near Infrared spectroscopy (NIR) [30, 32-36], Raman spectroscopy [30,33,37-41], X-ray diffraction (XRD) [42], colorimetry [43-47] and Nuclear Magnetic Resonance (NMR) [38,48,49] have demonstrated their usefulness to detect counterfeit or adulterated drugs. FT-IR and NMR are often used in the structure elucidation of active compounds or novel analogues found in illegal pharmaceutical preparations [25,28,29,38,48,50-74]. In most cases these techniques are used in combination with liquid chromatography with mass spectrometry detection (see section 2.2.2.2). NIR at the contrary is more used in the detection and the screening of counterfeit medicines. This is shown for example by Vredenbregt et al. [32], who described a method for the screening of Viagra® tablets (genuine, counterfeit and imitations)

which is able to check homogeneity of a batch, detect counterfeit tablets and imitations and reveal the presence of sildenafil citrate in the tablets. Another example was given by Been et al. [33] who related the NIR spectra of counterfeit medicines to their chemical profile and discriminate in that way counterfeits and genuines, but also different categories of counterfeit medicines. Dowell et al. [34] could discriminate between genuine and counterfeit artesunate tablets based on their NIR spectrum and Da Silva Fernandes et al. [35] used NIR to detect glibenclamide adulteration in tablets in a non-destructive way. A final example was given by Storme-Paris et al. [36], who used NIR spectra and chemometrics to discriminate between authentic samples, suspicious samples (samples with the same batch number as the counterfeits, withdrawn as a precaution) and counterfeit or imitation samples. Raman spectroscopy was also used in the discrimination of counterfeit and genuine tablets [30,33,37,38]. This discrimination is based on the presence of different excipients which could also be identified with Raman spectroscopy as described by Trefi et al. [38]. Been et al. [33] and Dégardin et al. [40] related the Raman spectra to the chemical profiles of counterfeit medicines and were able to discriminate genuines from counterfeits and to differentiate between different categories of counterfeit medicines. Raman spectroscopy could also be used in portable devices to detect counterfeit medicines. An example of this for artesunate tablets was given by Ricci et al. [41]. Another approach, which is becoming more popular is the combination of different spectroscopic techniques for the detection and characterisation of potential counterfeited samples. An example of a general approach where two techniques are used next to each other is given by De Peinder et al. [75], who used NIR and Raman spectroscopy to discriminate between genuine and counterfeit tablets of Lipitor®. Sacré et al. [30] analysed a group of counterfeit, imitated and genuine samples of both Viagra® and Cialis® with FT-IR, NIR and Raman spectroscopy and showed that the data is complementory. In that way they were able to combine different spectra in to one data set and

treat is as a whole using chemometrics. The combination of different spectra improved the classification and predictive properties of the models, compared to the ones calculated based on only one type of spectrum [76]. The combination of these techniques in the fight against counterfeit of medicines is promising, since the quality of the counterfeit tablets is increasing [30,76]. Recently the use of Raman microscopy was also described for the discrimination between counterfeit and genuine products [39,77].

Even if NMR spectroscopy is often used in combination with MS and FT-IR for structure elucidation, NMR as such is also able to reveal differences in composition of tablets. As an example Holzgrabe et al. [25] used NMR to reveal differences in composition between genuine and counterfeit tablets of Viagra®. Nyadong et al. [49] applied NMR for the characterisation of 14 different artesunate preparations, representative for the informal Asian market. The results revealed that only five preparations contained the active ingredient. NMR is without any doubt a very valuable technique in counterfeit detection and analysis, though it has some disadvantages. Next to the fact that it necessitates expensive equipment, it also needs experienced scientists to operate it and to interpret the data, especially in the analysis of unknown samples.

X-ray powder diffraction (XRPD), even if quite expensive and not present in a common laboratory for quality control of medicines, showed its usefulness. Maurin et al. [42] showed that XRPD enables a fast screening of tablets which is able to discriminate between counterfeit and genuine products as well as reveals differences in coating and product composition. Ortiz et al. [78] presented recently an application of X-ray Fluorescence spectrometry for the chemical profiling of sildenafil and tadalafil tablets. Based on these chemical profiles the authors were able to check the quality of the tablets as well as to detect suspicious samples.

Colorimetry is less used in the detection of counterfeits but can be useful to screen for the presence of an active ingredient and to quantitate it [43,45-47], even if in this case chromatographic methods seem more appropriate. Also the detection of counterfeit tablets based on colorimetric measurements of the tablets coatings or the secondary packaging is described [44]. In conclusion it can be said that a lot of spectroscopic methods can be used for counterfeit detection, but some necessitate expensive and sophisticated equipment. The more it has to be said that in general, spectroscopic techniques are used for detection of suspicious samples and that they have some disadvantages especially in the detection of impurities and the quantification of the active ingredients, since it are often "whole sample" approaches. Therefore next to the classical techniques like infrared, chromatographic approaches are interesting, since chromatography is a standard technique present in almost all laboratories for medicine control.

2.2. Chromatographic approaches

Chromatographic techniques have been extensively used in the detection and characterisation of counterfeit medicines and illegal pharmaceutical preparations. In the majority of the papers published, the chromatographic techniques were used for the separation of active ingredients in the samples, to quantify them or to isolate the active ingredients and detect or identify with e.g. mass spectrometry. In some papers and especially in papers concerning the counterfeit or falsification of Traditional Chinese Herbal medicines the use of chromatographic fingerprints is well described.

Different chromatographic techniques were described for the analysis of counterfeit medicines and illegal pharmaceutical preparations.

2.2.1. Thin Layer Chromatography

Thin layer chromatography (TLC) is a technique that has the advantages to be easy to implement and to be cheap. The principle of using TLC in counterfeit analysis is quite simple: the presence/identity of the active substance in a counterfeit or imitation sample is confirmed by comparing the results with a standard solution which is also applied to a TLC Silica plate.

TLC was used for the identification of essential drugs, like acetylsalicylic acid, paracetamol, ibuprofen, dexamethasone, prednisolone, hydrocortisone,… in preparations and for the identification of betamethasone, metamizol and hydrocortisone acetate [79]. TLC combined with UV detection and microcrystal tests was used for the detection and identification phentermine (Ionamin®) adulteration. The results showed that the counterfeit capsules contained only caffeine and phenylpropanolamine [80]. More recently Hu et al. [81] developed a Fast Chemical Identification System, consisting of two chemical colour reactions and two TLC systems for the characterization of counterfeit or suspected macrolide antibiotic preparations. The system is able to distinguish 14-membered and 16-membered macrolides based on the colour reactions. The TLC sytems (one for each group) are then used to identify the concerned macrolide. Another application was described by Moriyasu et al. [82,83] using TLC for the identification of sildenafil adulteration in health foods. TLC was applied to commercial health food products. After identification of sildenafil, HPLC-DAD revealed doses ranging from 25 to 45 mg sildenafil citrate per tablet or bottle, corresponding to the therapeutical doses and so constituting an important health risk. Also Reddy et al. [83,84] developed a HPTLC method for the identification and quantification of sildenafil in herbal formulations. Shewiyo et al. [85,86] developed and validated normal-phase HPTLC methods with densitometric detection for the quality control and the counterfeit detection of co-trimoxazole tablets and fixed-dose combination tablets of lamivudine, stavudine and nevirapine.

In the counterfeiting of herbal medicines, where wrong and cheaper herbs are sold in stead of the medicinal plant, TLC can be applied as well. An example was described by Wu [87] for the identification of the counterfeit of a traditional herbal medicine called *Curculigo Orchiode.* For this purpose TLC and UV-spectrometry was applied next to the classical morphology and histology tests.

Recently TLC played an important role in the basic quality control test performed on anti-malarian drugs in the Amazon Basin Countries. Together with other basic tests TLC could reveal an improvement of the quality of these kind of medicines in these countries over the years, starting from the beginning of the quality control program [88]. This is a good example how basic quality testing, without very sophisticated techniques, can lead to an improvement of the quality of sold medicines and the withdrawal of counterfeit and/or substandard medicines from the market.

2.2.2. Liquid chromatography

Liquid chromatography (LC) is often used in the analysis and the characterisation of counterfeit medicines and illegal pharmaceutical preparations. LC, in combination with different detectors, is used in this domain for several purposes. The first is as a method for target analysis (presence of one or more known compounds) and as a quantification method. LC in combination with MS is often used in screening of counterfeit samples, identification of ingredients and structure elucidation. Another application of liquid chromatography is the use of chromatographic fingerprints, in analogy with the fingerprints obtained with spectroscopic techniques like infrared. Chromatographic fingerprints are well described in the quality control of herbal products and especially in the discrimination of the plant needed from those who are sold as counterfeit or falsifications.

2.2.2.1. Liquid Chromatography-Ultra Violet Spectroscopy

LC with ultraviolet detection (UV) or Diode Array Detection (DAD) is still an important technique in the quality control of medicines and the characterisation of illegal pharmaceutical preparations. The advantages of the technique are its easiness to apply and to interpret and the technique is relatively cheap. The more High Performance LC (HPLC)-UV/DAD belongs to a standard equipment of a medicine control laboratory and is therefore available in the majority of the laboratories.

In literature several methods are described for the analysis of active ingredients in illegal preparations as well as for impurities and not registered analogues. HPLC-UV/DAD was extensively used in the detection of counterfeited, imitation and adulterated samples containing PDE-5 inhibitors. Nagaraju et al. [89] described a method able to separate and quantify sildenafil and its impurities. In a chromatographic run of 15 minutes they were able to determine sildenafil and its process related impurities, both in bulk products as in pharmaceutical formulations. Park et al. [90] screened 105 counterfeit samples, seized in Korea, for the presence of sildenafil and tadalafil using HPLC-UV. The results showed that 73 of the 105 samples contained sildenafil in doses ranging from 4.3 to 453.2 mg per tablet. Seven samples contained tadalafil in doses from 2.2 to 40.4 mg per tablet. The proportion of cases of having more than 100 mg sildenafil was 50% and 78% had more than 20 mg of tadalafil. The presence of amounts higher than the maximal allowed therapeutic dose is worrying and represents a huge risk to the patients. Recently our group developed and validated a UHPLC-DAD method for the quantification of the three registered PDE-5 inhibitors (Sildenafil, Tadalafil and Vardenafil) and seven of the most occurring analogues and impurities in counterfeit and imitation samples seized in Belgium. The method is applied in routine analysis after confirmation and identification with LC-Mass Spectrometry (MS) [91]. The same approach was followed by Gratz et al. [92] who developed a HPLC-UV

method for the quantification of the registered PDE-5 inhibitors, after their presence was confirmed with LC-MS. This group screened 40 botanical products, from which half were tested positive for PDE-5 inhibitors. The majority of the positive samples contained therapeutic doses of the active ingredients. Tomic et al. [93] conducted a HPLC-UV analysis on a group of erectile dysfunction drugs, seized by the Zagreb city police in Croatia. The results showed that even if all samples contained the correct active substance, more than 50% of the samples failed the content limits of 95-105%, raising the suspicion of counterfeit. De Orsi et al. [94] developed a HPLC-DAD method for the determination of PDE-5 inhibitors, testosterone and local anaesthetics in cosmetic creams sold as promising remedies for male erectile dysfunction and female genital stimulation. The results showed that in the majority of the analysed creams one or more of these substances, prohibited in cosmetics, was present. In India HPLC-DAD was used in a screening of Indian aphrodisiac ayurvedic/herbal healthcare products for adulteration with PDE-5 inhibitors [95]. In the study 85 samples of this product, well known on the regular market in India, were analysed and only one was tested positive for adulteration with sildenafil and this in a therapeutic dose. These results showed the initiation of the clandestine activity with a traditional Indian product. The previous two studies [94,95] clearly show an advantage of using HPLC over spectroscopic methods, i.e. the application to different kind of matrices as tablets, creams and herbal products. Zou et al. [96] applied HPLC-DAD in the screening of pre-market capsules and pre-mixed bulk powder for the presence of PDE-5 inhibitors and their analogues. Six out of seven samples were tested positive for non-approved analogues of sildenafil.

Also for the characterisation of other types of molecules/preparations HPLC with UV detection was applied. For example Amin et al. [97] used HPLC-UV in a quality control study of sulphadoxine-pyrimethamine and amodiaquine products in Kenya. These products used in the prevention and treatment of malaria are life saving medicines and the presence of

counterfeit and substandard medicines on the market constitute a huge health risk. The results of the tests showed that about one third of the preparations analysed failed the limits of 93-107% set by the USP [98]. Gaudiano et al. [99] applied HPLC-DAD for the quality control of antimalarial tablets purchased on the informal market of Goma (Democratic Republic of Congo). The results showed not only that the tablets contained only 88.6% of the indicated amount quinine, but also a high number of impurities in amounts higher than the reference samples and the samples purchased on the Italian market. Debrus et al. [100] proposed a HPLC-DAD method for the screening of 19 anti-malaria drugs in pharmaceutical preparations. The method was validated and intended for the use in developing countries, where the anti-malaria drugs are important on the black markets as substandard or counterfeit drugs.

