Investigating the Prevalence, Knowledge and Regulations Regarding Counterfeit Medicines

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ABSTRACT

The aim of this thesis is to investigate and quantify the prevalence, knowledge and regulations regarding counter medicines. Using various methods and analytical tools to aid in this investigation.

The problem of counterfeits is an ever-growing issue, especially with regards to the increase of production and sales of counterfeits. These medicines show to have an increasing health risk to the public. Everyone is at risk. On record 50% of products sold are counterfeits and 30% of those are counterfeit medicines.

The information that is widely known about counterfeit medicines is that they pose public health risks and how the chemical composition is a key to determining them. What is not widely known is the connection throughout the supply chain, from manufacturer to the individuals that are at risk.

The data used for this research includes; product data consisting of tablet, powders and mixture forms, individual opinions collected via questionnaire, background research about counterfeit medicines, specifically the directives used in place as a preventive measure and lastly the data collection for characteristics of online pharmacies.

The instrumentation used for the FT-NIR determination of counterfeit pharmaceuticals was made on the PerkinElmer Spectrum Two N Fourier-Transform Near Infrared Spectrometer. The data sets were processed via the use of standard normal variant second derivative spectra (SNV-D2).

The identification of the counterfeit medicines was a success along with identifying partial trends to how the public perceives self-prescription and their opinions of counterfeit medicines. Strengths and limitations regarding the new directives were also identified leading to possible adaptations to fortify the prevention of counterfeits being supplied in the future.

It is hoped that this research will inform practitioners about the management practices for preventing counterfeit medicines from entering the supply chain and endangering the public's health.

ORIGINALITY REPORT

I hereby certify that I am the sole author of this thesis and that no part of this thesis has been published or submitted for publication.

I certify that, to the best of my knowledge, my thesis does not infringe upon anyone's copyright nor violate any proprietary rights and that any ideas, techniques, quotations, methods or any other material from the work of other people included in my thesis published or otherwise are fully acknowledged in accordance with the standard referencing practises.

I declare that this is a true copy of my thesis, including my final revisions and amendments as approved by my thesis review board, and that this thesis has not been submitted for a higher degree to any other University or Institution.

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Abbreviation	Meaning
API	Active Pharmaceutical Ingredient
ATD	Anti-tampering Device
AVC	Atmospheric Vapour Compensation
AVI	Absolute Virtual Instrument
APV	Automatic Performance Verification
CDER	Centre for Drug Evaluation and Research
CHM	Commission on Human Medicine
CPRD	Clinical Practice Research Datalink
CSM	Committee on the Safety of Medicines
CVC	Card Verification Code
CWS	Correlation in Wavelength Space
D1	1st Derivative
D2	2nd Derivative
DPD	Data Protection Directive
DNA	Deoxyribonucleic Acid
EAASM	European Alliance of Access to Safe Medicines
ECHR	European Convention on Human Rights
EDQMH	European Directorate for the Quality of Medicines and Healthcare
EIMSC	Extended Inverse Multiplicative Scatter/Signal Correction
EMA	European Medicines Agency
EMSC	Extended Multiplicative Scatter/Signal Correction
EMVO	European Medicines Verification Organisation
EMVS	European Medicines Verification System
EU	European Union
EUC	European Union Council
FDA	Food and Drug Administration
FMD	Falsified Medicine Directive
FT	Fourier-Transform

FT - IR	Fourier-Transform Infrared Spectroscopy
FT - NIR	Fourier Transform Near Infrared Spectroscopy
GC	Gas Chromatography
GC - MS	Gas Chromatography & Mass Spectroscopy
GDPR	General Data Protection Directive
GMC	General Medicine Council
GMP	Good Manufacturing Practice
GPP	Good Procurement Practice
GPD	Goods-Distribution-Practice
GPhC	The General Pharmaceutical Council
GPRD	General Practice Research Database
GSLM	General Sales List Medicines
HPLC	High Performance/Pressure Liquid Chromatography
ICDRA	International Conference of Drug Regulation Authorities
IMPACT	International Medicinal Products Anti-Counterfeiting Taskforce
IMSC	Inverse Multiplicative Scatter/Signal Correction
IR	Infrared
LiTaO3	Lithium Tantalite
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MDCWS	Maximum Distance in CWS
MDPCA	Mahalanobis Distance in PCA
MHRA	Medicine and Healthcare Regulatory Agency
Mid - IR	Mid- Infrared
MS	Mass Spectroscopy
MSC	Multiplicative Scatter/Signal Correction
NCA	National Competent Authorities
NHS	Nation Health Service
NIBSC	National Institute for Biological Standards
NIR	Near Infrared
NW	Norris-Williams Derivatives

