FORENSIC EXAMINATION OF ORIGINAL AND COUNTERFEIT MEDICATIONS USING FTIR ANALYSIS

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FORENSIC EXAMINATION OF ORIGINAL AND COUNTERFEIT MEDICATIONS USING FTIR ANALYSIS

by

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LIST OF ABBREVIATIONS

FTIR	Fourier-transform infrared spectroscopy
NIR	Near Infrared
WHO	World Health Organization
IMPAC	Institute Malaysian Plantation and Commodities
IRACM	Institute of Research Against Counterfeit Medicines
NHS	National Health Service
KBr	Potassium bromide
HCl	hydrogen chloride
DTGS	Deuterated Triglycine Sulphate

PEMERIKSAAN FORENSIK UBAT ASLI DAN PALSU MENGGUNAKAN ANALISIS FTIR

ABSTRAK

Perkataan "palsu" menerangkan apa-apa yang tidak tulen tetapi dipersembahkan sebagai atau kelihatan tulen untuk membuat atau mengilang sesuatu dan mendakwa ia tulen sedangkan ia tidak. Pemalsuan komersial adalah amalan lama yang berkembang pesat di banyak negara dan terutamanya didorong oleh keuntungan besar yang akan diperolehi. Di kawasan Afrika, Asia dan Timur Tengah, mereka menyumbang 10%-50% daripada semua farmaseutikal. Dalam sains forensik, penjenayah boleh menggunakan kompaun palsu ini untuk mempertaruhkan nyawa mangsa. Oleh kerana pembungkusan dan penampilan visual ubat tiruan adalah serupa dengan ubat sebenar, penyiasat menghadapi kesukaran untuk mengenal pastinya. Sedikit pemikiran diberikan kepada kemungkinan menggunakan farmaseutikal palsu sebagai bukti untuk mewujudkan hubungan antara mangsa, suspek dan tapak jenayah. Memandangkan rangkaian alat analisis yang tersedia, seperti kromatografi dan spektroskopi, membezakan produk tiruan daripada produk tulen menjadi semakin sukar. Penilaian kimia pembungkusan dan kandungan farmaseutikal difasilitasi dengan pemeriksaan lanjut dengan spektroskopi FTIR. Matlamat kajian ini adalah untuk menyiasat secara fizikal dan menggunakan spektroskopi inframerah transformasi Fourier yang dilemahkan untuk memeriksa pelbagai ubat asli dan tiruan, termasuk Amaryl, Aircomb, dan Diamicron MR. Tiga sampel tiruan dan tiga sampel tulen bagi tiga ubat berbeza (dua anti-diabetes dan satu tidak radang) telah dikumpul daripada enam pengeluar berasingan. Pemeriksaan visual digunakan untuk menjalankan pemeriksaan fizikal awal sampel ubat. Sampel kemudian disediakan

untuk spektroskopi FTIR dengan zarah kalium bromida (KBr) menggunakan spektrometer Spectrum 100 FT-IR (Perkin-elmer, Waltham, MA, USA). Pemeriksaan fizikal ubat-ubatan mendedahkan perbezaan yang jelas dan jelas antara ubat-ubatan tiruan dan tulen. Untuk pelbagai ubat, spektrum FTIR mendedahkan puncak yang berbeza dalam kawasan cap jari n dan kawasan kumpulan berfungsi, yang mengandungi ikatan seperti kumpulan O-H, C=O, C=C, dan C-H pada pelbagai panjang gelombang. Seperti yang dijangkakan, profil spektrum purata bagi semua jenis tablet yang dikaji mempamerkan tahap persamaan yang tinggi kerana komposisi kimianya yang serupa. Walau bagaimanapun, masih terdapat beberapa perbezaan kecil antara susunan kumpulan berfungsi. Kesimpulannya, penilaian visual digabungkan dengan spektroskopi FTIR adalah kaedah yang sangat berkesan untuk membezakan antara jenama ubat yang berbeza. Penggunaan teknik tersebut mendedahkan kaedah penyiasatan forensik yang cepat, teguh, cekap, tidak merosakkan, dan kos efektif. Kajian masa depan dengan saiz sampel yang lebih besar mungkin menyiasat nilai sampel ubat yang dikumpul menggunakan instrumen pensampelan FTIR yang lain.

FORENSIC EXAMINATION OF ORIGINAL AND COUNTERFEIT MEDICATIONS USING FTIR ANALYSIS

ABSTRACT

The word "counterfeit" describes anything that is not genuine but is presented as or looks to be genuine in order to make or manufacture something and claim it is genuine when it is not. Commercial counterfeiting is an age-old practise that thrives in many countries and is primarily motivated by the enormous profits to be made. In regions of Africa, Asia, and the Middle East, they account for 10%-50% of all pharmaceuticals. In forensic science, a criminal could utilise these forged compounds to risk the victim's life. Because the packaging and visual appearance of the counterfeit drug are similar to those of the actual drugs, the investigator has difficulties identifying it. Little thought is given to the possibility of using counterfeit pharmaceuticals as evidence to establish a link between victim, suspect, and crime site by tracing the manufacturer information of the medications. Given the range of analytical tools available, such as chromatography and spectroscopy, differentiating counterfeit from genuine products is becoming increasingly difficult, since they provide limited information about the drug's identity. Chemical assessment of pharmaceutical packaging and content is facilitated by further screening with FTIR spectroscopy. The aim of this study was to physically investigate and utilise attenuated total reflection Fourier transform Infrared (FTIR) spectroscopy to examine various original and counterfeit medications, including Amaryl, Aircomb, and Diamicron MR. Three counterfeit and three authentic samples of three different drugs (two anti-diabetic and

one non-inflammatory) were collected from six separate manufacturers. Visual inspection was used to conduct the initial physical examination of the medication samples. The samples were then prepared for FTIR spectroscopy with potassium bromide (KBr) particle using a Spectrum 100 FT-IR (Perkin-elmer, Waltham, MA, USA) spectrometer. Physical examination of the medications revealed a plain and straightforward distinction between counterfeit and authentic medications. For various medications, the FTIR spectra revealed distinct peaks in the n fingerprint region and functional group regions, containing bonds such as O-H groups, C=O, C=C, and C-H at various wavelengths. As anticipated, the averaged spectral profiles of all studied tablet types exhibited a high degree of similarity due to their similar chemical composition. Nonetheless, there were still a few minor distinctions between the functional group arrangements. In conclusion, visual evaluation combined with FTIR spectroscopy is a highly effective method for distinguishing between distinct medication brands. The application of the technique revealed methods of forensic investigation that are rapid, robust, efficient, nondestructive, and cost-effective. Future studies with larger sample sizes may investigate the value of medication samples collected using other FTIR sampling instruments.