A validated HPLC-DAD method for the simultaneous screening of some antibiotics often present in counterfeit and sub-standard medicines was proposed by Gaudiano et al. [101]. Shad et al. [102] proposed a HPLC-UV method for the characterisation of potential counterfeit isometamidium products. Isometamidium is a product used in the prophylaxis of veterinary trypanosomiasis.

Another important problem, especially in the western world are the dietary supplements sold for weight control and presumed to be 100% natural and from herbal origin, though adulteration with different kinds of synthetic drugs were discovered. Also here HPLC-UV was extensively used. Kim et al. [103] developed and validated a LC-DAD method, applicable to routine drug-adulteration screening of dietary supplements for anti-diabetes and anti-obesity drugs. This kind of screening is very important, especially in the western world were adulterated dietary supplements, purchased via internet are one of the major groups of preparations seized and analysed. Dietary supplements adulterated with sibutramine and its analogues are encountered frequently. Stypulkowska et al. [104] proposed a strategy for the

characterisations of such adulterated supplements in which first the presence of a chemical is tested with X-ray powder diffraction, followed by an identification of sibutramine and/or its analogues with XRPD and/or LC-Time of Flight (TOF)-MS. LC-UV is used to quantify sibutramine and/or its analogues when their presence and identity is confirmed. Other examples of applications are given by Almeida et al. [105,106], who proposed HPLC-UV methods for the confirmation and quantification of amfepramone, fenproporex, diazepam and mazindol as adulterants in herbal preparations. Mikami et al. [107] proposed a HPLC-UV method for the screening of benzodiazepines in herbal slimming products. Benzodiazepines are often used to mask the side effects of anorexics. Recently our group developed and validated a UHPLC-DAD method for the simultaneous quantification of nine chemical compounds (Sibutramine, modafinil, metformine, orlistat, diethylpropion, ephedrine, nor-ephedrine, caffeine and theophyllin), often encountered in adulterated herbal dietary supplements with slimming as indication [108]. Liu et al. [109] described a HPLC-DAD method that, in combination with a GC-MS method is able to screen herbal dietary supplements for adulteration with 266 pharmaceuticals.

2.2.2.2. Liquid Chromatography-Mass Spectroscopy

Liquid chromatography coupled to mass spectrometry is the method of choice when dealing with counterfeit and illegal pharmaceutical preparations. The method not only allows target analysis, but also screening of unknown preparations for the presence of chemical drug compounds. The more, when an unknown compound is encountered, LC-MS in combination with other techniques like IR and NMR, allows identification and/or structure elucidation. The latter is very important since the companies producing counterfeit medicines and imitations are modifying the chemical structure of the registered active substances, creating non-tested analogues in order to avoid patent laws.

In both domains, LC-MS as screening method and LC-MS for structure elucidation, numerous papers were published.

In the group of the PDE- inhibitors a lot of not registered analogues and impurities were yet detected. The majority was detected and identified using LC-MS, generally combined with NMR and IR techniques [28,29,50-74]. An overview of the different analogues yet detected over the years was recently given by Venhuis et de Kaste [26], therefore this applications will not be discussed in detail here. Next to the use of LC-MS in the structure elucidation of analogues and impurities, several screening methods for the detection and identification of PDE-5 inhibitors, their analogues and impurities were described [92,96,110-112].

Even if the highest numbers of papers using LC-MS for screening and structure elucidation in the domain of counterfeiting medicines deal with the PDE-5 inhibitors, also other counterfeited medicines can be analysed with LC-MS. Amin et al. [97] used LC-MS in quality control and the detection of counterfeit and substandard sulphadoxine-pyrimethamine and amiodiaquine products. Li et al. [113] performed the structural elucidation of dapoxetine, a selective serotonin reuptake inhibitor, present as adulterant in a health supplement for sexual performance enhancement. Recently Dorlo et al. [114] applied LC-MS, combined with FT-IR and NIR, for the detection of counterfeit miltefosine capsules, used to treat a fatal parasitic disease in resource poor countries. Dai et al. [115] developed a UHPLC-MS method for the qualitative detection of alpha-glucosidase inhibitors in potential counterfeit products, sold to treat diabetes.

A group of medicines often encountered as adulterants in herbal slimming preparations are the anti-obesity drugs like sibutramine and analogues, but also other anorexics as well as diuretics, antidepressants and laxative molecules [116]. Also here LC-MS was applied both for screening as for identification purposes. Both Kim et al. [103] as Stypulkowka et al. [104] applied LC-MS for the screening of herbal dietary supplements for the presence of

sibutramine and its analogues. Venhuis et al. [117] applied LC-MS in the identification of rimonabant and sibutramine and their analogues in counterfeit Acomplia and imitation products while Wang et al. [118] used LC-MS to perform a survey of 22 herbal weight reducing preparations for the presence of sibutramine and its analogues, phenolphthalein, fenfluramine and orlistat. Out of the 22 samples, 10 were positive for sibutramine, 3 for phenolphtaleine and 2 contained N-mono-desmethyl sibutramine.

Bogusz et al. [119] developed a LC-MS/MS method to screen herbal remedies for the presence of synthetic adulterants. The proposed method was able to screen for adulterants of different clinical groups, comprising analgesic drugs, antibiotics, antidiabetic drugs, antiepileptic drugs, aphrodisiacs, hormones and anabolic drugs, psychotropic drugs and weight reducing compounds. A similar approach was followed by Chen et al. [120], who developed a LC-QTRAP-MS method to screen botanical health supplements for the presence of blood pressure and lipid lowering agents, sedative drugs, anti-diabetic drugs, weight reducing agents and aphrodisiac drugs. De Carvalho et al. [121] recently reviewed all the compounds found as adulterants in slimming phytotherapeutic formulations as well as their analytical approaches. The majority of the different groups of adulterants can be screened for with LC-MS and comprises anorexics, diuretics, benzodiazepines, antidepressants, analgesics, hypoglycemics,….

Another application was given by Hall et al. [122], who applied LC-MS for the characterisation of artesunate tablets purchased in different Asian countries; 23 of 34 samples did not contain artesunate; 10 of the 11 that did contained artesunate in the correct dose. From the 23 samples, not containing artesunate eight contained erythromycin and five paracetamol.

2.2.2.3. Chromatographic fingerprinting

Chromatographic fingerprinting is a technique that is extensively described in the domain of plant analysis and in specific for authentic species recognition of traditional herbal medicines. A fingerprint can be defined as a characteristic profile reflecting the (complex) chemical composition of the analysed sample and can be obtained by spectroscopic, chromatographic and electrophoretic techniques [123,124]. Spectroscopic fingerprints are very interesting and widely used for the identification of bulk materials. Pharmacopoeias use infrared spectra to compare the "fingerprint" regions of the spectra obtained from a sample with a reference spectra, identifying a bulk product as the concerned drug compound [98,125,126]. As described above infrared spectroscopy and other spectroscopic techniques have already proven to be very valuable in the analysis and the discrimination of counterfeit medicines. Nevertheless a disadvantage of spectroscopic fingerprints is the fact that the fingerprint is influenced by all compounds of the samples, since it is a whole sample analysis.

Therefore fingerprints based on separation techniques like chromatography and electrophoresis are very interesting. By spreading the information about the chemical composition of the sample over time, the individual compounds and their underlying information can be revealed [123,124]. Chromatographic fingerprinting is mostly used in plant analysis and this for several purposes: for classification of plants, especially to differentiate related species, who's minor differences in composition can largely affect the public health [128-130], for stability testing and quality control [130,131] and to predict pharmacological activities or to identify potential active compounds [132-136]. The first application is the one that is interesting in the detection and characterisation of counterfeit samples. Also in herbal medicines counterfeiting is occurring selling non standardized, related plants or even totally different plants, with huge health risks as a consequence.

Even if TLC [136-147] and GC-MS [148-159] (essentially for essential oils) are techniques that proved their usefulness in the identification of plants and the discrimination between

species, the literature is more and more turning to liquid chromatography combined with different detectors to differentiate between plants and so fighting counterfeits. The advantages of HPLC are the easiness to operate, the fully automatable character and the high resolution, selectivity and sensitivity. For herbal fingerprinting, many papers were published using UV absorbance as detection [160-174], ELSD [162,170], chemiluminescence detection and mass spectrometry [160,164,166,169,175,176].

Despite the potential of chromatographic fingerprints in the classification, identification and discrimination of herbs and traditional medicines, only few publications using them in the domain of counterfeit medicines were published. Dumarey et al. [177] used chromatographic fingerprints or impurity profiles to distinguish four clusters of paracetamol preparations based on their synthesis pathways. In fact paracetamol can be synthesised in different ways and each synthesis pathway has its own impurity profile. This approach can both be used for detecting patent infringements as for counterfeit identification, since both synthesis pathways as the amounts of impurities can differ between genuine and counterfeit/imitation medicines. Schneider and Wessjohann compared the impurity profiles of Orlistat pharmaceutical products [178]. The impurity profiles recorded both with LC-UV as LC-MS/MS showed a clear difference between the original product (Xenical®) and two generic (legal) products (Figure 3). Even if the major impurity was the same for the three products, the generic products contained respectively 17 and 14 different impurities above the detection limit compared to 4 for the original product. All impurities were well within quality limits, so no problem is to be expected with the generic products, but this study shows that impurity profiles or fingerprints can be used to discriminate between original and generic products. Since the discrimination between original and generic is often more difficult than the discrimination between counterfeit and genuine, the approach will also be valuable in the detection and discrimination of counterfeit or imitation products of Xenical®. Indeed generic

products have to meet the same quality requirements as the original products, where counterfeits and imitation often do not meet those requirements. These two studies illustrate the possibilities and the potential of chromatographic fingerprints in counterfeit detection. Our group conducted a feasibility study for the use of such fingerprints for the discrimination between genuine and counterfeit medicines. Two case studies were studied: one for a set of 73 counterfeit and imitation and 9 genuine samples of Viagra® and one for a set of 44 counterfeit and imitation and 5 genuine samples of Cialis® [179]. The fingerprints were recorded using HPLC-UV with adapted methods from the ones published in Pharmeuropa [180,181]. The fingerprints or impurity profiles showed clear differences between the genuine and counterfeit/imitation samples as can be deduced from figure 4. The results showed, as could be already concluded from the studies in [177,178], that it is possible to discriminate counterfeits and genuine based on chromatographic fingerprints or impurity profiles.

A disadvantage of the chromatographic fingerprint approach is the difficulty to extract the information from the data. In general chemometrics are necessary to handle the amounts of data generated, especially for large sample sets. When recording chromatographic fingerprints or impurity profiles, retention time shifts can occur under the influence of column ageing, temperature changes and mobile phase changes. These shifts influence the data analysis and interpretation and therefore the chromatograms should be aligned or warped. Different allignement or warping techniques exists [124,179,182,183]. The most popular technique is correlation optimized warping (COW) [124,182,183]. Next to the problem of data pre-treatment, chromatographic techniques applied for fingerprinting generate high amounts of data, which causes the problem of interpretability. Again chemometric approaches are necessary to interpret the data and to differentiate different samples, as genuine and counterfeits. In chromatographic fingerprinting and more specific in the discrimination between samples Principal Component Analysis (PCA), Partial Least Squares (PLS) and

clustering techniques are often used [124,179]. Only few papers used modelling techniques in order to be able to predict the nature of a sample based on its chromatographic fingerprint. As modelling techniques basic techniques as k-Nearest Neighbours (k-NN) and Soft Independent Modelling by Class Analogy (SIMCA), seems to work perfectly for the discrimination between counterfeit and genuine samples [179,184]. Our group recently showed that some more advanced chemometrics can be valuable in the discrimination of genuine and counterfeit samples based on chromatographic fingerprints and more specific in the differentiation between the different classes/groups of counterfeit samples [184].

2.2.3. Gas chromatography

Also Gas Chromatographic (GC) techniques were used in the detection and the characterisation of counterfeit medicines. Gas chromatography was used to confirm the identity of essential oils, the presence of residual solvents, volatile constituents (especially in the quality control of herbal medicines) and unknown compounds or analogues [185]. Two examples of the latter are the detection of amphetamine in stead of sildenafil citrate with GC-MS in counterfeited tablets of Viagra® in Hungary [4,186] and the detection of oxycodone and dihydrocodeinone in counterfeit Ritalin® with GC-Flame Ionisation Detection and GC-MS [187]. Reepmeyer et al. [2,57] used chemical derivatization and GC-MS to differentiate the four different possible structures of piperidenafil. To resolve the structure, the presence of the piperidine moiety was confirmed with acid hydrolysis of the sulphonamide bond, followed by analysis of the amine and the sulfonic acid by GC-MS. The same approach was used to elucidate structures of nor-acetildenafil [2,57] and aildenafil [188]. Liu et al. [109] proposed a GC-MS screening method, which, in combination with LC-DAD, is able to screen for 266 pharmaceuticals present as adulteration in herbal preparations. Among these pharmaceuticals are the important groups of anorexics, anxioletics, antidepressants and

diuretics, often found in so called natural slimming products. A German group analysed 42 products of anabolic steroids from the illegal German market with GC-MS and found that 15 of these products did not contain the compounds that were labelled [189]. This is an example of the performance of GC-MS for the analysis of steroids. In fact this is the major application of GC-MS in the analysis of illegal pharmaceutical preparations in medicine control laboratories.