NMVS	National Medicine Verification System
OECD	Organisation for Economic Co-operation and Development
OTC	Over the Counter
PCA	Principle Component Analysis
PCR	Principle Component Regression
PC	Principle Components
PLSR	Principle Least Squares Regression
PMDA	Pharmaceutical and Medical Devices Agency
POM	Prescription Only Medicine
Px	Prescription
S/N	Signal to Noise Ratio
SFFC	Spurious / Falsely Labelled / Falsified / Counterfeit
SG	Savitzky-Golay Derivatives
SIMCA	Soft Independent Modelling of Class Analogy
SNV	Standard Normal Variate
UI	Unique Identifier
UK	United Kingdom
US	United States
WHO	World Health Organisation

Chapter One: Introduction

1.1 Introduction

Counterfeit products occur in all aspects of life, be it what we eat, what we wear and even in how we simply tell the time. As progress is made in each field of knowledge, there is an environment being produced where either individuals or organisations can attempt to gain an unfair profit from the market. This is where counterfeits are produced via false advertisements, duplicates and modified products (Eser et al. 2015).

Unfortunately, medicinal products, even those that are lifesavers, cannot escape the problem of having counterfeit versions.

The use of medicinal products has been documented for over 60,000 years. Physical evidence of the use of herbal remedies was found in a burial site in Shanidar Cave in Iraq, showing a Neanderthal man buried with a variety of plants and herbs surrounding him.

Nine plants and herbs were found to be surrounding him, seven of which are used for medicinal purposes to this day. Among those found were ephedrine, daises, blue bonnets, grape hyacinths, hollyhocks, St Barnaby's and other thistles. Neanderthals lived from about 200,000 years ago to roughly 30,000 years ago (Lietava 1992).

With this find, it shows that medicine has been synthesised to aid in the alleviation of ailments first with the use of simple plants such as ephedrine, later moving on to more advance substances such as cannabis and more (Duffin 2016).

Over the years this then progressed onto more synthetic medicines that would help reduce pain, infection or diseases that once eradicated the populations of the world, such as smallpox, which was finally eradicated with a vaccine (Riedel 2005).

With the development and advancement in medicines, the distribution of such products also adapts, thus creating openings in the chain for counterfeits to be placed.

This section will discuss the following issues of counterfeit medicines; the history, what they are, the distribution and how widely spread they are, why are they perceived to be a problem, the regulation and industry practices regarding them.

1.2 History of Counterfeits Medicines

Medicines are an essential part of society, the public perception of them is an avenue that is hardly explored in great depth. As the need for medicines rises, the need for profit and gain on such expenditures also increases.

This enables a way for more advanced counterfeit medicines to be produced, which could in turn cause more harm than good to the wellbeing of the public (Houston 2012).

In the last few decades there has been huge strides in the; advancement in the scope of science, history being made and multiple creations in technology. One of the main improvements to our knowledge base as a society was the creation of the Internet. With the Internet came vast openings in the marketplace for a variety of trades and the method of sales (Brady 2020).

Before the Internet was created medicines were bought from brick-and-mortar pharmacies where a doctor would advise with the patient and prescribe the correct medicine. With the use of the Internet, medicines can be bought online and delivered to your door.

This has had profound changes in society. For instance, in 1983 before the Internet went online, 18% of medicines were domestically produced and distributed, rising to 75.5% in the year 2000 (née Lybecker 2020).

For society the populace is overworked, stress builds up and mental illness is everywhere. The struggle that goes on opens and creates doors for counterfeits to be passed through. Counterfeits at the base of the problem are created for a gain in profit.

With the stress of illness building up around the United Kingdom (UK) there has become a shortage of medicines to cope with the excess. This of course opens avenues

for profiteers to take advantage of, and with a new avenue of distribution such as the Internet becomes available (Buckley & Gostin 2014).