CHAPTER 1

INTRODUCTION

1.1 Background

Drugs are used to treat or cure various diseases, relieve symptoms, ease disease-related pain, prevent disease or symptoms, and their progression. Many people take medication on a daily basis, and these medications are used to treat disease and improve health. Although drugs can help you feel better and recover, it is vital to understand that all medications, both prescription and over-the-counter, might possess benefits as well as risks. The term "counterfeit" refers to something that is not authentic but is presented as or appears to be authentic in order to make or produce something and claim it is authentic when it is not (Hoe et al., 2003). Shelf life is the amount of time it takes for a product to become unusable due to chemical degradation of the active ingredient or physical deterioration during storage. It can also be defined as the length of time a drug or product will remain effective when stored under the manufacturer-recommended storage conditions. The maximum shelf life or expiration date of a drug is typically five years. Counterfeit is something created with the intent to deceive; a deliberate deception (Buowari, 2012).

Counterfeit or counterfeit medications are defined as medicines that have been fraudulently produced or packaged (Alefan et al., 2020). The World Health Organization defines counterfeit drugs as those that are intentionally and fraudulently mislabeled with regard to their source and/or identification (Buowari, 2012). The counterfeiting of commercial goods is an age-old practice that thrives in many nations and is primarily motivated by the enormous profits to be made. The international trade in counterfeit drugs appears to be extensive, affecting both developed and developing

nations. In countries where the manufacture, importation, distribution, supply, and sale of pharmaceuticals are less regulated and where law enforcement may be relaxed, the prevalence of counterfeit drugs is typically greater. In addition, health authorities have not approved these medications, they are not presented with quality regulation standards, along with being not effective in the treatment of diseases with selling and usage being banned across various countries (FDA, 2017).

Counterfeit medicines are widespread and mostly impact developing countries, accounting for up to 10.5% of all drugs sold globally. Accounting for as high as approximately 10–50% of total medications in regions of Middle East, Asia and the Africa, counterfeit medications are abundantly present (Pathak et al., 2023). Counterfeit medicines are banned, less expensive, possess lower standards, posing a significant health hazard to public (Matos et al., 2007). Furthermore, people are able to purchase medicines online, which may lead to a greater prevalence of counterfeit medications worldwide. Moreover, significant lacking of public awareness may also result in increase in the usage of counterfeit drugs (Al-Worafi, 2020). Even though the counterfeit medications can be distributed in identical both registered and scientific labels of medications, sometimes, even medical examiners may struggle to recognize a falsified/counterfeit medication due to its high efficacy, however this cannot guarantee its safety and sale.

Indeed, some are lacking any Active Pharmaceutical Ingredient (API) or included with toxic substances. The economy as a whole is also under threat. In addition, counterfeiting is both profitable and relatively risk-free (Wertheimer *et al.,* 2009). Previous reports report that, terrorist organisations fund their operations across the counterfeit business, and key crime organizing agents are also taking part

(Dégardin et al., 2015). Understanding and deconstructing this sophisticated and dark sector remains difficult since counterfeiting has evolved into an organised economy including manufacturers, wholesalers, distributors, and local vendors (Przyswa, 2013). Support from other anti-counterfeiting organisations is even sluggish or limited to a specific region or locality. Furthermore, the reaction must be prompted by the threat: it must be immediate, reactive, and global (Shepherd, 2010; Dégardin et al., 2014). Manufacturers are progressively implementing product protection strategies such as labelling as well as coding of container or drug.

In addition, analytical services remain generally used for quality control and also have been used to detect counterfeits or prove a product is counterfeit. Analytical data collection and organisation was always a challenge related to chemistry to be more precise than a forensic science challenge because of its expensive and complicated nature. Moreover, rapidly, it became apparent that the packaging and chemical study's analytical data can be combined in order to generate forensic intelligence as well as better understanding into the process on three different levels (Dégardin et al., 2014). Initially, for local counterfeit cases, fast detection methods can be created and used.

Given the variety of analytical technologies, like chromatography and spectroscopy (Sacre et al., 2010; Roggo et al., 2010), used in the lab or field (Bate et al., 2009), distinguishing counterfeit from real products is now rare. Rapid detection technologies can be created and applied to expedite the management of counterfeit cases on a regional level. Discriminating among the falsified/counterfeit and real compounds is no longer a problem, thanks to the abundance of analytical instruments shown to be efficient, such as chromatography and spectroscopy (Kwok and Taylor,

2012) used in the laboratory or in the field (Bate et al., 2009). To avoid putting patients at risk, the chemical composition of the drugs must be established using techniques such as vibrational spectroscopy, imaging, and mass spectrometry. Raman and Near Infrared (NIR) spectroscopy are both widely employed in the analysis of pharmaceutical tablet (solid dosage) formulations. Even though Raman spectroscopy does not involve sample preparation and samples are able to analyzed through packaging, it may be difficult to acquire good data/Raman spectra via inadequately homogenised solid dosage forms or fluorescent medications. NIR, on the contrary hand, produces spectra with wide peaks that have characteristics that are fewer specific and more suggestive of vibrational combinations and harmonics of oxygen-hydrogen (-OH), nitrogen-hydrogen (-NH), and carbon-hydrogen (-CH), as opposed to particular vibrations or rotations of functional groupings. Since it reduces the necessity for solvent extraction of the APIs/excipients, Fourier transform infrared (FTIR) examination of counterfeit drugs has been researched. (Custers et al., 2011) FTIR spectroscopy may tackle problems recognized through Raman and NIR spectroscopy. The spectral bands via FTIR spectroscopy are additionally more precise, resolving the drawbacks of NIR spectroscopy's weak specificity. In addition, no sample preparation is necessary; solid pharmaceutical formulations have been simply pulverized prior to analysis. Tablet analysis requires just sufficient powder to completely cover the top of a micro spatula. In an instant of seconds, the FTIR spectrum is acquired. This technique has been utilized predominantly for qualitative evaluation of drugs to date.