Lin et al. [190] used GC-MS in a study about counterfeiting of musk, a highly valued ingredient in Chinese Traditional Medicines, and found that no muscone, the compound believed to be the active ingredient was present in products seized by the customs or in Musk-Tiger Bone plaster preparations. On the contrary muscone was clearly present in the preparations purchased in the Chinese medicines stores.

In Iran GC-MS and HPLC was used in the analysis of counterfeit preparations of buprenorphine, the active ingredient of Temgesic® and Bungesic®, one of the most popular drugs of abuse by the young opioid-addicted population in Iran. Researchers revealed the presence of diacetylmorphine, acetylcodeine and pheniramine in stead of buprenorphine in the majority of the samples originating from the black market [191]. In Jordan GC-MS was applied in the screening of seized counterfeit Captagon® tablets (fenethylline), a popular drug of abuse in the Middle-East. The results revealed the presence of amphetamine and methamphetamine, responsible for the stimulant effect experienced by the abuser, but also different other compounds like anti-malarial drugs, antibiotics, sympaticomimetica,…. The presence of these compounds in these preparations represent huge health risks, especially since they are often present in combination with fenethylline and that the interactions between these drugs are unknown [192]. Lee et al. [193] used impurity profiles, recorded with GC-FID and GC-MS, of illicit methamphetamine seized in Japan and Korea as chemical fingerprints to cluster samples with possibly the same origin. The study revealed similarities between

samples seized in different regions of Japan and Korea, showing the international nature of the trade in methamphetamine.

The analysis of organic volatile impurities is a useful tool in the quality control of bulk pharmaceuticals and allows also the detection of counterfeit drugs and even tracing their source. Static headspace analysis in combination with GC-MS is often used in the detection of organic volatile impurities, e.g. residual solvents [194-199]. This approach was used successfully in the detection of counterfeit sulfamethazine, ranitidine hydrochloride and doxycycline hyclate [200]. In each case the different sources could be distinguished based on the profile of the organic volatile impurities present. Recently our group conducted a study in which a group of counterfeit and imitation Viagra® and a group of counterfeit and imitation Cialis® samples were tested for their residual solvent content [201]. The content was compared to the residual solvent content of the respective genuine products and revealed a clear difference between genuine and counterfeit/imitation samples. In the non genuine samples more residual solvents were present and in higher doses, often in amounts exceeding the limits as set by the International Committee for Harmonisation guideline for residual solvents [202] and the Pharmacopoeia's [98,125,126].

2.3. electrophoretic approaches

Electrophoresis is another separation technique that was described for some applications in the analysis of counterfeit medicines, substandard medicines and adulterated herbal preparations. Capillary electrophoresis (CE) has some advantages like the high resolution power (selectivity), short analysis time and the low consumption of chemicals and samples. Marini et al. [203] developed and validated methods for a prototype of a portable CE device, based on capillary zone electrophoresis (CZE) for the quantification of some important antimalarial drugs for quality control and counterfeit detection. The idea is to apply this

device and the corresponding methods as quality control device in some African regions were counterfeiting is reaching high proportions. Recently Amin et al. [204] proposed a CE method for the quality control of fixed dose combination tablets of artesunate and amodiaquine. Also here the authors considered the advantages of CE (long lifetime, low price of capillaries, low volumes and simplicity) over HPLC in the fight against low quality medicines in developing countries. Recently Lamalle et al. [205] proposed a Micellar Electrokinetic Chromatography (MEKZ) method to detect and quantify 15 antimalarial drugs in pharmaceutical preparations. The method was applied to four pharmaceutical preparations purchased on the African market. The results showed that all preparations contained the correct ingredients, though three of the four did not meet the 95-105% content limits set by the pharmacopoeia's and two of them contained the active ingredients in a dose inferior to 90% of the one claimed on the package.

Another domain in which CE was applied was in the determination of adulterants in herbal preparations. The most frequently used techniques are CZE and MEKZ. CZE methods were proposed for the determination of anorexics [206,207], amphetamines [206,208], benzodiazepines [207] and some other frequently found adulterants [206,207,209]. MEKZ methods were proposed for benzodiazepines [210,211,212] and nortriptyline, sulpiride and pyridoxine [211]. The use of CE in the domain of counterfeit medicines is not well described in literature, as is the same for the use of CE-MS, that could have a potential as confirmation method for adulterants.

3. Discussion and conclusion

The idea of this review was to give a general overview of the role chromatography plays nowadays in the detection, the analysis/characterisation and the risk assessment of illegal and counterfeited pharmaceutical preparations. In literature the spectroscopic techniques and

especially NIR and Raman spectroscopy are still very popular in the detection of counterfeited and illegal preparations. The spectroscopic methods surely have a lot of advantages especially for the detection of counterfeit medicines, where the spectrum of a sample can be compared to the one of the genuine product. Though in the analysis of illegal pharmaceutical preparations, like imitated medicines or adulterated dietary supplements these methods have the disadvantage of being a whole sample approach. For the detection of a chemical compound in a matrix and especially in an herbal matrix with spectroscopy, the compound should be present in a considerable dose and no masking effects from matrix compounds should occur. If this is not the case, it is possible to classify a sample as legal and safe based on the spectroscopic results alone, especially when the sample is not send to a laboratory, but screened with a portable device by the customs. The more, in the case of adulterated dietary supplements, it is not unthinkable that illicit producers add components to the matrix in order to mask the synthetic compounds from detection with spectroscopy.

These disadvantages of the spectroscopic techniques can be solved by applying separation methods as chromatography. Here the synthetic compounds are first extracted from the matrix and secondly separated on the TLC plate, chromatographic column or capillary, depending of the technique chosen. After separation the components are detected separately, identified and if wanted quantified. When an unknown component is detected, mass spectrometry and spectroscopic techniques (FT-IR, NMR) can be applied for structure elucidation.

Another field in which separation methods and especially chromatography has to be preferred over spectroscopic methods is the field of health sciences. In this domain it is not enough to divide samples in counterfeit and genuine, but they should also be evaluated for the risk they represent to the patient or in general to public health. In this case chromatographic fingerprinting can be of interest, since it does not only allow identifying and quantifying the active ingredients and detecting counterfeit products, it also gives a complete image of the

product. A lot of impurities in the fingerprint, means, in comparison with the genuine, that it is a counterfeit and one of low quality and so potentially dangerous. The more a chromatographic fingerprint can reveal the presence of a chemical substance (concentration >0.1%) in a dietary supplement, presumed to be of herbal origin.

In conclusion it can be said that all techniques, spectroscopic and chromatographic, have their use in the detection and analysis of illegal pharmaceutical preparations, depending on the purpose of the study. For simple counterfeit detection spectroscopic methods are very useful, but they have some disadvantages in the detection of adulterations and the evaluation of the risk for public health. Separation techniques have the advantage to enable a complete analysis of the sample: detection/identification of active substances, classification as counterfeit, imitation or genuine and risk evaluation. The disadvantage is the limited possibilities for miniaturization and application in portable devices.

In general it can be concluded that authorities, health practitioners and patients should be vigilant. Despite the initiatives concerning tampering, holograms and other to protect the legal supply chain, the presence of counterfeited products can not entirely be excluded. The more the patients should be aware that buying medicines or dietary supplements via internet or from an illegal source can seriously endanger their health.

Unfortunately the literature discussing or reporting incidents of counterfeit medicines, imitations or adulterated dietary supplements are only showing the tip of the iceberg. Therefore the development of efficient analytical methods for detection, characterization and risk evaluation should continue and probably their use and necessity will not diminish in the near future. Analytical results concerning these products are necessary to support the health authorities in their decisions and prevention campaigns, but also as part of legal dossiers for pharmaceutical crime.

References

[1]WHO, Counterfeit drugs – guidelines for the development of measures to combat counterfeit drugs. WHO/EDM/QSM/99.1. Geneva: WHO, 1999

[2] Newton, P., Green, M., Fernandèz, F., Day, N., White, N.; Counterfeit anti-infective drugs; *The Lancet Infectious Diseases* (2006); 6: 602-613.

[3]http://www.prlog.org/10124036-global-pharceutical-market-forcast-to-2012.html (last accessed 14-04-2011)

[4] Deisingh, A.; Pharmaceutical counterfeiting; Analyst (2005); 130: 271-279.

[5] http://www.who.int/impact/FinalBrochureWHA2008a.pdf (last accessed 14-04-2011)

[6] http://www.psi-inc.org (last accessed 20/08/2012)

[7]http://www.who.int/mediacentre/factsheets/fs275/en/index.html (last accessed 14-04-2011)

[8]http://www.prlog.org/10124036-global-pharmaceutical-market-forecast-to-2012.html (last accessed 14-04-2011)

[9]http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/default.htm

[10] Clift, C.; Combating Counterfeit, Falsified and Substandard Medicines Defining the Way Forward?; Chatham House Briefing Papers, November 2010

[11] European Alliance For Acces to Safe Medicines: www.eaasm.eu

[12] http://www.emea.europa.eu/docs/en_GB/document_library/ Regulatory_and_procedural_guideline /2009/10/WC500004481.pdf

[13] www.coe.int/medicrime

[14] WHO, sixty-second world health assembly item 12.9, counterfeit medical products, april 2009. http://aps.who.int/gb/ebhwa/pdf_files/A62/A62_13-en.pdf

[15] http://www.europarl.europe.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2011-0056+0+DOC+XML+V0//EN (last accessed 14-04-2011)

[16] Venhuis, B.J., Barends, D.M., Zwaagstra, M.E., de Kaste, D.; Recent developments in counterfeit and imitations of Viagra, Cialis and Levitra, RIVM report 370030001/2007, Bilthoven, 2007.

[17] http://www.who.int/impact/finalbrochureWHA2008a.pdf (last accessed 14-04-2011)

[18] http://www.securingpharma.com/40/articles/378.php (last accessed 14-04-2011)

[19] http://www.who.int/bulletin/volumes/88/4/10-020410.pdf (last accessed 14-04-2011)

[20] Blok-Tip, L., Vogelpoel, H., Vredenbregt,M.J., Barends, D.M., de Kast, D.; Counterfeit and imitations of Viagra and Cialis tablets: trends and risks to public health, RIVM report 267041001/2005, Bilthoven, 2005

[21] http://www.fagg-afmps.be/fr/news/news_pangea_III.jsp (last accessed 14-04-2011)

[22] http://www.who.int/medicines/services/counterfeit/overview/en/index1.html (last accessed 14-04-2011)

[23] Liang, Q. Qu, J. Luo, G. Wang, Y.; Rapid and reliable determination of illegal adulterant in herbal medicines and dietary supplements by LC/MS/MS; *Journal of Pharmaceutical and Biomedical Analysis*, (2006); 40: 305–311.

[24] Cianchino, V., Acosta, G., Ortega, C., Martı´nez, L.D., Gomez, M.R.; Analysis of potential adulteration in herbal medicines and dietary supplements for the weight control by capillary electrophoresis; *Food Chemistry*, (2008); 108: 1075–1081.

[25] Holzgrabe, U., Malet-Martino, M. ; Analytical challenges in drug counterfeiting and falsification-The NMR approach; *Journal of Pharmaceutical and Biomedical Analysis*, (2011); 55: 679-687.

[26] Venhuis, B.J., de Kaste, D., Towards a decade of detecting new analogues of sildenafil, tadalafil and vardenafil in food supplements: A history, analytical aspects and health risks ; *Journal of Pharmaceutical and Biomedical Analysis,* (2012); 69: 196-208.

[27] Martino, R., Malet-Martino, M., Gilard, V., Counterfeit drugs : analytical techniques for their identification ; *Analytical and Bioanalytical Chemistry,* (2010); 398: 77-92.

[28] Venhuis, B.J., Zomer, G., de Kaste, D.; Structure elucidation of a novel synthetic thiono analogue of sildenafil detected in an alleged herbal aphrodisiac; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 46: 814-817.

[29] Venhuis, B.J., Zomer, G., Hamzink, M., Meiring, H.D., Aubin, Y., de Kaste D.; The identification of a nitrosated prodrug of the PDE-5 inhibitor aildenafil in a dietary supplement: a Viagra with a pop; *Journal of Pharmaceutical and Biomedical Analysis*, (2011); 54: 735-741.