Unfortunately, the end user base (the consumer) is not considered when data is collected, when identifying perspective on counterfeits, or purchases of medicines.

Often, the manufacturer, chain of supply and other points of entry in the purchase scheme are mainly focused upon during analysis by health care professionals (Settanni et al. 2017). This causes issues as we do not know the scale of consumer knowledge with regards to process of purchasing medicines.

In some countries brand named medicine are treated as authenticate and non-brand names are treated as counterfeit, whereas that may not be the case at all. This is often overlooked when samples are tested, and in the end, there is a lack of protection for the end users who really need the health care (Settanni et al. 2017).

With regards to counterfeit medicines, there is no discrimination between developing and developed countries, both being at risk. Developing countries are more at risk with having counterfeit medicines such as antibiotics, anti-tuberculosis, anti-malarial and anti-AIDS drugs.

Developed countries are more likely to suffer with having counterfeit lifestyle medications such as anti-cancer, anti-hypertensive, hormonal and anti-cholesterol drugs, (World Health Organisation, 2010).

1.3 Counterfeit Medicines

Due to the changes that society has undergone, and the fact that our knowledge has expanded, the overall definition of a counterfeit medicine has changed. Since 2010 when the World Health Organisation (WHO) stated that "*Counterfeit medicines are deliberately and fraudulently mislabelled with respect to identity or source*" (World Health Organisation 2010) the definition has now been adapted to include "*spurious / falsely labelled / falsified / counterfeit (SFFC) medicines*" (WHO 2018).

The European Union Council (EUC) on the other hand classifies a falsified medicinal product as something else entirely. As definitions change, the appropriate policing alters to accommodate the relevant laws which in turn drives further definition changes.

With regards to SFFCs, the WHO is concerned with life-threatening aspects to public health. Other substandard medicines do not always qualify under the definitions of a counterfeit (Newton 2011).

As there are many terms that can be used for the description of a counterfeit, it is prudent that there is distinguishability between a substandard drug and a counterfeit, and what is known as a fake or falsified version.

Counterfeits are not genuine in any form and are made simply to gain profit. This is also the same with a falsified medicine, with the aid of false advertising and other false production methods.

Substandard drugs however are genuine for the most part. What makes them different is that they fail to fulfil or achieve the quality specifications that are set for drugs to pass, depending on the governing bodies' regulations and standards (Wertheimer 2003, Wertheimer 2005).

This is most commonly the result of a defect in the manufacturing process. The terminology and distinction between substandard and counterfeit medicines becomes more complex when despite having understanding knowledge of the defect it is still supplied.

If a substandard drug is known to have been produced, yet is knowingly fraudulently labelled and sold, the drug then becomes a counterfeit. The simple act of *Mens Rea* can subtlety change the defining characteristic of a batch of medicine or drug, and the crime committed.

It is important to understand and be able to identify the differences between them. Even though they can both be harmful, a substandard drug is mainly manufactured from a known source and thus the authorities can work with the manufacturers to limit the risk to public health and stop production.

An example of this would be in 2011, when a drug that prevented blood clots was removed from the market. This was because the manufacturer responsible for the medicine in question, noticed an error with the chemical makeup of the medicine and voluntarily removed it.

The error that was identified was that the level of the Active Pharmaceutical Ingredient (API) in the formula was incorrect for that medicine (Fan et al. 2018).

Counterfeit medicines are identifiable from their authentic counterparts on a chemical level, thus when examined more closely by sensitive instruments they can be identified (Newton 2011).

The most crucial part of any drug formulation is the level of API present. The various concentration and deviations from the published amount determine what type of medicines they are; substandard, counterfeit or authentic.

1.3.1 Substandard Characteristics:

- Impurities/ Unknown Ingredients (Alumuzaini 2013):
  - Substandard weight or a tablet or capsule.
  - Altered odour due to diluted API or harmful additives Inactive or harmful ingredients, impurities, or contamination such as meld.
- Reduced bioavailability and stability (Hogerzeil 1991; Pandit 1997; Nazerali 1998; Risha 2002; Rimoy 2002; Kayumba 2004; Lon 2006; Alumuzaini 2013):
  - Solubility or release of API is not within the specified time range due to reduced stability of the drug, and this leads to reduced bioavailability of the antibiotic.
  - Most of the limited number of studies that have assessed the stability of antimicrobials had suboptimal design.
  - Antibiotics such as ampicillin, but not others such as penicillin and tetracyclines, may degrade with high temperatures and humidity.