Finally, the rational and organized application of analytical information to generate forensic intelligence understanding into this offensive behavior as well as an information-led ability to combat it. Falsified/counterfeit medication screening is yet in their early stages, forensic studies being primarily a study interest. According to

findings in the illicit drugs area, it might generate very useful info on fake/counterfeit chains in order to investigating authorities (Salim et al., 2021). The objective of the study is to analyse various counterfeit and original drugs like Amaryl, Aircomb, and Diamicron MR by physical examination and using a FTIR spectroscopy.

1.2 Problem Statement

A counterfeit drug may contain insufficient or no active ingredients, may be inadequately processed within the body, such as absorption, or may contain unlisted ingredients. The counterfeiting of medicines is a growing hazard that is not restricted to developing nations, where it accounts for up to 40% of the market. In the case of antimalarials with insufficient amounts of active ingredients, for example, their use can lead to treatment collapse and increased resistance, or sometimes even fatality. Some individuals seek for less expensive medications. In rural areas of developing nations, these are commonly accessible from unauthorised outlets, where the prevalence of counterfeit medications is likely to be higher. In the past decade, the counterfeit drug threat has increased, and the present situation is alarming.

In forensic science, a criminal could exploit the use of these fake substances to endanger the victim's life. The investigator faces difficulty in identifying the counterfeit drug because its packaging and visual appearance are comparable to those of the original drugs. Little consideration is given to the potential of counterfeit medications as evidence to establish a connection between victim, suspect, and crime scene site by tracing the manufacturer information of the medications. Despite the fact that visual inspection is the first stage in the investigation process, most-often it is challenging to discriminate between counterfeit and authentic medicines due to their

strikingly similar appearances. Additional screening with FTIR spectroscopy facilitates chemical examination of the packaging and composition of medications.

1.3 Objectives of the Study

1.3.1 General objective

To profile original and counterfeit medications using FTIR analysis.

1.3.2 Specific Objectives

1. To perform preliminary screening of original and counterfeit medications drugs such as Amaryl, Aircomb, and Diamicron MR by physical examination.

2. To analyse the original and counterfeit medications of Amaryl, Aircomb, and Diamicron MR brands using FTIR spectroscopy.

1.4 Significance of the Study

The physical trace/evidence is essential for identifying the suspect or unauthorised seller at a crime scene, as well as the associated motives. Due to the paucity of prior research, the forensic importance of medications as trace proof was not fully studied or determined. The results of this study can be used to distinguish and categorise counterfeit and original medications that are likely to be used by criminal suspects to kill their victims or to regulate the illegal sale of counterfeit medicines that endanger people's lives.

In addition, the results of our study may help identify the manufacturer of medications with distinct chemical compositions. The displayed FTIR spectra can be used to classify each medication type and identify its manufacturer. Consequently, assisting the investigator or regulatory authorities in identifying the manufacturer. In comparison to other detection methods, such as NIR detection, which is laborious, devastating, and tedious, FTIR spectroscopy together with visual inspection can serve as an substituting approach for analysing traces of medications recovered at a crime scene. This approach is straightforward, quick, nondestructive, and capable of distinguishing between brands of matches based on their unique spectral characteristics.

CHAPTER 2

LITERATURE REVIEW

2.1 Definitions

The following are some examples of counterfeit or substandard medications:

According to the World Health Organisation (WHO), a counterfeit pharmaceutical is one that has been intentionally and fraudulently mislabeled with regard to its identity and/or source. Both branded and generic products are susceptible to counterfeiting, and counterfeit products may contain the correct or incorrect ingredients, no active ingredients, insufficient active ingredients, or counterfeit packaging.

According to IMPACT, 2003, a counterfeit medical product is one whose (a) identity (b) and/or source (c) have been misrepresented. This pertains to the product, its container, and any other packaging or labelling details. Counterfeiting is applicable to both branded and non-branded goods. Products with correct ingredients/components (d), incorrect ingredients/components, no active ingredients, incorrect concentrations of active ingredients, or counterfeit packaging may be counterfeit. Contradictions between patent violations and counterfeiting of medical products must be avoided. Medical products (generic or brand-name) that are not authorised for marketing in a given country but are authorised in another are not counterfeit. Original medical products with substandard batches, quality defects, or noncompliance with Good Manufacturing Practices/Good Distribution Practises (GMPs/GDPs) must not be confounded with counterfeiting.

Notably, (a) Counterfeiting is intentional and fraudulent. During legal proceedings, criminal intent and/or irresponsible behaviour shall be considered for imposition of sanctions. (b) It involves any misrepresentation of a product's name, composition,

efficacy, or other characteristics. (c) This refers to any false representation of the producer, country of manufacture, country of origin, market authorization holder, or distribution stages. This applies to every component of a medical product.

2.2 History of counterfeit drugs

In accordance to the International Institute of Research Against Counterfeit Medicines (IRACM), the origins of counterfeiting dates as far back as the second century B.C., when a Gallic winemaker tried to market his wine as a vintage of exceptional quality. In the year 40 A.D., Dioscorides, a Greek physician and botanist, established criteria for differentiating between genuine and counterfeit drugs (Al-Worafi, 2020).

Eventually in the 15th and 17th centuries, apothecaries became their own trade and were implicated in cases of tainted medications (Holloway, 1966). The Nairobi conference introduced the topic of counterfeit pharmaceuticals to the world stage for the very first time in 1985. First formal description of a counterfeit medicine was defined in 1992 at a meeting in Geneva (WHO, 1992).

In 2006, the WHO hosted the Rome Conference. Recognised as a grievous and terrible act that endangers lives and diminishes the credibility of healthcare systems, the counterfeiting of pharmaceuticals poses a significant threat to public health. IMPACT was founded as a consequence of this conference (Burns, 2006).

In October of 2009, in Cotonou, Benin, Jacques Chirac implored all nations to tackle the international trade of fake pharmaceuticals. The appeal was signed by 50 heads of state who were committed to the fight against counterfeit medicines (Al-Worafi, 2020).

Subsequently, in November 2010, the Council of Ministers of the African, Caribbean, and Pacific group held its 92nd session. Adopted a resolution to combat the production and distribution of counterfeit drugs. Efforts to combat counterfeit drugs were created and strengthened.