[30] Sacré, P-Y., Deconinck, E., De Beer, T., Courselle, P., Vancauwenberghe, R., Chiap, P., Crommen, J., De Beer, J.O.: Comparison and combination of spectroscopic techniques for the detection of counterfeit medicines; *Journal of Pharmaceutical and Biomedical Analysis*, (2010); 53: 445-453.

[31] Ricci, C., Nyadong, L., Fernandez F.M., Newton P.N., Kazarian S.G.; Combined Fourier-transform infrared imaging and desorption electrospray-ionization linear ion-trap mass spectrometry for analysis of counterfeit antimalarial tablets ; *Analytical & Bioanalytical Chemistry*, (2007); 387: 551-559.

[32] Vredenbregt, M.J., Blok-Tip, L., Hoogerbrugge, R., Barends, D.M., de Kaste, D.; Screening suspected counterfeit Viagra and imitations of Viagra with near-infrared spectroscopy; *Journal of Pharmaceutical and Biomedical Analysis*, (2006); 40: 840-849.

[33] Been, F., Roggo, Y., Degardin, K., Esseiva, P., Margot, P.; Profiling of counterfeit medicines by vibrational spectroscopy; *Forensic Science International*, (2011); 211: 83-100.

[34] Dowell, F.E., Maghirang, E.B., Fernandez, F.M., Newton P.N., Green M.D.; Detecting counterfeit antimalarial tablets by near-infrared spectroscopy ; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 48: 1011-1014.

[35] da Silva Fernandes, R., da Costa, F.S., Valderrama, P., Março P.H., de Lima K.M.; Non-destructive detection of adulterated tablets of glibenclamide using NIR and solid-phase fluorescence spectroscopy and chemometric methods; *Journal of Pharmaceutical and Biomedical Analysis*, (2012); 66: 85-90.

[36] Storme-Paris, I., Rebiere, H., Matoga, M., Civade, C., Bonnet, P.A., Tissier, M.H., Chaminade, P. ; Challenging near infrared spectroscopy discriminating ability for counterfeit pharmaceuticals detection; *Analytica Chimica Acta,(2010);* 658:163-174.

[37] de Veij, M., Deneckere, A., Vandenabeele, P., de Kaste, D., Moens, L.; Detection of counterfeit Viagra with Raman spectroscopy; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 46: 303-309.

[38] Trefi, S., Routaboul, C., Hamieh, S., Gilard, V., Malet-Martino, M., Martino, R.; Analysis of illegally manufactured formulations of tadalafil (Cialis) by ^{1}H NMR, 2D DOSY ^{1}H NMR and Raman spectroscopy; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 47: 103-113.

[39] Sacré, P.-Y., Deconinck, E., Saerens, L., De Beer, T., Courselle, P., Vancauwenberghe, R., Chiap, P., Crommen, J., De Beer, J.; Detection of counterfeit Viagra® by Raman Microspectroscopy imaging and multivariate analysis; *Journal of Pharmaceutical and Biomedical analysis*, (2011); 56: 454-461.

[40] Dégardin, K., Roggo, Y., Been, F., Margot, P.; Detection and chemical profiling of medicine counterfeits by Raman spectroscopy and chemometrics; *Analytica Chimica Acta*, (2011); 705: 334-341.

[41] Ricci, C., Nyadong, L., Yang, F., Fernandez, F.M., Brown, C.D., Newton, P.N., Kazarian, S.G.; Assessment of hand-held Raman instrumentation for in situ screening for potentially counterfeit artesunate antimalarial tablets by FT-Raman spectroscopy and direct ionization mass spectrometry ; *Analytica Chimica Acta*, (2008); 623: 178-186.

[42] Maurin, J.K., Pluciński, F., Mazurek, A.P., Fijałek, Z.; The usefulness of simple X-ray powder diffraction analysis for counterfeit control - the Viagra example; *Journal of Pharmaceutical and Biomedical Analysis*, (2007); 43: 1514-1518.

[43] Amin, A.S., Moustafa, M.E., El-Dosoky, R.; Colorimetric determination of sildenafil citrate (Viagra) through ion-associate complex formation; *Journal of AOAC International*, (2009); 92: 125-130.

[44] Rodomonte, A.L., Gaudiano, M.C., Antoniella, E., Lucente, D., Crusco, V., Bartolomei, M., Bertocchi, P., Manna, L., Valvo, L., Muleri, N.; Counterfeit drugs detection by measurement of tablets and secondary packaging colour; *Journal of Pharmaceutical and Biomedical Analysis*, (2010); 53: 215-220.

[45] Green, M.D., Mount, D.L., Wirtz, R.A., White, N.J.; A colorimetric field method to assess the authenticity of drugs sold as the antimalarial artesunate ; *Journal of Pharmaceutical and Biomedical Analysis*, (2000); 24: 65-70.

[46] Green, M.D., Mount, D.L., Wirtz, R.A.; Authentication of artemether, artesunate and dihydroartemisinin antimalarial tablets using a simple colorimetric method; *Tropical Medicine & International Health*, (2001); 6: 980-982.

[47] Green, M.D., Nettey, H., Villalva Rojas, O., Pamanivong, C., Khounsaknalath, L., Grande Ortiz, M., Newton P.N., Fernández F.M., Vongsack, L., Manolin, O.; Use of refractometry and colorimetry as field methods to rapidly assess antimalarial drug quality ; *Journal of Pharmaceutical and Biomedical Analysis*, (2007); 43: 105-110.

[48] Wawer, I., Pisklak, M., Chilmonczyk, Z.; ^{1}H, ^{13}C, ^{15}N NMR analysis of sildenafil base and citrate (Viagra) in solution, solid state and pharmaceutical dosage forms; *Journal of Pharmaceutical and Biomedical Analysis*, (2005); 38: 865-870.

[49] Nyadong, L., Harris, G.A., Balayssac, S., Galhena, A.S., Malet-Martino, M., Martino, R., Parry, R.M., Wang, M.D., Fernández, F.M., Gilard, V.; Combining two-dimensional diffusion-ordered nuclear magnetic resonance spectroscopy, imaging desorption electrospray ionization mass spectrometry, and direct analysis in real-time mass spectrometry for the integral investigation of counterfeit pharmaceuticals; *Analyical Chemistry,* (2009); 81: 4803-4812.

[50] Venhuis, B.J., Zomer, G., Vredenbregt, M.J., de Kaste, D.; The identification of (-)-trans-tadalafil and sildenafil in counterfeit Cialis® and the optical purity of tadalafil stereoisomers; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 51: 723-727.

[51] Vaysse, J., Gilard, V., Balayssac, S., Zedde, C., Martino, R., Malet-Martino, M.; Identification of a novel sildenafil analogue in an adulterated herbal supplement; *Journal of Pharmaceutical and Biomedical Analysis*, (2012); 59: 58-66.

[52] Wollein, U., Eisenreich, W., Schramek, N.; Identification of novel sildenafil-analogues in an adulterated herbal food supplement; *Journal of Pharmaceutical and Biomedical Analysis*, (2011); 56: 705-712.

[53] Ge, X., Li, L., Koh, H.L., Low, M.Y.; Identification of a new sildenafil analogue in a health supplement ; *Journal of Pharmaceutical and Biomedical Analysis*, (2011); 56: 491-496.

[54] Gratz, S.R., Zeller, M., Mincey, D.W., Flurer, C.L.; Structural characterization of sulfoaildenafil, an analog of sildenafil; *Journal of Pharmaceutical and Biomedical Analysis*, (2009); 50: 228-231.

[55] Reepmeyer, J.C., d'Avignon, D.A. ; Structure elucidation of thioketone analogues of sildenafil detected as adulterants in herbal aphrodisiacs ; *Journal of Pharmaceutical and Biomedical Analysis*, (2009); 49: 145-150.

[56] Zou, P., Hou, P., Oh, S.S., Chong, Y.M., Bloodworth, B.C., Low, M.Y., Koh, H.L.; Isolation and identification of thiohomosildenafil and thiosildenafil in health supplements; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 47: 279-284.

[57] Reepmeyer, J.C., Woodruff, J.T.; Use of liquid chromatography-mass spectrometry and a chemical cleavage reaction for the structure elucidation of a new sildenafil analogue detected as an adulterant in an herbal dietary supplement; *Journal of Pharmaceutical and Biomedical Analysis*, (2007); 44: 887-893.

[58] Lin, M.C., Liu, Y.C., Lin, J.H.; Identification of a sildenafil analogue adulterated in two herbal food supplements; *Journal of Food & Drug Analysis*, (2006); 14: 260-264.

[59] Lai, K.C., Liu, Y. C., Tseng, M.C., Lin, J. H.; Isolation and identification of a sildenafil analogue illegally added in dietary supplements; *Journal of Food & Drug Analysis*, (2006); 14: 19-23.

[60] Shin, C., Hong, M., Kim, D., Lim, Y.; Structure determination of a sildenafil analogue contained in commercial herb drinks ; *Magnetic Resonance in Chemistry,* (2004); 42: 1060-1062.

[61] Hou, P., Zou, P., Low, M.Y., Chan, E., Koh, H.L.; Structural identification of a new acetildenafil analogue from pre-mixed bulk powder intended as a dietary supplement; *Food Additives & Contaminants*, (2006); 23: 870-875.

[62] Blok-Tip, L., Zomer, B., Bakker, F., Hartog, K.D., Hamzink, M., Ten Hove, J., Vredenbregt, M., De Kaste, D.; Structure elucidation of sildenafil analogues in herbal products. *Food Additives & Contaminants*, (2004); 21: 737-748.

[63] Shin, M.H., Hong, M.K,, Kim, W.S,, Lee, Y.J., Jeoung, Y.C.; Identification of a new analogue of sildenafil added illegally to a functional food marketed for penile erectile dysfunction; *Food Additives & Contaminants*, (2003); 20: 793-796.

[64] Toomey, V.M., Litzau, J.J., Flurer, C.L.; Isolation and structural characterization of two tadalafil analogs found in dietary supplements; *Journal of Pharmaceutical and Biomedical Analysis*, (2012); 59: 50-57.

[65] Häberli, A., Girard, P., Low, M.Y., Ge, X.; Isolation and structure elucidation of an interaction product of aminotadalafil found in an illegal health food product; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 53: 24-28.

[66] Lam, Y.H., Poon, W.T., Lai, C.K., Chan, A.Y., Mak, T.W., Identification of a novel vardenafil analogue in herbal product; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 46: 804-807.

[67] Lai, K.C., Liu, Y.C., Tseng, M.C., Lin, Y.L., Lin, J.H.; Isolation and identification of a Vardenafil Analogue in a dietary supplement; *Journal of Food & Drug Analysis,* (2007); 15: 220-227.

[68] Lee, H.M., Kim, C.S., Jang, Y.M., Kwon, S.W., Lee, B.J.; Separation and structural elucidation of a novel analogue of vardenafil included as an adulterant in a dietary supplement by liquid chromatography-electrospray ionization mass spectrometry, infrared spectroscopy and nuclear magnetic resonance spectroscopy; *Journal of Pharmaceutical and Biomedical Analysis,* (2011); 54: 491-496.

[69] Reepmeyer, J.C., Woodruff, J.T.; Use of liquid chromatography-mass spectrometry and a hydrolytic technique for the detection and structure elucidation of a novel synthetic vardenafil designer drug added illegally to a "natural" herbal dietary supplement; *Journal of Chromatography A,* (2006); 1125: 67-75.

[70] Hasegawa, T., Takahashi, K., Saijo, M., Ishii, T., Nagata, T., Kurihara, M., Haishima, Y., Goda, Y., Kawahara, N.; Isolation and structural elucidation of cyclopentynafil and N-octylnortadalafil found in a dietary supplement ; *Chemical & Pharmaceutical Bulletin* (Tokyo), (2009); 57: 185-189.

[71] Ge, X., Low, M.Y., Zou, P., Lin, L., Yin, S.O., Bloodworth, B.C., Koh, H.L.; Structural elucidation of a PDE-5 inhibitor detected as an adulterant in a health supplement; *Journal of Pharmaceutical and Biomedical Analysis,* (2008); 48: 1070-1075.

[72] Choi, D.M., Park, S., Yoon, T.H., Jeong,,H.K., Pyo, J.S., Park, J., Kim, D., Kwon, S.W., Determination of analogs of sildenafil and vardenafil in foods by column liquid chromatography with a photodiode array detector, mass spectrometry, and nuclear magnetic resonance spectrometry ; *Journal of AOAC International*, (2008); 91: 580-588.

[73] Park, H.J., Jeong, H.K., Chang, M.I., Im, M.H., Jeong, J.Y., Choi, D.M., Park, K., Hong, M.K., Youm, J., Han, S.B., Kim, D.J., Park, J.H., Kwon, S.W.; Structure determination of new analogues of vardenafil and sildenafil in dietary supplements; *Food Additives & Contaminants,* (2007); 24: 122-129.