- Reduced bioavailability may lead to suboptimal activity of antimicrobials; examples include antibacterial such as cotrimoxazole, tetracyclines and metronidazole and antiparasitic agents such as chloroquine, mefloquine and pyrimethamine.

- Reduced concentration of API: (Nazerali 1998; Reidenberg 2001; Rimoy 2002; Moken 2003):
  - Quantification of the API content of an antimicrobial agent shows that the concentration of the API is lower than the claimed content declared on the packaging.
  - Poor manufacturing or transportation, decomposition, and poor storage conditions and dilution of drugs with other chemicals may lead to low concentration of the API.

1.3.2 Counterfeit Characteristics:

- Reduced volume of API (Alumuzaini 2013):
  - The antimicrobial may be considered counterfeit when the substandard amt of the API is included deliberately in the drug.
- No API available (Ten Ham 1992; Newton 2001; Rozendaal 2001; Kelesidis 2007; Delepierre 2012; Alumuzaini 2013):
  - Quantification of the API content of an antimicrobial agent shows that the API as declared on the packaging is absent.
  - Antibiotics may contain no API.
  - The AI is replaced by cheap substances, such as flour in oral presentations and water in drinkable or injectable presentations.
- Increased Volume of API (Alumuzaini 2013;):
  - The concentration of the API may be higher than the amount reported in the packaging.
- Altered chemical content (incorrect ingredient or false substitution) (Ten Ham 1992; Rozendaal 2001; Moken 2003; Kelesidis 2007; Delepierre 2012; Alumuzaini 2013):

    - Detection of AI in the drug that is not declared on the packaging
    - These products may contain toxic chemical impurities
    - Examples of wrong ingredients include erythromycin, flour, starch, or powder, and tap water.
- Failure of the mass uniformity test (Alumuzaini 2013):
    - The weight of a tablet or capsule is not within the average range specified (if done deliberately and not the result of poor manufacturing).
- Inappropriate packaging (Sesay 1998; WHOa 1999; WHOb 1999; Gaudiana 2010; Alumuzaini 2013):
    - Packaging has incorrect labelling information about a drugs origin or authenticity, and the colour, size of pills, and bar codes are often similar to those for the original drug.
    - False representation of identity is commonly used, by copying the packaging of another marketed product; the brand name may be modified to try to escape laws on infringing intellectual property
    - They are generally undisguisable in their outward packaging
    - In developing countries, many of the purchased drugs without packaging were counterfeit.
    - Antimicrobials with false packaging and labelling include penicillin's, co-trimoxazole, tetracyclines, chloramphenicol, quinolones, aminoglycosides and antimalarials.

There are four main categories of medicines: (i) those that contain the incorrect API, (ii) those that contain the correct API but an incorrect dosage level, (iii) those with no API (e.g placebos), and lastly (iv) those with the correct API and the correct dosage (Krekora 2008).

Another classification of a counterfeit, a more complex version, is when the API is the correct chemical but the wrong isomer, either (R) or (S). On a rare occasion this version finds it way on the marketplace.

One such example of the (R) or (S) medicine isomer is that of ibuprofen, the (R) being ineffective compared with the effective (S) version as seen in figure 1.

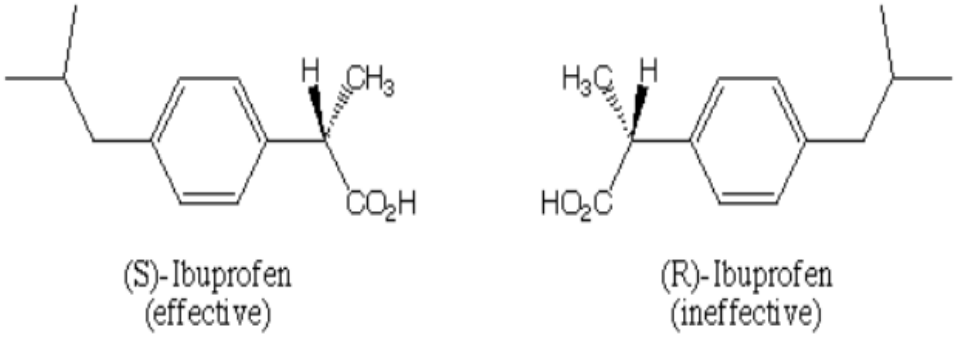


Figure 1:FThe comparison between (S) and (R) isomers of ibuprofen to illustrate the mirror images of the compound that leads to different properties of the compound overall and how they interact within the body. (Singh et al. 2009)