2.3 Prevalence

In developing nations, counterfeit and faulty drugs are more common than in developed nations. The actual number of fraudulent and subpar medicines has not been documented and may be challenging to determine because of multiple factors; nevertheless, the amount of counterfeit drugs varied from 10% of the worldwide market to as high as 60% in countries that are developing, according to the literature (Al-Worafi et al., 2020). Figure 2.1 shows globally reported incidents of counterfeit medications.

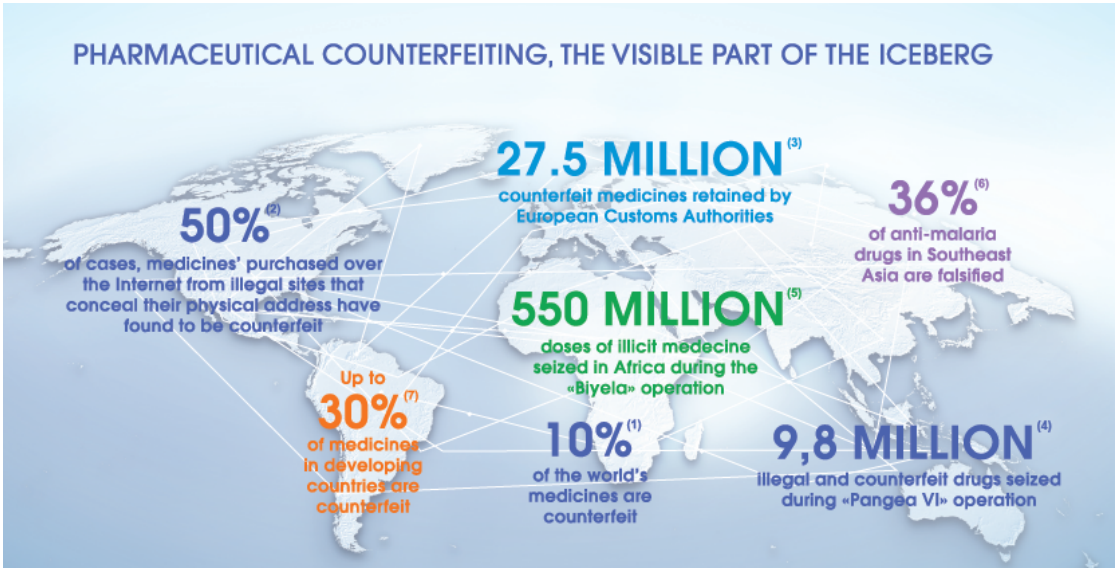

Figure 2.1: Global reported incidents of counterfeit pharmaceuticals. Adapted from (https://www.stibosystems.com/blog/how-data-can-help-fight-the-deadly-consequences-of-counterfeit-pharmaceuticals)

2.4 Types, factors, and risks of counterfeit medicines

Pertaining to the literature, counterfeit medicines include nearly all medications such as antimicrobials, anitmalarials, cancer, antiretroviral, antituberculosis, Hear

diseases, Diabetes, Analgesics, Herbal, Vaccines, Weight control, and others (Figure 2.2).

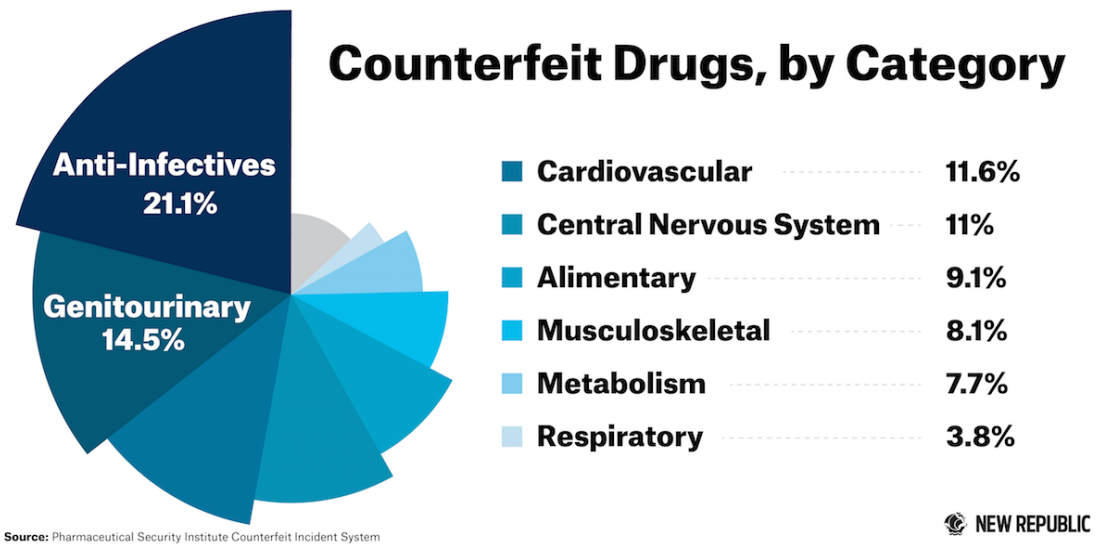

Figure 2.2: Global counterfeit drugs distributed by disease categories.

In the meantime, the counterfeit and unacceptable medicines are caused by the absence or fragility of drug regulatory organisations and laws, inadequate manufacturing quality, corrupt behavior and well-organized crime, insufficient implementation and penalties, scarcity of medicines, price of medications, cost, a lack of knowledge and internet commerce.

Counterfeit medicines pose several risks to the human health, industries, authorities, Ministries and Countries economy through increased morbidity; increased drug resistance; elevated death rate; elevated harmful impacts; treatment dropout; harming the components of health, fiscal losses to patients, families, healthcare bodies, and distributors and manufacturers of high-quality medications; massive wastage of financial and human resources in drug research and growth, dosage optimisation, policy discussion, clinical trials, and manufacturing; higher pressure for healthcare professionals, medication control bodies, customs authorities, as well as law enforcement (Figure 2.3) (Glass, 2014).