[74] Gratz, S.R., Gamble, B.M., Flurer, R.A.; Accurate mass measurement using Fourier transform ion cyclotron resonance mass spectrometry for structure elucidation of designer drug analogs of tadalafil, vardenafil and sildenafil in herbal and pharmaceutical matrices; *Rapid Communications in Mass Spectrometry,* (2006); 20: 2317-2327.

[75] de Peinder, P., Vredenbregt, M.J., Visser, T., de Kaste, D.; Detection of Lipitor counterfeits: a comparison of NIR and Raman spectroscopy in combination with chemometrics; *Journal of Pharmaceutical and Biomedical Analysis,* (2008); 47: 688-694.

[76] Deconinck, E., Sacré, P.-Y., Coomans, D., De Beer, J.; Classification trees based on infrared spectroscopic data to discriminate between genuine and counterfeit medicines; *Journal of Pharmaceutical and Biomedical Analysis,* (2012); 57: 68-75

[77] Kwok, K., Taylor, L.S.; Analysis of counterfeit Cialis® tablets using Raman microscopy and multivariate curve resolution ; *Journal of Pharmaceutical and Biomedical Analysis,* (2012); 66: 126-135.

[78] Ortiz, R.S., Mariotti, K.C., Schwab, N.V., Sabin, G.P., Rocha, W.F., de Castro, E.V., Limberger, R.P., Mayorga, P., Bueno, M.I., Romão, W.; Fingerprinting of sildenafil citrate and tadalafil tablets in pharmaceutical formulations via X-ray fluorescence (XRF) spectrometry; *Journal of Pharmaceutical and Biomedical Analysis,* (2012); (58): 7-11.

[79] Pachaly, P., Schick, W.; Simple thin-layer chromatographic identification of active principles in finished products; *Pharmazeutische Industrie* (1993); 55: 259-267.

[80] Hadzija, B.W., Mattocks, A.M.; Simple techniques to detect and identify phentermine adulteration; *Forenscic Science International*, (1983); 23: 143-147.

[81] Hu, C.Q., Zou, W.B., Hu, W.S., Ma, X.K., Yang, M.Z., Zhou, S.L., Sheng, J.F., Li, Y., Cheng, S.H., Xue, J.; Establishment of a Fast Chemical Identification System for screening of counterfeit drugs of macrolide antibiotics; *Journal of Pharmaceutical and Biomedical Analysis,* (2006); 40: 68-74.

[82] Moriyasu, T., Shigeoka, S., Kishimoto, K., Ishikawa, F., Nakajima, J., Kamimura, H., Yasuda, I.; Identification system for Sildenafil in health foods; *Yakugaku Zasshi ;* (2001), 121: 765-769.

[83] Singh, S., Prasad, B., Savaliya, A.A., Shah, R.P., Gohil, V.M., Kaur, A.; Strategies for characterizing sildenafil, vardenafil, tadalafil and their analogues in herbal dietary supplements, and detecting counterfeit products containing these drugs; *Trends in Analytical Chemistry*, (2009); 28: 13-28.

[84] Reddy, T.S., Reddy, A.S., Devi, P.S.; Quantitative determination of sildenafil citrate in herbal medicinal formulations by high-performance thin-layer chromatography; *Journal of Planar Chromatography - Modern TLC*, (2006); 19: 427-431.

[85] Shewiyo, D.H., Kaale, E., Risha, P.G., Dejaegher, B., Smeyers-Verbeke, J., Vander Heyden, Y.; Development and validation of a normal-phase high-performance thin layer chromatographic method for the analysis of sulfamethoxazole and trimethoprim in co-trimoxazole tablets; *Journal of Chromatography A*, (2009); 1216: 7102-7107.

[86] Shewiyo, D.H., Kaale, E., Ugullum, C., Sigonda, M.N., Risha, P.G., Dejaegher, B., Smeyers-Verbeke, J., Vander Heyden, Y.; Development and validation of a normal-phase HPTLC method for the simultaneous analysis of lamivudine, stavudine and nevirapine in fixed-dose combination tablets; *Journal of Pharmaceutical and Biomedical Analysis,* (2011); 54: 445-450.

[87] Wu, Y.W.; The identification of microscopic, physical and chemistrical analysis on Curculigo orchiode and its counterfeit ; *Zhong Yao Cai*, (2006); 29: 553-554.

[88] Pribluda V.S., Barajos, A., Añez, A., López, C.G., Figueroa, R., Herrera, R. et al. ; 3rd. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period, *Malaria Journal*, (2012); 11: 202-213.

[89] Nagaraju, V., Sreenath, D., Tirumala Rao, J., Nageswara Rao, R.; Separation of synthetic impurities of sildenafil (Viagra) by Reversed-Phase High-Performance Liquid Chromatography; *Analytical Sciences,* (2003); 19: 1007-1011.

[90] Park, M., Ahn, S.; Quantitative Analysis of Sildenafil and Tadalafil in Various Fake Drugs Recently Distributed in Korea; *Journal Forensic Science.* (2012); 57: 1637-1640.

[91] Sacré, P.-Y., Deconinck, E., Chiap, P., Crommen, J., Mansion, F., Rozet, E., Courselle, P., De Beer, J.; Development and validation of a UHPLC-UV method for the detection and quantification of erectile dysfunction drugs and some of their analogues found in counterfeit medicines; *Journal of Chromatography A*, (2011); 1218: 6439-6447.

[92] Gratz, S.R., Flurer, C.L., Wolnik, K.A.; Analysis of undeclared synthetic phosphodiesterase-5 inhibitors in dietary supplements and herbal matrices by LC-ESI-MS and LC-UV; *Journal of Pharmaceutical and Biomedical Analysis,* (2004); 36: 525-533.

[93] Tomic, S., Micic, N., Sokolic, M., Martinac, A.I.; Identification of counterfeit medicines for erectile dysfunction from an illegal supply chain; *Arhiv za Higijenu Rada i Toksikologiju,* (2010); 61: 69-75.

[94] De Orsi, D., Pellegrini, M., Marchei, E., Nebuloni, P., Gallinella, B., Scaravelli, G., Martufi, A., Gagliardi, L., Pichini, S. ; High performance liquid chromatography-diode array and electrospray-mass spectrometry analysis of vardenafil, sildenafil, tadalafil, testosterone and local anesthetics in cosmetic creams sold on the Internet web sites; *Journal of Pharmaceutical and Biomedical Analysis,* (2009); 50: 362-369.

[95] Savaliya, A.A., Shah, R.P., Prasad, B., Singh, S.; Screening of Indian aphrodisiac ayurvedic/herbal healthcare products for adulteration with sildenafil, tadalafil and/or vardenafil using LC/PDA and extracted ion LC-MS/TOF; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 52: 406-409.

[96] Zou, P., Oh, S.S., Hou, P., Low, M.Y., Koh, H.L.; Simultaneous determination of synthetic phosphodiesterase-5 inhibitors found in a dietary supplement and pre-mixed bulk powders for dietary supplements using high-performance liquid chromatography with diode array detection and liquid chromatography-electrospray ionization tandem mass spectrometry ; *Journal of Chromatography A*, (2006); 1104: 113-122.

[97] Amin, A.A., Snow, R.W., Kokwaro, G.O.; The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector; *Journal of Clinical Pharmacy and Therapeutics,* (2005); 30: 559-565.

[98] United States Pharmacopoeia 35, United States Pharmacopoeial Convention, Inc., Rockville, MD, USA (2010)

[99] Gaudiano, M.C., Antoniella, E., Bertocchi, P., Valvo, L. ; Development and validation of a reversed-phase LC method for analysing potentially counterfeit antimalarial medicines ; *Journal of Pharmaceutical and Biomedical Analysis,* (2006); 42: 132-135.

[100] Debrus, B., Lebrun, P., Kindenge, J.M., Lecomte, F., Ceccato, A., Caliaro, G., Mbay, J.M., Boulanger, B., Marini, R.D., Rozet, E., Hubert, P.; Innovative high-performance liquid chromatography method development for the screening of 19 antimalarial drugs based on a generic approach, using design of experiments, independent component analysis and design space ; *Journal of Chromatography A*, (2011); 1218: 5205-5215.

[101] Gaudiano, M. C., Di Maggio, A., Antoniella, E., Valvo, L., Bertocchi, P., Manna, L., Bartolomei, M., Alimonti, S., Rodomonte, A.L.; An LC method for the simultaneous screening of some common counterfeit and sub-standard antibiotics Validation and uncertainty estimation; *Journal of Pharmaceutical and Biomedical Analysis,* (2008); 48: 303-309.

[102] Schad, G.J., Allanson, A., Mackay, S.P., Cannavan, A., Tettey, J.N.; Development and validation of an improved HPLC method for the control of potentially counterfeit isometamidium products ; *Journal of Pharmaceutical and Biomedical Analysis,* (2008); 46: 45-51.

[103] Kim, S.H., Lee, J., Yoon, T., Choi, J., Choi, D., Kim, D., Kwon, S.W.; Simultaneous determination of anti-diabetes/anti-obesity drugs by LC/PDA, and targeted analysis of sibutramine analog in dietary supplement by LC/MS/MS; *Biomedical Chromatography,* (2009); 23: 1259-1265.

[104] Stypulkowska, K., Blazewicz, A., Maurin, J., Sarna, K., Fijalek, Z.; X-ray powder difractometry and liquid chromatography studies of sibutrmine and its analogues content in herbal dietary supplements; *Journal of Pharmaceutical and Biomedical Analysis,* (2011); 56: 969-975.

[105] Almeida, A.E., Ribeiro, M.L., Polese, L.; Determination of amfepramone hydrochloride, femproporex, and diazepam in so-called “natural” capsules used in the treatment of obesity; *Journal of Liquid Chromatography & Related Technologies*, (2000); 23: 1109–1118.

[106] Almeida, A.E., Ribeiro, M.L.; High-performance liquid chromatographic determination of amfepramone hydrochloride, mazindol, and diazepam in tablets; *Journal of Liquid Chromatography & Related Technologies*, (1999); 22: 1759–1769.

[107] Mikami, E., Goto, T., Ohno, T., Oka, H., Kanamori, H.; Simultaneous analysis of seven benzodiazepines in dietary supplements as adulterants using high performance liquid chromatography and its application to an identification system for diazepam; *Journal of Health Science*, (2005); 51: 278–283.

[108] Deconinck, E ., Verlinde, K., Courselle, P., Beer, J.O.; A validated Ultra High Pressure Liquid Chromatographic method for the characterisation of confiscated illegal slimming products containing anorexics; *Journal of Pharmaceutical and Biomedical Analysis*, (2012); 59: 38-43.

[109] Liu, S.-Y., Woo, S.-O., Koh, H.-L.; HPLC and GC–MS screening of Chinese proprietary medicine for undeclared therapeutic substances; *Journal of Pharmaceutical and Biomedical Analysis*, (2001); 24: 983–992.

[110] Gryniewicz, C.M., Reepmeyer, J.C., Kauffman, J.F., Buhse, L.F.; Detection of undeclared erectile dysfunction drugs and analogues in dietary supplements by ion mobility spectrometry ; *Journal of Pharmaceutical and Biomedical Analysis,* (2009); 49: 601-606.

[111] Zhu, X., Xiao, S., Chen, B., Zhang, F., Yao, S., Wan, Z., Yang, D., Han, H.; Simultaneous determination of sildenafil, vardenafil and tadalafil as forbidden components in natural dietary supplements for male sexual potency by high-performance liquid chromatography-electrospray ionization mass spectrometry ; *Journal of Chromatography A*, (2005); 1066: 89-95.

[112] Fleshner, N., Harvey, M., Adomat, H., Wood, C., Eberding, A., Hersey, K., Guns, E.; Evidence for contamination of herbal erectile dysfunction products with phosphodiesterase type 5 inhibitors ; *Journal of Urology*, (2005); 174: 636-641.

[113] Li, L., Low, M.Y., Ge, X., Bloodworth, B.C., Koh, H.L.; Isolation and structural elucidation of dapoxetine as an adulterant in a health supplement used for sexual performance enhancement; *Journal of Pharmaceutical and Biomedical Analysis*, (2009); 50: 724-728.

[114] Dorlo, T.P., Eggelte, T.A., de Vries, P.J., Beijnen, J.H.; Characterization and identification of suspected counterfeit miltefosine capsules ; *Analyst*, (2012); 137: 1265-1274.

[115] Dai, X.M., An, N., Wu, J.M., Li, H.Y., Zhang, Q.M.; Development and validation of HPLC-UV-MS method for the control of four anti-diabetic drugs in suspected counterfeit products ; *Yao Xue Xue Bao*, (2010); 45: 347-352.

[116] Tang, M.H., Chen, S.P., Ng, S.W., Chan, A.Y., Mak, T.W.; Case series on a diversity of illicit weight-reducing agents: from the well known to the unexpected ; *British Journal of Clinical Pharmacology*, (2011); 71: 250-253.

[117] Venhuis, B.J., Vredenbregt, M.V., Kaun, N., Maurin, J.K., Fijałek, Z., de Kaste, D.; The identification of rimonabant polymorphs, sibutramine and analogues of both in counterfeit

Acomplia bought on the internet ; *Journal of Pharmaceutical and Biomedical Analysis,* (2011); 54: 21-26.