Further research is being completed regarding the potential of ineffective isomers being distributed along the supply chain. Ineffective isomers cause the same problem as counterfeit medicines themselves.

The isomers control if the mixture is an active or inactive ingredient, thus it is responsible for how a medicine effects the individuals

But what is the true difference between the R and S isomers? The letter 'R' comes from the Latin word 'Rectus' meaning right-handed which gives way to the relative direction of order in which the isomers rotate in the clockwise direction.

This is visible – under a microscope - when light is passed through the sample. The letter 'S' however comes from the word 'sinister' meaning left-handed justly meaning the isomer rotates in an anticlockwise direction. These rotational directions of order are seen when light is shined through the mixture.

1.4 Distribution of Counterfeits

Unfortunately, with a profit to be gained, no country, product or manufacturer is exempt from the possibility of counterfeits being placed in the supply chain. Over 10% of all counterfeit products are counterfeit medicines.

Counterfeit medicines are one of the most severe threats to public health (Dégardin 2014) due to 50% of products being bought over the Internet, of which 30% are a counterfeit version of the product being advertised (Sacré 2010).

Regrettably, a high percentage of counterfeit medicines are accounted for with purchases over the Internet. Most of the time the medicines are from an unknown source.

According to the WHO:

> *"A product that is deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting occurs with both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredient or with insufficient active ingredients" (WHO 2012).*

In 2018, the WHO Global Surveillance and Monitoring System recorded 17% of the total reports were on antibiotics and 20% were on anti-malarial drugs, which makes the antimicrobials the largest falsified and substandard drugs category.

These numbers may not be an accurate representation as some countries do not have the ability to test for poor quality drugs, and some countries do not report to the system (WHO 2018).

The most common counterfeits are antimicrobials (38%), hormone treatments (22%), antihistamines (17%), vasodilators (7%), and drugs for erectile dysfunction (5%) and anticonvulsants (2%) (Krakowska 2016).

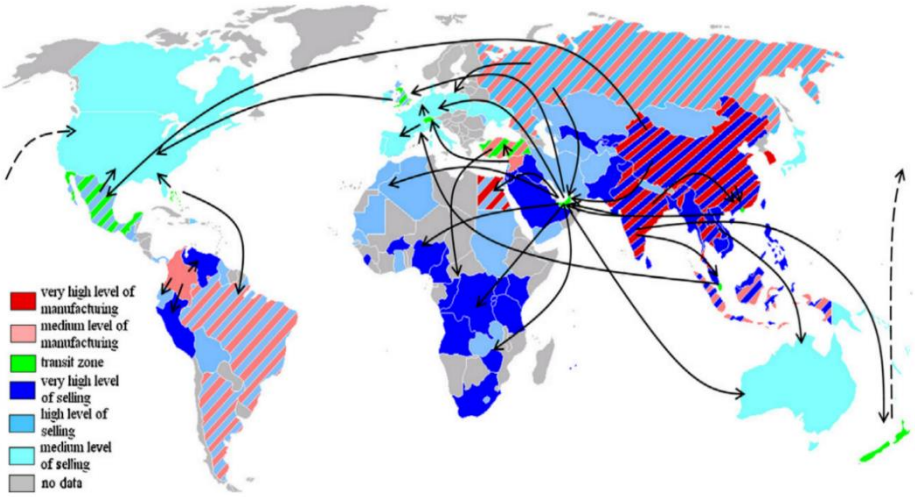


Figure 2: An illustration of the global transportation of counterfeiting medicine from around the world, demonstrating how large of a reach this market has. It also shows the paths from the producers/manufacturers to the local sellers and thus the consumers. (Dégardin 2014)

The progression of counterfeit medicines within the industry has created links between distributors, local sellers, manufacturers and wholesalers. The links can be seen in figure 2 which shows that counterfeits can be found almost anywhere.