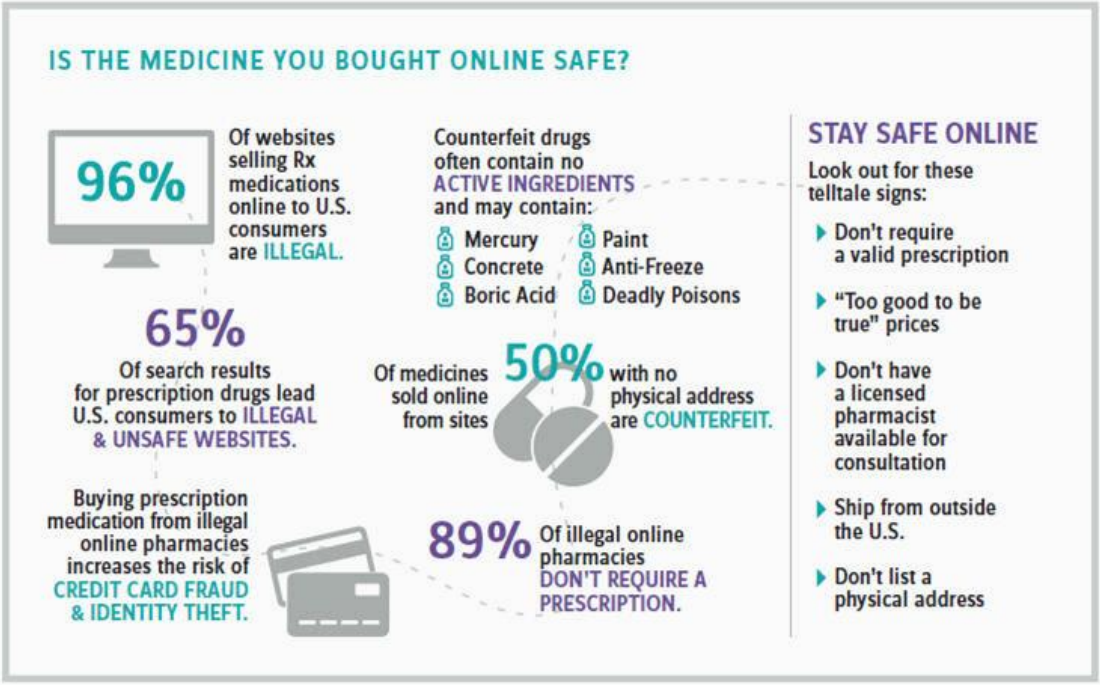

Figure 2.3: Different factors contributing to counterfeit drugs.

2.5 Overview of the counterfeit medicines market

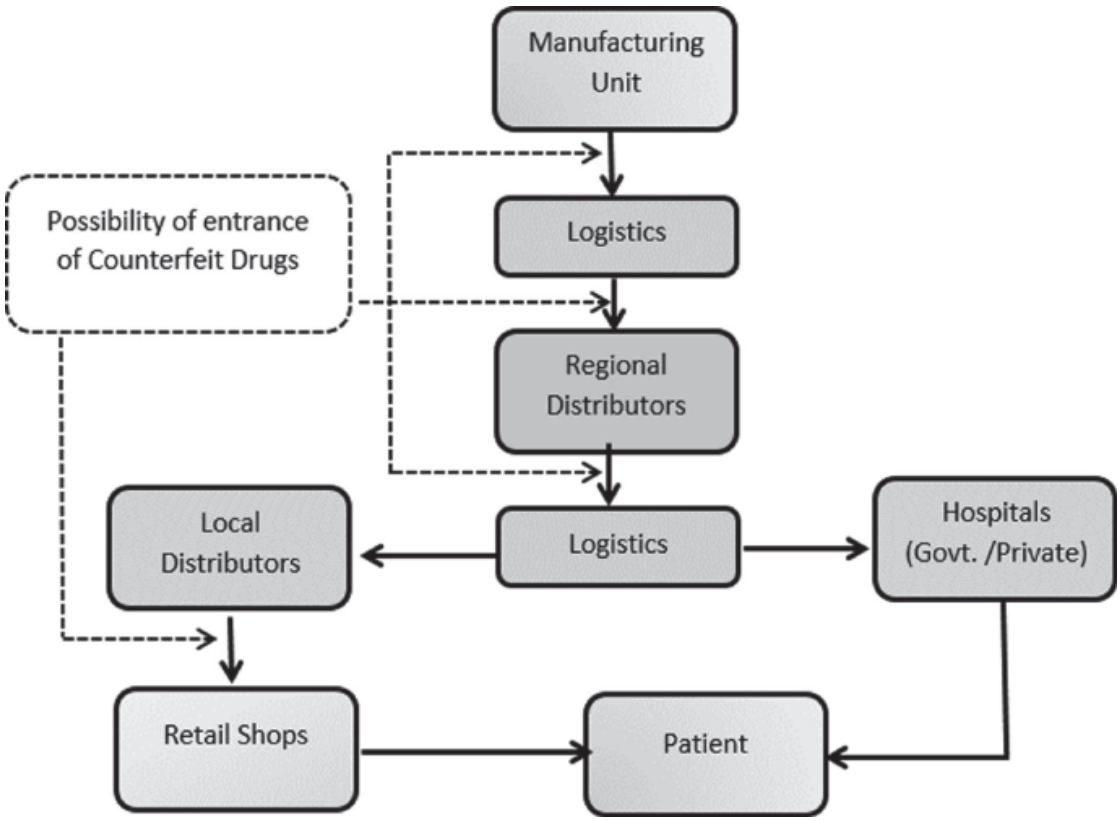

Figure 2.4: Blockchain framework for counterfeit medicines detection

As demonstrated in Figure 2.4, medicine falsification has turned into an organized market, having few parties such as manufacturers, distributors, along with the vendors and local dealers) involved in each and every stage of the drug supply network. Security elements on medicines, such as the manufacturer's packaging, logo, and outer seal, can easily be reproduced during the production phase and used on faked copies of the similar medicine to facilitate preliminary validation of the medication. Few dishonest pharmaceutical merchants and suppliers are even implicated in this organized syndicate (medicine counterfeiters), manipulating with medicine inspections, either done on the other side of the national border or by national modulatory institutions.

These pharmaceutical marketers and distributors wreak havoc on the industry by diverting medications from their intended path. Medicine diversion facilitates the smuggling of drugs into countries while avoiding mandatory security inspections. Healthcare facilities, drugstores, or medicine suppliers are frequently the final link in the drug circulation system as they deliver the necessary or prescribed medicines to consumers. Furthermore, Figure 2.4 suggests that unethical entities working in healthcare facilities, drugstores, and as medication sellers can still function as medicine falsifiers, particularly in locations where laws are inadequate.