[118] Wang, J., Chen, B., Yao, S.; Analysis of six synthetic adulterants in herbal weight-reducing dietary supplements by LC electrospray ionization-MS ; *Food Additives & Contaminants: Part A,* (2008): 822-830.

[119] Bogusz, M.J., Hassan, H., Al-Enazi, E., Ibrahim, Z., Al-Tufail, M.; Application of LC-ESI-MS-MS for detection of synthetic adulterants in herbal remedies; *Journal of Pharmaceutical and Biomedical Analysis,* (2006); 41: 554-564.

[120] Chen, Y., Zhao, L., Lu, F., Yu, Y., Chai, Y., Wu, Y. ; Determination of synthetic drugs used to adulterate botanical dietary supplements using QTRAP LC-MS/MS ; *Food Additives & Contaminants: Part A,* (2009) ; 26: 595-603.

[121] de Carvalho, L.M., Martini, M., Moreira, A.P., de Lima, A.P., Correia, D., Falcão, T., Garcia, S.C., de Bairros, A.V., do Nascimento, P.C., Bohrer, D.; Presence of synthetic pharmaceuticals as adulterants in slimming phytotherapeutic formulations and their analytical determination ; *Forensic Science International,* (2011); 204: 6-12.

[122] Hall, K.A., Newton, P.N., Green, M.D., De Veij, M., Vandenabeele, P., Pizzanelli, D., Mayxay, M., Dondorp, A., Fernandez, F.M.; Characterization of counterfeit artesunate antimalarial tablets from southeast Asia ; *The American Journal of Tropical Medicine and Hygien,* (2006); 75: 804-811.

[123] IUPAC compendium of chemical terminology, Royal Society of Chemistry, Cambridge, UK, 1997

[124] Tistaert, C., Dejaegher, B., Vander Heyden, Y.; Chromatographic separation techniques and data handling methods for herbal fingerprints: a review ; *Analytica Chimica Acta*, (2011); 690: 148-161.

[125] European Pharmacopoeia 7.0 (2010), Council of Europe, Strasbourg, France

[126] Japanese Pharmacopoeia, 16th ed., Society of Japanese Pharmacopoeia, Tokyo (2011)

[127] Hubert, M., Rousseeuw, P.J., Verboven, S.; A fast method for robust principal components with applications to chemometrics ; *Chemometrics and Intelligent Laboratory Systems*, (2002); 60: 101–111.

[128] Chen, Y., Zhu, S.B., Xie, M.Y., Nie, S.P., Liu, W., Li, C., Gong, X.F., Wang, Y.X.; Quality control and original discrimination of Ganoderma lucidum based on high-performance liquid chromatographic fingerprints and combined chemometrics methods ; *Analytica Chimica Acta*, (2008); 623: 146–156.

[129] Gan, F., Ye, R.; New approach on similarity analysis of chromatographic fingerprint of herbal medicine ; *Journal of Chromatography A*, (2006); 1104: 100–105.

[130] Li, B.Y., Hua, Y., Liang, Y.Z., Xie, P.S., Duc, Y.P.; Quality evaluation of fingerprints of herbal medicine with chromatographic data ; *Analytica Chimica Acta*, (2004); 514: 69–77.

[131] Xie, P., Chen, S., Liang, Y.Z., Wang, X., Tian, R., Upton, R.; Chromatographic fingerprint analysis—a rational approach for quality assessment of traditional Chinese herbal medicine ; *Journal of Chromatography A*, (2006); 1112: 171–180.

[132] Daszykowski, M., Vander Heyden, Y., Walczak, B.; Robust partial least squares model for prediction of green tea antioxidant capacity from chromatograms ; *Journal of Chromatography A*, (2007), 1176: 12–18.

[133] van Nederkassel, A.M., Daszykowski, M., Massart, D.L., Vander Heyden, Y.; Prediction of total green tea antioxidant capacity from chromatograms by multivariate modeling ; *Journal of Chromatography A,* (2005); 1096: 177–186.

[134] Tistaert, C., Dejaegher, B., Nguyen Hoai, N., Chataigné, G., Rivière, C., Nguyen, T.H., Chau Van, M., Quetin-Leclercq, J., Vander Heyden Y.; Potential antioxidant compounds in Mallotus species fingerprints. Part I: Indication, using linear multivariate calibration techniques; *Analytica Chimica Acta,* (2009); 652: 189–197.

[135] Tistaert, C., Dejaegher, B., Chataigné, G., Rivière, C., Chau Van, M., Quetin-Leclercq, J., Vander Heyden, Y.; Potential antioxidant compounds in Mallotus species fingerprints. Part II: Alignment, Analysis and identification; *Analytica Chimica Acta,* (2012); 721: 35-43.

[136] Tistaert, C., Dejaegher, B., Chataigné, G., van Minh, C., Quetin-Leclercq, J., Vander Heyden, Y.; Dissimilar chromatographic systems to indicate and identify antioxidants from Mallotus species ; *Talanta*, (2011); 83: 1198–1208.

[137] Tian, R.T., Xie, P.S., Liu, H.P.; Evaluation of traditional Chinese herbal medicine: Chaihu (Bupleuri Radix) by both high-performance liquid chromatographic and high-performance thin-layer chromatographic fingerprint and chemometric analysis ; *Journal of Chromatography A,* (2009): 1216: 2150–2155.

[138] Chopra, S., Ahmad, F.J., Khar, R.K., Motwani, S.K., Mahdi, S., Iqbal, Z., Talegaonkar, S.; Validated high-performance thin-layer chromatography method for determination of trigonelline in herbal extract and pharmaceutical dosage form ; *Analytica Chimica Acta*, (2006); 577: 46–51.

[139] Kaur, A.D., Ravichandran, V., Jain, P.K., Agrawal, R.K.; High-performance thin layer chromatography method for estimation of conessine in herbal extract and pharmaceutical

dosage formulations; *Journal of Pharmaceutical and Biomedical Analysis*, (2008); 46: 391–394.

[140] Apers, S., Naessens, T., Pieters, L., Vlietinck, A.; Densitometric thin-layer chromatographic determination of aescin in a herbal medicinal product containing *Aesculus* and *Vitis* dry extracts ; *Journal of Chromatography A*, (2006); 1112: 165–170.

[141] Marchand, E., Atemnkeng, M.A., Vanermen, S., Plaizier-Vercammen, J.; Development and validation of a simple thin layer chromatographic method for the analysis of artemisinin in Artemisia annua L. plant extracts. *Biomedical Chromatography*, (2008); 22: 454–459.

[142] Vogel, H., Gonzalez, M., Faini, F., Razmilic, I., Rodrıguez, J., San Martın, J., Urbina, F.; Antioxidant properties and TLC characterization of four Chilean Haplopappus-species known as bailahuén, *Journal of Ethnopharmacology*, (2005); 97: 97–100.

[143] Biringanine, G., Chiarelli, M.T., Faes, M., Duez, P.; A validation protocol for the HPTLC standardization of herbal products: Application to the determination of acteoside in leaves of *Plantago palmata* Hook. f.s. ;*Talanta*, (2006); 69: 418–424.

[144] Vanhaelen-Fastre, R.J., Faes, M.L., Vanhaelen, M.H.; High-performance thin-layer chromatographic determination of six major ginsenosides in *Panax ginseng* ; *Journal of Chromatography A*, (2000); 868: 269–276.

[145] Cui, S., Fu, B., Sen-Chun Lee, F., Wang, X.; Application of microemulsion thin layer chromatography for the fingerprinting of licorice (Glycyrrhiza spp.)**,** *Journal of Chromatography B*, (2005); 828: 33–40.

[146] Ettre, L.S.; Milestones in the Evolution of Chromatography; ChromSource, Franklin, TN, USA, 2002.

[147] Ciesla, L., Bogucka-Kocka, A., Hajnos, M., Petruczynik, A., Waksmundzka-

Hajnosa, M.; Two-dimensional thin-layer chromatography with adsorbent gradient as a method of chromatographic fingerprinting of furanocoumarins for distinguishing selected varieties and forms of *Heracleum* spp ; *Journal of Chromatography A*,(2008); 1207: 160–168.

[148] Ciesla, L., Waksmundzka-Hajnos, M.; Two-dimensional thin-layer chromatography in the analysis of secondary plant metabolites ; *Journal of Chromatography A,* (2009) ; 1216 : 1035–1052.

[149] Bombarda, I., Dupuy, N., Le Van Da, J.-P., Gaydou, E.M. ; Comparative chemometric analyses of geographic origins and compositions of lavandin var. Grosso essential oils by mid infrared spectroscopy and gas chromatography ; *Analytica Chimica Acta*, (2008); 613: 31–39.

[150] Grob, R.L., Barry, E.F.; Modern Practice of Gas Chromatography; fourth ed., Wiley, Hoboken, NJ, USA, 2004.

[151] Zhu, H., Wang, Y., Liang, H., Chen, Q., Zhao, P., Tao, J.; Identification of *Portulaca oleracea* L. from different sources using GC–MS and FT-IR spectroscopy ; *Talanta*, (2010); 81: 129–135.

[152] David, F., Gere, D.R., Scanlan, F., Sandra, P.; Instrumentation and applications of fast high-resolution capillary gas chromatography ; *Journal of Chromatography A*,(1999); 842: 309–319.

[153] Mondello, L., Shellie, R.A.,Casilli, A., Tranchida, P., Marriott, P.J., Dugo, G.;Ultra-fast essential oil characterization by capillary GC on 50 μm ID column **;** *Journal of Separation Science*, (2004); 27 699–702.

[154] Bicchi, C., Brunelli, C., Cordero, C., Rubiolo, P., Galli, M., Sironi, A.; Direct resistively heated column gas chromatography (Ultrafast module-GC) for high-speed analysis

of essential oils of differing complexities ; *Journal of Chromatography A*,(2004); 1024: 195–207.

[155] Bicchi, C., Brunelli, C., Galli, M., Sironi, A. ; Conventional inner diameter short capillary columns: an approach to speeding up gas chromatographic analysis of medium complexity samples ; *Journal of Chromatography A,* (2001); 931: 129–140.

[156] Poynter, S.D.H., Shellie, R.A.; High-speed, low-pressure gas chromatography–mass spectrometry for essential oil analysis ; *Journal of Chromatography A,* (2008); 1200: 28–33.

[157] Godoi, A.F.L., Vilegas, W., Godoi, R.H.M., Van Vaeck, L., Van Grieken, R.; Application of low-pressure gas chromatography–ion-trap mass spectrometry to the analysis of the essential oil of *Turnera diffusa* (Ward.) Urb. *Journal of Chromatography A,* (2004); 1027: 127–130.

[158] Ravindra, K., Dirtu, A.C., Covaci, A. ; Low-pressure gas chromatography: Recent trends and developments**;** *Trends in Analytical Chemistry*, (2008); 27: 291–303.

[159] Mena Granero, A., Egea González, F.J., Garrido Frenich, A., Guerra Sanz, J.M., Martınez Vidal, J.L.; Single step determination of fragrances in *Cucurbita* flowers by coupling headspace solid-phase microextraction low-pressure gas chromatography–tandem mass spectrometry ; *Journal of Chromatography A,* (2004) ; 1045 : 173–179.

[160] Lu, G.H., Chan, K., Liang, Y.Z., Leung, K., Chan, C.L., Jiang, Z.H., Zhao, Z.Z.; Development of high-performance liquid chromatographic fingerprints for distinguishing Chinese Angelica from related umbelliferae herbs *Journal of Chromatography A,* (2005) ; 1073 : 383–392.

[161] Li, Y., Wu, T., Zhu, J., Wan, L., Yu, Q., Li, X., Cheng, Z., Guo, C.; Combinative method using HPLC fingerprint and quantitative analyses for quality consistency evaluation

of an herbal medicinal preparation produced by different manufacturers ; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 52: 597–602.

[162] Alaerts, G., Matthijs, N., Smeyers-Verbeke, J., Vander Heyden, Y.; Chromatographic fingerprint development for herbal extracts: A screening and optimization methodology on monolithic columns ; *Journal of Chromatography A,* (2007) ; 1172 : 1–8.

[163] Ni, Y., Lai, Y., Brandes, S., Kokot, S. ; Multi-wavelength HPLC fingerprints from complex substances: An exploratory chemometrics study of the *Cassia seed* example ; *Analytica Chimica Acta,* (2009) ; 647: 149–158.

[164] Li, W., Deng, Y., Dai, R., Yu, Y., Saeed, M.K., Li, L., Meng, W., Zhang, X.; Chromatographic fingerprint analysis of *Cephalotaxus sinensis* from various sources by high-performance liquid chromatography–diodearray detection–electrospray ionization-tandem mass spectrometry ; *Journal of Pharmaceutical and Biomedical Analysis,* (2007): 45: 38–46.