Even countries such as Germany, France, Spain and the United Kingdom (UK) are not immune for the problem that is counterfeit medicines, as can be seen in figure 2. This illustrates that nowhere is safe from counterfeits, due to the process in the supply chain.

1.5 Counterfeit Medicine Consequences

Counterfeit products can be extremely dangerous and detrimental to a patient's health. The best-case scenario of a counterfeit medication being used is that the product can be harmless like a sugar pill, whereas on the other hand they can be lethal.

This is because, even at the best of times, medicines have a toxic effect on the body, whereas in worst case scenarios they cause death. This is a serious problem as in some cases these drugs are intended to be lifesavers (Blackstone et al. 2014).

In 2005, a 23-year-old male was admitted to a rural hospital in eastern Burma with a fever and was diagnosed with uncomplicated hypercarotenemic falciparum malaria by microscopy (where he had 4.2% infected red blood cells).

Consequently, he was given 4 mg/kg of oral artesunate, which was a common treatment in that area. However, on the third night he became comatose when he was injected with intravenous artesunate in response to kidney and liver failure.

Subsequently, he died of cerebral malaria. The original hospital sent the artesunate medicine that was used as treatment for analysis (Islam et al. 2018). The Fast-Red dye test was conducted, and it was found that the medicine administered was counterfeit.

Regrettably, it was not an isolated incident. In 2018 the WHO reported that 158,000 people die each year from counterfeit anti-malarial drugs in sub-Sahara Africa alone (Christensen 2020).

As medicines are an essential part of society, the public perception of them is an avenue that is rarely explored into great depth. As the need for medicines grows, so the need for financial and personal gain on such expenditure also increases.

This provides an incentive for more advanced counterfeit medicines to be produced, which could in turn cause more harm than good to the wellbeing of the public (Houston 2012).

The risk to the public's health is due to the toxicity of the medicine and combinations within the body. An example of a toxic or adverse effect occurring would be the consumption of alcohol combining with a prescribed medicine (Weathermon & Crabb 1999).

The risk can be limited be calculating and prescribing the correct quantity of the drug, considered its level of toxicity. Everything has a toxicity; sugar, water, tea even chocolate. The level depends on the quantity consumed.

Toxicity is the capacity that a substance has to be either poisonous or toxic (Houston 2012). It can come in multiple forms, and each person will have a reaction that is unique to themselves, just at varying degrees of severity. Biochemical interactions occur between the toxicants - that are formed when metabolised - and the target organisms.

The classification of the toxicity reflects the mechanism of action that is used by the target organism and the duration of which it takes for the substance to take effect. Acute and chronic are the two categories in which toxicity can be separated into. Acute is the effect when a substance is taken in a single or multiple dosage within 24 hours. Chronic is repeated exposure to the substance over an extended period (Zaitsu et al. 2016).

For counterfeit medicines, patients would experience a range of problems, dependent on the chemical makeup of the medicine used. As there are multiple classes of a counterfeit medicine, the first requirement is to establish if there is any API.

If not, the medicine fails to aid the patient by relieving the ailment or helping them to become healthier. In extreme cases this can cause a chain reaction to occur that can be harmful to the patient.

In the case of antibiotics, if a patient with a urinary tract infection is given a counterfeit version, the medicine would do little to treat the infection and consequently the patient can later develop blood poisoning that could be fatal in some cases (Hariharan 2007).

In another incidence where there was no API but instead there are harmful chemicals in its place, for example, powdered cement floor wax, coloured dye, paint and even antifreeze in some cases. An example of the latter unfortunately being an incident in which over 500 children worldwide had a fatal reaction as a result of ingesting a cough syrup that was in fact tainted with diethylene glycol (ie antifreeze) (Houston 2012).

In some cases, the medicine may contain the correct API but in an excessive amount compared to what it should be. Regrettably this was the case in 2012 when over 1,000 people became seriously ill.

Unfortunately, there were over 200 fatalities. This was because the medicine that was used for the treatment of individuals with cardiac problems, contained 14 times the recommended volume of pyrimethamine (WHO 2013).