Falsifiers of pharmaceuticals make a concerted effort to make the market complex so that FSM traffic is not detected (Roudaut, 2011). In addition, the counterfeit medications (for example: anti-cancer and anti-psychotic medications) that were identified to have been produced in China with French packaging and supplied to Singapore before being shipped to Liverpool and being distributed to the NHS in the United Kingdom (Townsend, 2009).

The paper by Townsend (2009) amply reveals the intricacies of the market for fake and subpar medications. This indicates that drug falsification may take place at any stage of the drug distribution process, but it must be carried out in a way that keeps the identity of the drug falsifiers a secret. Although outdated or expired stocks could be re-labelled as permissible and still in thier useful lifespan, discarded packaging for genuine medications, for example, may be retrieved and utilised to package counterfeit versions of the same product (Davison, 2011). Reusing the original packaging from acquired medications will give counterfeiters access to serial numbers and other credentials required to pass the FSMs during the initial screening of the medications as the genuine product.

2.6 Forensic Science and Counterfeit Drugs

2.6.1 Role of forensic scientist

The danger that counterfeit medications present to public health and safety has been established in prior chapters. Individuals and criminal organisations that manufacture and disseminate these items must be identified and brought to justice. (Office of the United Nations Drugs and Crime, 2014) Implementing this capability requires the application of sound forensic science.

Authenticity of counterfeit samples must be determined using court admissible analysis techniques. Categorization of these samples yields investigative knowledge that can be utilised to determine origin and identify counterfeiting organisations or groups. This ability must be conducted in the field in order to decisions regarding the authenticity of a sample can be made with no delay. Regularly and for a variety of reasons, fake drugs are traded in foreign countries far from their place of origin. (Dean,

2013). If a Customs agent were capable of quickly and effectively establishes authenticity, the import of these products to the target nation might be denied prior to their introduction into the local supply chain.

2.6.2 Forensic intelligence for medicine anti-counterfeiting

Based on the data from WHO, 10.5% of the world's pharmaceuticals were counterfeit (IMPACT, 2008). Manufacturing and process conditions endanger patients' health (Avery, 2008; Seiter, 2009). Indeed, numerous types lack any (API) Active Pharmaceutical Ingredient or are usually loaded with harmful substances (Martino et al., 2010). The economy as a whole is also under threat (Seiter, 2009; Roudaut, 2011; Wertheimer and Norris, 2009). There are various causes for the phenomenon's growth, including the difficulties in correspondence to the meaning of medication counterfeiting along with significant gaps at regulation and implementation (Newton et al., 2011; Seiter, 2009; Attaran et al., 2011). According to certain authorities (Reynolds and McKee, 2010; Hyeans, 2011), terrorist organisations and significant crime syndicates are both active in the counterfeit trade. Rapid communications, such as the online websites, further strengthened ties amongst criminal illegal networks. Moreover, rapidly, it became apparent that the packaging and chemical study's analytical data can be combined in order to generate forensic intelligence as well as better understanding into the process on three different levels (Dégardin et al., 2014).

To begin, rapid detection procedures can be created and deployed to expedite the management of falsified/counterfeit instances on a regional level. Whereas, rapid and effective identification of counterfeit medicines remains a study subject (Hu et al., 2006), many studies on the discrimination of counterfeit medications have been reported (Fernandez et al., 2008). Differentiating between genuine and counterfeit

products is no longer a problem, thanks to the abundance of analytical techniques which have shown to be efficient like spectroscopy and chromatography (Roggo et al., 2010; Sacre et al., 2010; Kwok and Taylor, 2012), which can be used in the laboratory or in the field (Degardin et al., 2010; Bate et al., 2009).

Next, when a falsified/counterfeit compounds are detected, their chemical constitution must then be identified in order to assess the risk to patients. Several analytical approaches, including as mass spectrometry, imaging, and vibrational spectroscopy, have been developed for this purpose (Ricci et al., 2007; Samms et al., 2011; Degardin et al., 2011).

The third phase is to employ analytical data logically and structuredly to generate forensic intelligence understanding into the criminal behaviour and an intelligence-led ability to deal with it. Falsified/counterfeit medication screening is currently in the early stages (Newton et al., 2008; Been et al., 2011), with forensic studies being a research focus. According to findings in the illicit substances area [38], it might generate very useful knowledge on counterfeit chains for investigating authorities.

The process of grasping a criminal event is referred to as intelligence (Figure 2.5). The process begins with the collection of relevant data using various analytical approaches. A database is created to store data from chemical and packaging analyses, much like a memory. Novel information keeps continually being reposited into the memory. Future memory analyses offer a present perspective on the phenomenon being studied, allowing both operational and strategic choices aimed at informing and influencing decisionmakers.

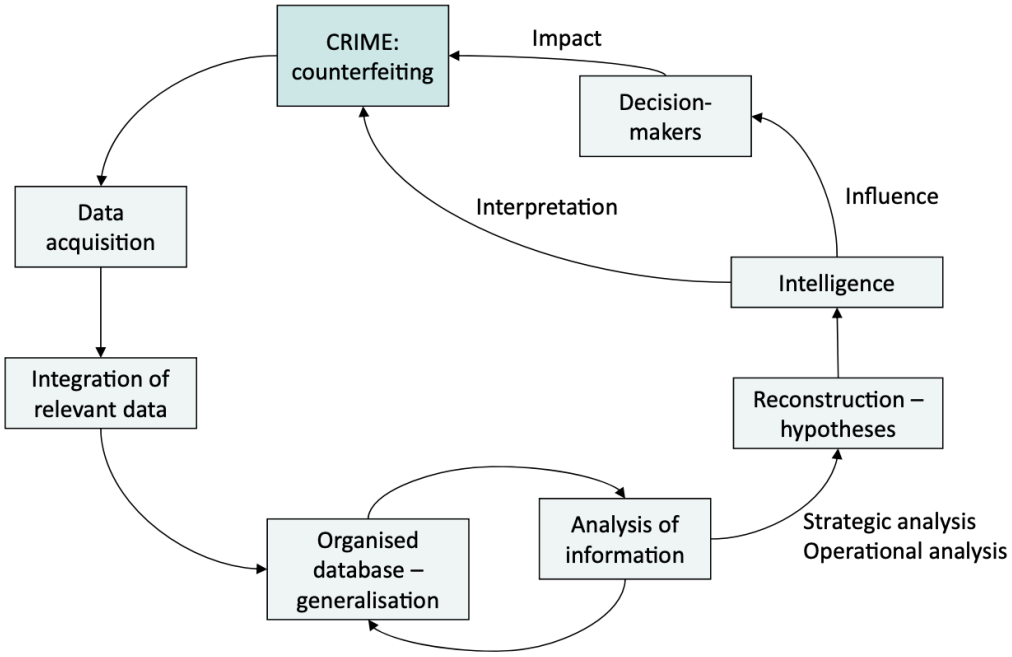

Figure 2.5 Key steps of iterative process of intelligence applied to counterfeit analysis (adapted from Ribaux and Margot, (2003))