[165] Tan, X.J., Li, Q., Chen, X.H., Wang, Z.W., Shi, Z.Y., Bi, K.S., Jia, Y.; Simultaneous determination of 13 bioactive compounds in Herba Artemisiae Scopariae (Yin Chen) from different harvest seasons by HPLC–DAD ; *Journal of Pharmaceutical and Biomedical Analysis,* (2008) ; 47 : 847–853.

[166] Agnolet, S., Jaroszewski, J.W., Verpoorte, R., Staerk, D.; 1H NMR-based metabolomics combined with HPLC-PDA-MS-SPE-NMR for investigation of standardized Ginkgo biloba preparations **;** *Metabolomics*; (2010); 292–302.

[167] Ji, Y.B., Xu, Q.S., Hu, Y.Z., Vander Heyden, Y. ; Development, optimization and validation of a fingerprint of *Ginkgo biloba* extracts by high-performance liquid chromatography ; *Journal of Chromatography A,* (2005) ; 1066: 97–104.

[168] Fan, X.H., Cheng, Y.Y., Ye, Z.L., Lin, R.C., Qian, Z.Z.; Multiple chromatographic fingerprinting and its application to the quality control of herbal medicines ; *Analytica Chimica Acta*, (2006); 555: 217–224.

[169] Tong, L., Wang, Y., Xiong, J., Cui, Y., Zhou, Y., Yi, L.; Selection and fingerprints of the control substances for plant drug *Eucommia ulmodies Oliver* by HPLC and LC–MS ; *Talanta*, (2008); 76: 80–84.

[170] van Nederkassel, A.M., Vijverman, V., Massart, D.L., Vander Heyden, Y.; Development of a ginkgo biloba fingerprint chromatogram with UV and evaporative light scattering detection and optimization of the evaporative light scattering detector operating conditions. *Journal of Chromatography A*, (2005); 1085: 230–239.

[171] Xie, B., Gong, T., Tang, M., Mi, D., Zhang, X., Liu, J., Zhang, Z.; An approach based on HPLC-fingerprint and chemometrics to quality consistency evaluation of Liuwei Dihuang Pills produced by different manufacturers ; *Journal of Pharmaceutical and Biomedical Analysis*,(2008); 48: 1261–1266.

[172] Faghihi, J., Jiang, X., Vierling, R., Goldman, S., Sharfstein, S., Sarver, J., Erhardt, P.; Reproducibility of the high-performance liquid chromatographic fingerprints obtained from two soybean cultivars and a selected progeny ; *Journal of Chromatography A*, (2001); 915: 61–74.

[173] Wei, H., Sun, L., Tai, Z., Gao, S., Xu, W., Chen, W.; A simple and sensitive HPLC method for the simultaneous determination of eight bioactive components and fingerprint analysis of *Schisandra sphenanthera* ; *Analytica Chimica Acta*, (2010); 662: 97–104.

[174] Lucio-Gutiérrez, J.R., Coello, J., Maspoch, S.; Enhanced chromatographic fingerprinting of herb materials by multi-wavelength selection and chemometrics ; *Analytica Chimica Acta*, (2012); 710: 40-49.

[175] Su, J., Fu, P., Shen, Y., Zhang, C., Liang, M., Liu, R., Li, H., Zhang, W.; Simultaneous analysis of flavonoids from *Hypericum japonicum* Thunb.ex Murray (Hypericaceae) by HPLC-DAD–ESI/MS ; *Journal of Pharmaceutical and Biomedical Analysis,* (2008); 46: 342–348.

[176] Kumar, V., Mehrotra, N., Lal, J., Gupta, R.C.; Pattern profiling of the herbal preparation picroliv using liquid chromatography–tandem mass spectrometry ; *Journal of Chromatography A,*(2004); 1045: 145–152.

[177] Dumarey, M., van Nederkassel, A.M., Deconinck, E., Vander Heyden, Y.; Exploration of linear multivariate calibration techniques to predict the total antioxidant capacity of green tea from chromatographic fingerprints. *Journal of Chromatography A,* (2008); 1192: 81–88.

[178] Schneider, A., Wessjohann, L.A.; Comparison of impurity profiles of Orlistat pharmaceutical products using HPLC tandem mass spectrometry ; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 53: 767-772.

[179] Sacré, P.Y., Deconinck, E., Daszykowski, M., Courselle, P., Vancauwenberghe, R., Chiap, P., Crommen, J., De Beer, J.O.; Impurity fingerprints for the identification of counterfeit medicines: a feasibility study ; *Analytica Chimica Acta,* (2011); 701: 224-231.

[180] European Directorate for the Quality of Medicines; Draft monography of sildenafil Citrate; Pharmeuropa (2011); 23: 381–383.

[181] European Directorate for the Quality of Medicines; Draft monography of Tadalafil; Pharmeuropa, (2010); 22: 328–332.

[182] van Nederkassel, A.M., Xu, C.J., Lancelin, P., Sarraf, M., Mackenzie, D.A., Walton, N.J., Bensaid, F., Lees, M., Martin, G.J., Desmurs, J.R., Massart, D.L., Smeyers-Verbeke, J., Vander Heyden, Y.; Chemometric treatment of vanillin fingerprint chromatograms. Effect of different signal alignments on principal component analysis plots ; *Journal of Chromatography A,* (2006); 1120: 291-298.

[183] van Nederkassel, A.M., Daszykowski, M., Eilers, P.H., Vander Heyden, Y.; A comparison of three algorithms for chromatograms alignment ; *Journal of Chromatography A,* (2006); 1118: 199-210.

[184] Deconinck, E., Sacré, P.Y., Courselle, P.; De Beer, J.O.; Chemometrics and chromatographic fingerprints to discriminate and classify counterfeit medicines containing PDE-5 inhibitors; *Talanta,* (2012); 100: 123-133.

[185] Phillips, G.; Anticounterfeiting measures **;** *Pharmaceutical Journal,* (2003); 271: 465.

[186] Microgram Bulletin, June 2004, http://www.justice.gov/dea/programs/forensicsci/microgram/mg0604/mg0604.pdf (last accessed 08/08/2012)

[187] Microgram bulletin, april 2004, http://www.justice.gov/dea/programs/forensicsci/microgram/mg0404/mg0404.pdf (last accessed 08/08/2012)

[188] Reepmeyer, J.C., Woodruff, J.T., d'Avignon, D.A.; Structure elucidation of a novel analogue of sildenafil detected as an adulterant in an herbal dietary supplement ; *Journal of Pharmaceutical and Biomedical Analysis,* (2007); 43: 1615-1621.

[189] Musshoff, F., Daldrup, T., Ritsch, M.; Anabolic steroids on the German black Market; *Archiv für Kriminologie,* (1997); 199: 152-158.

[190] Lin, D.L., Chang, H.C., Huang, S.H.; Characterization of allegedly musk-containing medicinal products in Taiwan ; *Journal of Forensic science*, (2004); 49: 1187-1193.

[191] Soltaninejad, K., Faryadi, M., Akhgari, M., Bahmanabadi, L.; Chemical profile of counterfeit buprenorphine vials seized in Tehran, Iran; *Forensic Science International,* (2007);172: e4-5.

[192] Alabdalla M.A.; Chemical characterization of counterfeit captagon tablets seized in Jordan ; *Forensic Science International*,(2005);152: 185-188.

[193] Lee, J.S., Chung, H.S., Kuwayama, K., Inoue, H., Lee, M.Y., Park, J.H.; Determination of impurities in illicit methamphetamine seized in Korea and Japan ; *Analytica Chimica Acta,* (2008); 619: 20-25.

[194] Grodowska, K., Parczewski, A.; Organic solvents in the pharmaceutical industry, *Acta Poloniae Pharmaceutica,* (2010); 67: 3-12.

[195] Grodowska, K., Parczewski, A.; Analytical methods for residual solvents determination in pharmaceutical products, *Acta Poloniae Pharmaceutica,* (2010); 67: 13-26.

[196] D'Autry, W., Zheng, C., Wolfs, K., Yarramraju, S., Hoogmartens, J., Van Schepdael, A., Adams, E.; Mixed aqueous solutions as dilution media in the determination of residual solvents by static headspace gas chromatography, *Journal of Separation Science,* (2011); 34: 1299-1308.

[197] D'Autry, W., Zheng, C., Bugalama, J., Wolfs, K., Hoogmartens, J., Adams, E., Wang, B., Van Schepdael, A.; Liquid paraffin as new dilution medium for the analysis of high boiling point residual solvents with static headspace-gas chromatography; *Journal of Pharmaceutical and Biomedical Analysis,* (2011); 55: 1017-1023.

[198] D'Autry, W., Wolfs, K., Hoogmartens, J., Adams, E., Van Schepdael, A.; Improving quantitative gas chromatography-electron ionization mass spectrometry results using a modified ion source: demonstration for a pharmaceutical application; *Journal of Chromatography A,* (2011); 18: 4034-4038.

[199] Deconinck, E., Canfyn, M., Sacré, P.Y., Baudewyns, S., Courselle, P., De Beer, J.O.; A validated GC-MS method for the determination and quantification of residual solvents in counterfeit tablets and capsules. *Journal of Pharmaceutical and Biomedical Analysis,* (2012); 70: 64-70.

[200] Mulligan, K.J., Brueggemeyer, T.W., Crockett, D.F., Schepman, J.B.; Analysis of organic volatile impurities as a forensic tool for the examination of bulk pharmaceuticals; *Journal of Chromatography A,* (1996); 686: 85-95.

[201] Deconinck, E., Canfyn, M., Sacré, P.-Y., Courselle, P., De Beer, J.O.; Evaluation of the residual solvent content of counterfeit tablets and capsules**; in preparation.**

[202] International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use, Q3C: impurities: Guidelines for Residual Solvents, Step 4 (1997)

[203] Marini, R.D., Rozet, E., Montes, M.L., Rohrbasser, C., Roht, S., Rhème, D., Bonnabry, P., Schappler, J., Veuthey, J.L., Hubert, P., Rudaz, S.; Reliable low-cost capillary electrophoresis device for drug quality control and counterfeit medicines ; *Journal of Pharmaceutical and Biomedical Analysis,* (2010); 53: 1278-1287.

[204] Amin, N.C., Blanchin, M.D., Aké, M., Montels, J., Fabre, H.; Capillary electrophoresis for the assay of fixed-dose combination tablets of artesunate and amodiaquine ; *Malaria Journal,* (2012); 11: 149-156.

[205] Lamalle, C., Marini, R.D., Debrus, B., Lebrun, P., Crommen, J., Hubert, P., Servais, A.C., Fillet, M.; Development of a generic micellar electrokinetic chromatography method for the separation of 15 antimalarial drugs as a tool to detect medicine counterfeiting ; *Electrophoresis,* (2012); 33: 1669-1678.

[206] Ku, Y.R., Chang, Y.S., Wen, K.C., Ho, L.K.; Analysis and confirmation of synthetic anorexics in adulterated traditional Chinese medicines by high-performance capillary electrophoresis; *Journal of Chromatography A,* (1999); 848: 537–543.

[207] de Carvalho, L.M., Martini, M., Moreira, A.P., Garcia, S.C., do Nascimento, P.C., Bohrer, D.; Determination of synthetic pharmaceuticals in phytotherapeutics by capillary zone electrophoresis with contactless conductivity detection (CE-C^4D); *Microchemical Journal*, (2010); 96: 114-119.

[208] Piette, V., Parmentier, F.; Analysis of illicit amphetamine seizures by capillary zone electrophoresis; *Journal of Chromatography A*, (2002); 979: 345–352.

[209] Cianchino, V., Acosta, G., Ortega, C., Martínez, L.D., Gomez, M.R.; Analysis of potential adulteration in herbal medicines and dietary supplements for the weight control by capillary electrophoresis; *Food Chemistry*, (2008); 108: 1075–1081.

[210] Renou-Gonnord, M.F., David, K.; Optimized micellar electrokinetic chromatographic separation of benzodiazepines; *Journal of Chromatography A*, (1996); 735: 249–261.

[211] Berzas, J.J., Castafieda, G., Pinilla, M.J.; Determination of diazepam and associated compounds in pharmaceutical preparations; *Fresenius' Journal of Analytical Chemistry*, (1999); 364: 570–575.

[212] Hancu, G., Gaspár, A., Gyèresi, A.; Separation of 1,4-benzodiazepines by micellar electrokinetic capillary chromatography; *Journal of Biochemical and Biophysical Methods*, (2007); 69: 251–259.

Figure captions:

Figure 1: Total number of reports of counterfeiting, illegal diversion and theft incidents for nine consecutive years [6].

Figure 2: Counterfeit drug cases opened by the FDA's office of criminal investigation per fiscal year.