Ultimately causing the patients to suffer from severe folate deficiency, which later triggered heavy internal bleeding after the bone marrow platelets were destroyed (Guo 1999).

Medicines are always changing and adapting due to the knowledge and experience that is gained, processed and developed from the testing and the application of them. Not only that, but the distribution of them is also adapting and having a wider reach.

With the access to the Internet more people have access to the medicinal products. This in turn means there are more access points within the supply chain for counterfeit medicines to be procured (Khan et al. 2011).

Multiple studies have been conducted regarding different counterfeit products, (Assi 2011) and (Moffatt 2010) focused on counterfeit pharmaceuticals with the use of spectroscopy. Others such as (Quayle 2016) are more focused on counterfeit tobacco.

Fourier Transform Near Infrared (FT- NIR) has been proven to be among the most common approaches to analyse the pharmaceutical products. This, being because it is non-destructive to the materials it is measuring, can be used to build quantitative regression models as well as being used for the creation of a reference library of materials (Assi 2011).

The reference library constitutes chemical fingerprinting in the sense that each chemical is unique in functional groups that are represented in overtones. It is also a beneficial tool to use because it can be used in conjunction with multivariate analytical tools such as Principal Component Analysis (PCA) for example.

1.6 The Monitoring of Medicines Sales within the Market

When a failure in the manufacturing process causes a defect to occur, such defects can be considered accidental within the supply chain (Almuzaini et al. 2013). When such problems take place, the product can be ultimately removed/ withdrawn from the market by the manufacturer.

One example of a medicine having undesired results when available on the market would be the use of thalidomide, which of course infamously was used as an anti-emetic almost 60 years ago. After many incidents, it was discovered to be the pre-cursor for almost 10,000 babies to be born with various birth defects.

Even though the medicine itself was preventing women from suffering with morning sickness which was its main goal. The mothers suffered from peripheral neuropathy (Vargesson 2015).

This was due to the inability of the drug to perform the desired result without causing harm. Consequently, thalidomide was removed from the market. Thalidomide has now been modified in recent years to successfully treat multiple myeloma, some cancers and even Crohn's disease (Gupta 2017).

With regards to other medicines, there are different types of defects that are catalogued that cause different responses to occur; i.e. contamination, deflect in API, delivery, minor packaging defect, major packaging defect, potency, stability failure, and other possible defects.

Various types of defects are assigned by the Medicine and Healthcare Regulatory Agency (MHRA) into drug alert classes1-4 depending on the risk associated with the defects the medicines were found to have.

Drug alerts classes 1 ,2 and 3 require the relevant medicine batches to be recalled, whereas drug alert class 4 does not require a recall of the batches, it does however advise caution when dealing with a defective medicine.

Depending on the severity of harm caused by the medicines, that occur within different time frames, various action is required.

The European Union Council (EUC) on the other hand classifies a falsified medicinal product as (EMA 2020):

"Any medicinal product with a false representation of:

- Its identity, including its packaging and labelling, its name or its composition about any of the ingredients including excipients and the strength of those ingredients;
- Its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or
- Its history, including the records and documents relating to the distribution channels used. This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights."

And classes a substandard drug as:

"Substandard drugs are manufactured with the intent of making a genuine pharmaceutical product, but the manufacturer saves costs by not following GMP (Good Manufacturing Practice) or using poor quality raw materials. Another potential problem relates to inadequate storage or transport conditions, leading to deterioration of the product. The performance of such medicines is questionable" (EMA 2020)

With regards to other medicines there are different types of defects that are catalogued which cause different responses to occur, they are as follows (Gov.UK 2020):

Contamination: A defect that is in relation to microbial contaminations and issues that are related to the sterility as well as the chemical and particulates (e.g impurities) contamination

Deflect in API: Are defects that are the product of the API being either inadequate or excessive in the formulation.

Delivery: A physical or technical such as a broken capsule or leaking bottle.

Minor Packaging Defect: Are the defects that occur such as the printing/ labelling of the packaging, these printing box errors can involve missing batch number or either a missing of incorrect expiry date of the medicine. Minor packaging defects also includes any errors that are occur in the patients' information leaflet and even the summary of the products characteristics.

Major Packaging Defect: Are defects that involve missing or incorrect name or strength of the medicine dosage, as well as the packaging of a medicine in the incorrect box or carton.