2.7 Drug Abuse

Addiction to drugs is a global issue, whether it involves high-risk substances or off-label usage of authorised medications. This dynamic, multifaceted problem impacts all age groups, particularly those aged 14-35 (Concheiro et al., 2010; Brunet et al., 2008). Abuse and substance addiction, as well as their implications, are one of the most pressing issues across the globe. This is because of the significant impacts on the individual, familial, and social levels (crime, social exclusion, and death by overdose or suicide) as well as the economic level: not only the costs of treatment for viral and bacterial infections related to intravenous drug use (AIDS, HCV, or recurrence of TBC), as well as the costs of treatment for dependence. Drugs of abuse are substances with legal restrictions on possession, transit, and storage due to potential harm to consumers. These include licenced and illicit items, as well as natural products (Baconi et al., 2013).

2.7.1 Antidiabetic drugs

At least 20% of insulin or oral antidiabetic medication users have hypoglycemia once in their lifetime. Type 2 diabetes mellitus is treated with the second-generation medications glimepiride and glibenclamide, which stimulate the release of insulin and are members of the sulfonylurea group (Zhong et al., 2005; Krentz et al., 2005). There are several classes of oral anti-diabetic medications, such as alpha-glucosidase inhibitors, metformin, thiazolidinediones, and sulphonylureas. Most hypoglycemia cases are caused by glucose-lowering drugs like insulin and sulfonylureas, which enhance circulating insulin gradually. Furthermore, hypoglycemia is commonly documented in metformin overdoses and glibenclamide poisonings (Al-Abri et al., 2013). Oral antidiabetic medications can result in fatal hypoglycemia; despite the fact that they can be chemically identified and quantified, biochemical investigations are necessary for determining the biological effects of an overdose. In cases involving an oral antidiabetic overdose, other lifestyle-related medications, particularly antihypertensives, may also be ingested. There are numerous clinical reports of calcium channel blocker toxicity (Adams and Browne, 1998).

Furthermore, hypoglycemia caused by antidiabetic drug overuse or abuse, as well as various pathological diseases, may be associated with unexpected or violent death. Previous studies in forensic biochemistry have suggested that vitreous humour could be used as postmortem evidence for glucose measurement to examine metabolic diseases in diabetes mellitus because serum glucose levels change during and after death, whereas HbA1c, a biochemical marker, is relatively stable (Thierauf et al., 2009).

Gliclazide is one of the sulphonylureas employed for the treatment of type 2 diabetes, which produce the release of insulin by inhibiting ATP-dependent potassium

channels within pancreatic ß cells. This appears in an extended decrease in blood sugar levels throughout both short- and long-term administration.

Due to hypoglycemia, treating with sulphonylureas may prove potentially fatal (Inkster et al., 2012). Additionally, sulfonylureas have been linked with an increased likelihood of cardiovascular events compared to other anti-diabetic medications, but gliclazide is regarded as the drug with the lowest cardiovascular-related mortality within this class (Simpson et al., 2015). Because the biological time of action of sulfonylureas typically is not correlated with their half-life or blood concentration, it is challenging to determine "toxic" ranges for these types of medications. It has been established the fact that the likelihood of hypoglycemia is greater with long-acting sulphonylureas than with short-acting sulphonylureas.

2.7.2 Anti-inflammatory drugs

NSAIDs are a structurally heterogeneous group of drugs with a common mode of action (reversible inhibition of cyclooxygenase). They are widely utilised for their analgesic, antipyretic, and anti-inflammatory properties and can be found in pharmaceutical formulations, compound analgesic products, and cough and cold remedies. Each year, more than 70 million NSAID prescriptions are written in the United States. In the United States alone, more than 30 billion doses of nonprescription anti-inflammatory drugs are ingested annually (Wiegand and Vernetti, 2016).

The majority of frequently used NSAIDs possess a handful toxic effects, despite being taken in large quantities; however, as prescriptions and consumption of over-the-counter (OTC) NSAIDs increase annually, so do the amount of overdoses and NSAID-related challenges according to poison control centres across the country (Rainsford, 2003). The underlying cause of toxicity of NSAIDs in overdose tends to be primarily

due to excess suppression of COX-1 and consequent reduction of prostaglandin synthesis. The accumulation of acidic metabolites, not COX inhibition, is responsible for the metabolic acidosis seen in severe NSAID toxicity. In both medicinal use and acute overdose, the digestive, renal, and central nervous systems (CNS) are primarily affected. It is also known that NSAIDs are highly cytotoxic to the gastric mucosa. This causes gastrointestinal symptoms, ranging from nausea and moderate abdominal pain to gastric/duodenal ulcers and gastrointestinal haemorrhage, with prolonged use.

In those who have normal physiological regulation of renal blood flow, therapeutic doses of NSAIDs are unlikely to cause nephrotoxicity. Ibuprofen remains the NSAID with the largest amount of published data in acute overdose, and several studies of large series corroborate that the vast majority of patients with ibuprofen toxicity exhibit few significant clinical manifestations. Several reports of mefenamic acid overdose emphasise the drug's propensity to induce convulsions in acute overdose (Balali-Mood et al., 1981).10 Significant clinical sequelae, such as renal failure, acid/base disturbances, and CNS toxicity, have been reported in a subset of patients with extremely high NSAID overdoses.23–42 NSAID-related fatalities are frequently confounded by coingestants, although isolated NSAID-related fatalities have been reported (Wood et al., 2006). Table 2.1 shows the list of few cases of fatalities caused due to NSAIDS.