Figure 3: HPLC-UV chromatograms of samples of Roche A: (Xenical® – blue line), Ranbaxy B: (Cobese™ – red line) and KRKA C: (Orsoten – green line) tetrahydrolipstatin drugs (Reprinted with permission from [178])

Figure 4: A. Impurity profile of a counterfeit tablet of Viagra®. B. Impurity profile of a genuine tablet of Viagra®. C. Impurity profile of a coloured imitation tablet of Cialis®. D. Impurity profile of a genuine tablet of Cialis® (Reprinted with permission from [179]).

Table 1: Definition of the RIVM classes [13]

Main category	Subcategory	Inclusion and exclusion criteria
Counterfeit	Professional	Appearance in conformity with genuine medicine; Content of correct API within 90 - 110 % of declared value; No other APIs; not genuine medicine.
	Non-professional	Appearance in conformity with genuine medicine; Content of correct API outside 90 - 110 % of declared value; No other APIs.
	Mixed	Appearance in conformity with genuine medicine; Contains correct API and another, known API
	Fraudulent	Appearance in conformity with genuine medicine; Contains a different, known API.
	Analog	Appearance in conformity with genuine medicine, Contains other, unapproved API
	Placebo	Appearance in conformity with genuine medicine; Does not contain APIs.
Imitation	Professional	Appearance not in conformity with genuine medicine; Content of correct API within 90 - 110 % of declared value; No other APIs.
	Non-professional	Appearance not in conformity with genuine medicine; Content of declared API outside 90 - 110 % of declared value; No other APIs.
	Mixed	Appearance not in conformity with genuine medicine; Contains declared API and another API.
	Fraudulent	Appearance not in conformity with genuine medicine; Contains an undeclared API.
	Analog	Appearance not in conformity with genuine medicine; Contains other, unapproved API
	Placebo	Appearance not in conformity with genuine medicine; Does not contain APIs.

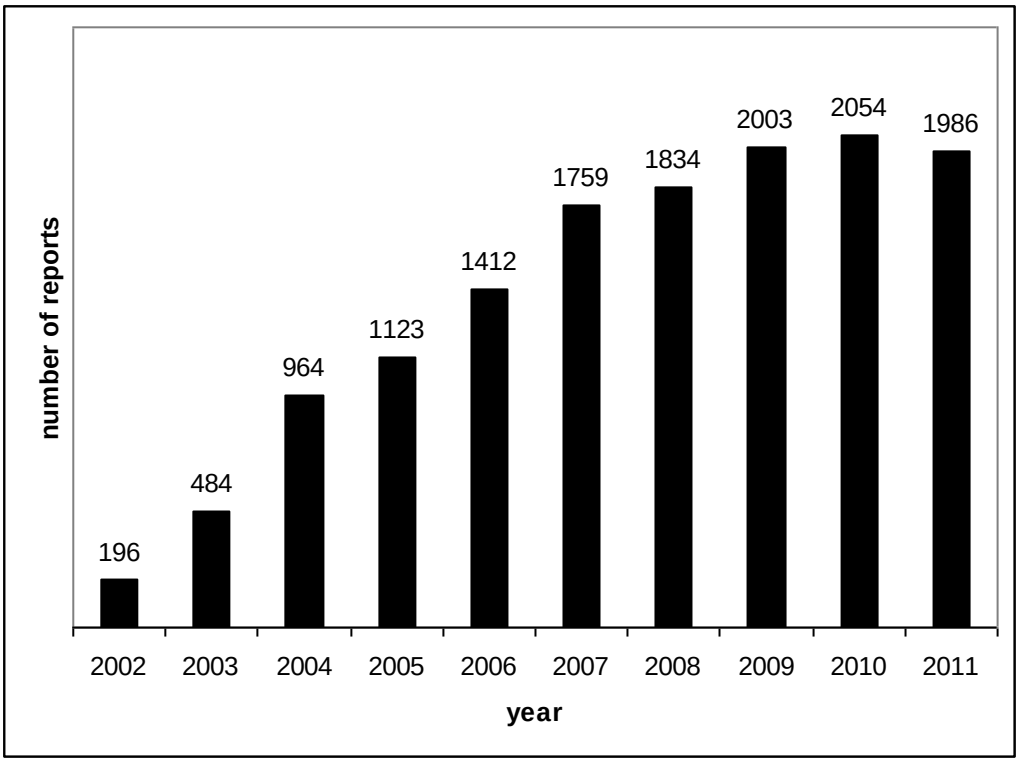

Figure 1

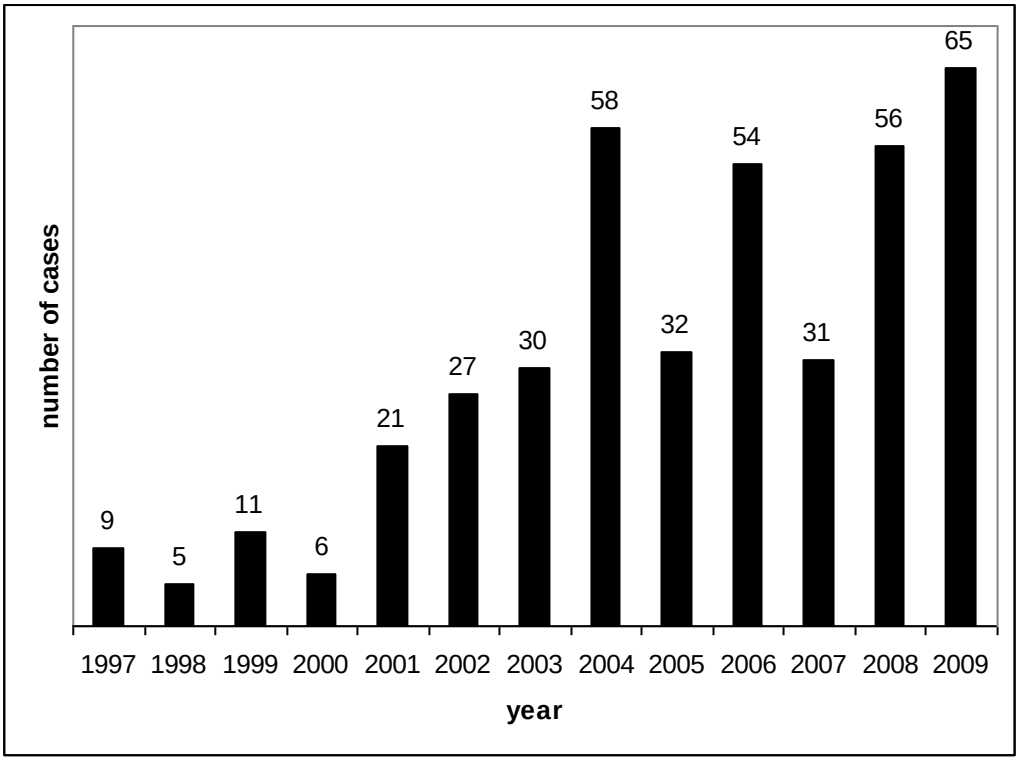

Figure 2

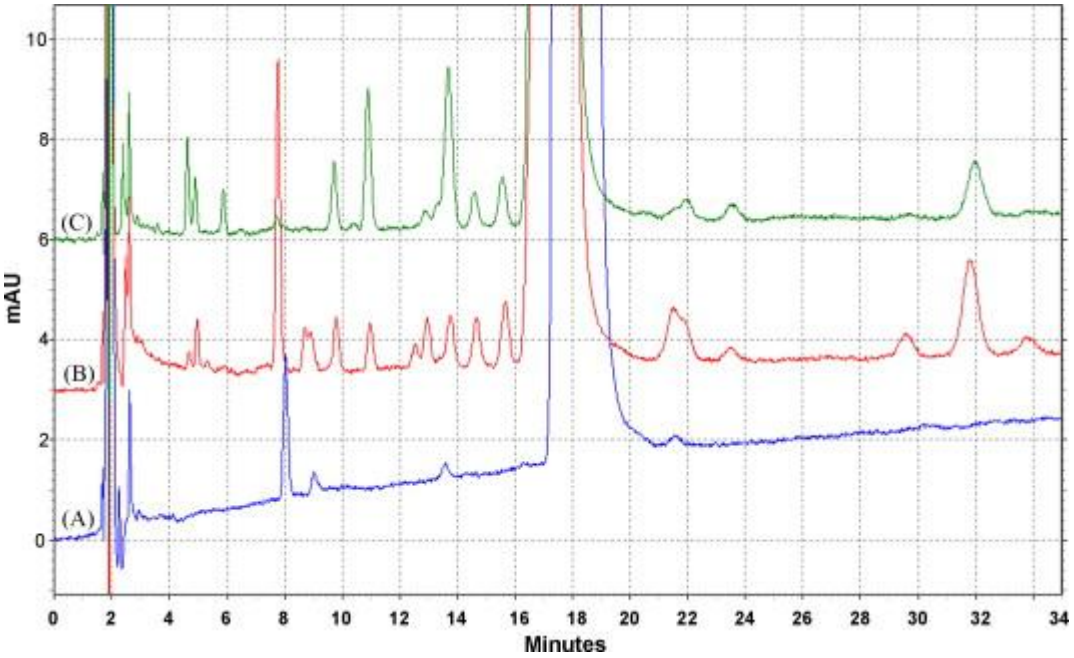

Figure 3

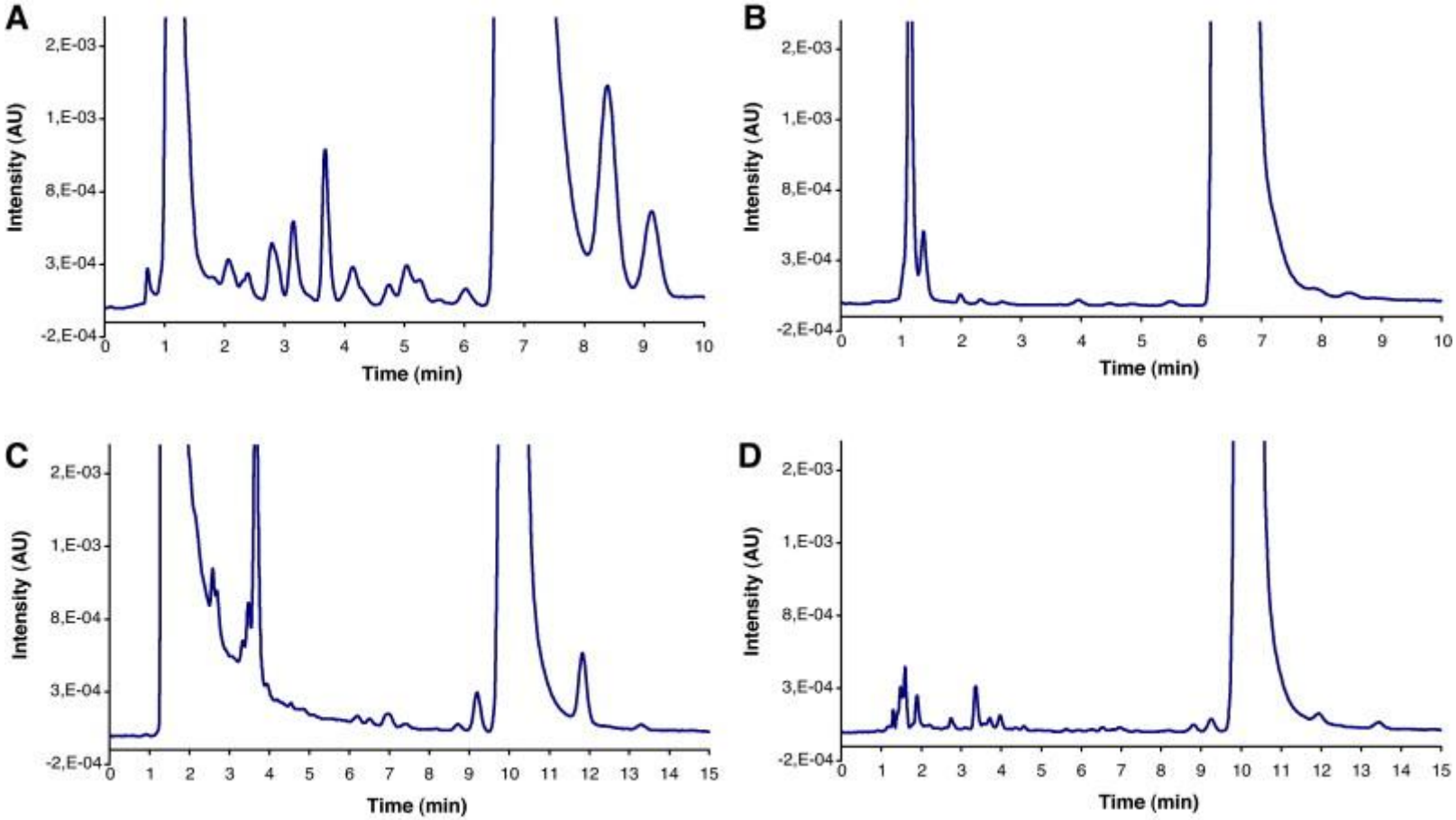

Figure 4