Table 2.1 Some cases of fatalities involving NSAIDS.

Patient	NSAID	Dose	Serum level	Co-ingestants	Symptoms/signs	Treatment	Comments
67 year old female	Ibuprofen	Unknown	440 mg/L	Aspirin (240 mg/L)	Hyperventilation, confusion, hearing loss, cardiac arrest	Not documented	Features consistent with aspirin toxicity
3 year old Child	Indomethacin	75 mg	0.19 mg/L	Naftidrofuryl oxalate	Vomiting, seizure, reduced GCS	Intubation and ventilation "Supportive treatment"	Death attributed to co-ingestant
16 months old	Ibuprofen	469 mg/kg	Unknown	Nil	Apnoeic episodes, aspiration, pneumonitis	Supportive	Death due to infective complications
70 year old female	Flurbiprofen	Unknown	Unknown	Ethanol 1000 mg/L	Dead on arrival	Not applicable	History of Chronic Obstructive Pulmonary Disease (COPD)
48 year old male	Ibuprofen	Unknown	80.8 mg/L PM	Paracetamol Level 200 mg/L at postmortem Ibuprofen 80.8 mcg/ml	Found dead	Not applicable	High risk patient – Cachectic History of repeated suicide attempts. Significant paracetamol co-ingestion
Child	Indomethacin	Unknown (30–40 tablets strength not stated)	Unknown	Nil known	Vomiting and drowsiness two days post ingestion. Cerebral edema and subsequent respiratory arrest	Intubation and ventilation Supportive treatment	Unsurvivable brain injury

2.8 Methods for Analyzing Counterfeit Medicines

According to Marini (2010) and Dégardin et al. (2014), to make it possible for pharmaceutical companies as well as other regulatory authorities to initiate prompt action against the falsification of pharmaceutical products, analytical methods for medicine authentication must first be able to identify or differentiate between authentic and counterfeit medications.

2.8.1 Preliminary screening

The screening process for counterfeit and subpar medications is started with a visual assessment of the medications. The information is then compared to that of the actual product after a careful study of the suspected medicine's label, container, and contents. Examining characteristics like holograms, logos, taggants, and printing is part of the visual inspection process for packaging materials such boxes, leaflet inserts, blister packs, and vials (Deisingh, 2005; Rodomonte et al., 2010; Shah et al., 2010; Ortiz et al., 2012). Although this is not always possible, physical properties of the dose form, such as colour, weight, and shape, can be assessed and compared with reference samples of the medication. Despite this, due to the complexity of counterfeiters who employ high-tech machinery to create almost identical replicas of genuine medications, physical inspection is unable to distinguish between genuine and counterfeit drugs (Rodomonte et al., 2010; WHO, 2017).

2.8.2 Authentication techniques

Spectroscopic techniques are often used to evaluate counterfeit and inferior medications since they are quick and need little or no sample preparation (Sacré et al., 2010; Kovacs et al., 2014). Whereas such spectroscopic methods tend to be more expensive than the early detection procedures discussed in 2.2.1 (about £50,000), they are faster, more durable, highly sensitive, and portable, and hence are able to be used for research in the field. Mid-Infrared (MIR) spectroscopy, also known as FTIR spectroscopy (Farouk et al, 2011), NIR spectroscopy (Moffat et al, 2010; Assi et al, 2011), as well as Raman spectroscopy (Dégardin et al, 2011), can all produce measurements and analyses in minutes. Direct observation of overlaid spectra or mathematical models (chemometrics) can be used to identify suspect counterfeit drugs.

ATR-FTIR requires direct sample-to-crystal contact; therefore, samples must be removed from their packaging prior to analysis. Raman spectroscopy is a scattering technique, whereas FTIR and NIR spectroscopy are absorption techniques (Martino et al., 2010; Zou et al., 2017). Furthermore, NIR imaging data (Puchert et al., 2010) and Raman microscopy (Kwok and Taylor, 2012) present straightforward and easy-to-understand information on the drug's legitimacy. Hand-held devices, notably Raman and NIR spectrometers, are able to be used in the field in order to verify the legitimacy of the dosage form's contents (Hajjou et al., 2013; Ricci et al., 2008). Table 2.2 enumerates the various comparison instruments used to distinguish between counterfeit and authentic medications.

Table 2.2 Devices for identifying counterfeit and substandard pharmaceuticals are compared.

Technique	Use/Purpose	Performance	Needs sample preparation	Speed	Training required	Cost*	Facility requirements	Reference(s)
Colorimetry	Preliminary classification/assessment	High specificity (0.94-1.00)	Yes	Fast	Lab. technician	Low	Portable	Green et al, 2000; Chikowe et al, 2015
Paper chromatography cards	Preliminary classification/assessment	High sensitivity (0.92-1) and specificity (0.88-1)	Yes	Fast	Lab technician	Low	Portable	Koesdjojo et al, 2014
Counterfeit Device #3	Chemical profiling with visual inspection	Unknown	No	Fast	Minimal training	Low	Portable	Batson et al, 2016; Platek et al, 2016
PharmaCheck	Chemical separation, identification and quantification	High specificity with dissolution component detected within 3%	Yes	Fast	Lab technician	Low	Portable	Amirfar, 2016
TLC-GPHF-MiniLab	Chemical separation, identification and quantification	Low as it is only able to detect wide variation/disparities in the expected amounts of API I the medicine	Yes	Fast	Lab technician	Low	Portable	Risha et al, 2008; Kaale et al, 2011; Petersen et al, 2017
Near Infrared Spectroscopy	Chemical profiling	Medium	No	Fast	Lab technician	Medium	Portable	De Peinder, 2008; Dégardin, 2016; Rodionova et al, 2018
Raman Spectroscopy	Chemical profiling	Medium	No	Fast	Lab technician	Medium	Portable	De Peinder, 2008, Hajjou et al, 2013; Rebiere et al, 2017
Fourier Transform Infrared (FTIR) spectroscopy	Chemical profiling	Moderate as it analyses only the surface of the sample	No but samples is dispersed in a matrix	Fast	Lab technician	Medium	Portable	Farouk et al, 2011
Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR) spectroscopy	Chemical profiling with quantification of APIs	Medium and simpler than FTIR	No	Fast	Lab technician	Medium	Portable	Custers et al, 2015; Lawson et al, 2018