Potency: The failure of the medicine to produce a desired effect within the stated strength.

Stability Failure: Are defects which result from the failure of the medicine attempting to remain within the established standards throughout the expiration period. An example of this would be the low assay of an API prior to the product expiry.

Other Defects: Deviations which concern non-compliance with the good manufacturing practice (GMP) at manufacturing site.

Different types of defects the Medicine and Healthcare Regulatory Agency (MHRA) assign different classes of drug alerts categories 1-4 depending on the risk associated with the defects the medicines were found to have (Gov.UK 2020):

Drug Alert 1: The defective medicine is life-threatening and there is a serious risk to patient health.

Drug Alert 2: The defective medicine is not life-threatening and but there is a still a harmful risk to patient health.

Drug Alert 3: Alert issued due to problems relating to the compliance with GMP or marketing authorities, even though the medicine is unlikely to be hazardous.

Drug Alert 4: Advises "caution in use" as it is the least critical alert.

Classes 1 ,2 and 3 drug alerts require the medicines batches to be recalled, where-as drug alert 4 does not require a recall of the batches however caution is advised when dealing with defective medicines. Depending on the scale of harm that can occur results in different time frames of actions (Gov.UK 2020):

Drug Alert 1: CLASS 1 MEDICINES RECALL

Action Now – including out of hours Pharmacy, Dispensing Clinic, and Wholesale Level Recall

Drug Alert 2: CLASS 2 MEDICINES RECALL

Action Within 48 Hours Pharmacy, Dispensing Clinic, and Wholesale Level Recall

Drug Alert 3: CLASS 3 MEDICINES RECALL

Action Within 5 Days Pharmacy, Dispensing Clinic, and Wholesale Level Recall

Drug Alert 4: CLASS 4 MEDICINES DEFECT INFORMATION

Caution in Use Distribute to Pharmacy, Dispensing Clinic, and Wholesale Level

One example would be Valsartan, that was used to treat high blood pressure, and subsequently was withdrawn from the market in 2018 due to impurities that were found (Farrukh et al. 2019). However, many poor-quality products go unreported.

1.7 Regulations

Regulations, which include laws and policies, are fashioned in a way that adapt to change and are there to safeguard the problem of counterfeits. In most cases they work.

However, just like any created rule and regulation, there is always someone who is willing to break that ruling and generate a loophole in the justice system. These specific loopholes give way to the rise to the sale and production of counterfeits, that can be bought Over the Counter (OTC) or on the Internet.

Many government authorities over the years have been created to uphold and create new rules and regulations to help battle counterfeiting in various areas such as medicines, clothes and even toys.

Unfortunately, there is no single governing body that has created a solid definition on what can be classed as a counterfeit or substandard imitation of a product. Due to this, loopholes are created, and counterfeits can be passed on to the consumers.

The International Conference of Drug Regulation Authorities (ICDRA) was established to create countermeasures and is organised biennially by WHO.

Those that have a governing body that regulates and polices the problem of counterfeits are the European Union (EU) who has the European Medicines Agency (EMA), the United States (US) that houses the Food and Drug Administration (FDA), and Japan with its Japanese Pharmaceutical and Medical Devices Agency (PMDA) (Stationary Office 2017).

Together these authorities brought about the formation of the Centre for Drug Evaluation and Research (CDER).

As Zou (2006) suggested, there are six main categories for regulating medicines, each of which contain several subsets. These resulted from Zou synthesising a clear and precise representation of the laws regulating them.

- Assessing the safety, efficacy and quality of medicines.
- Assessing the issuing and marketing authorisation of the individual products.
- Controlling/ monitoring the medicine quality on the market.
- Analysing the adverse reactions in reports and therefore monitoring the safety of marketed medicines.
- Regulating the licencing of the import, manufacture, distribution, export, advertising and promotion of medicines.

- Overall inspection of the manufacturers, wholesalers and importers, as well as the dispensers of medicines.

One important fact that always needs to be considered with medicines is that they need to pass/meet three criteria: they must be safe, effective and to be of good quality. The terms effective and efficacy can be interchangeable depending on the circumstances within Zou's work.

To combat counterfeit medicines various directives have been created, the most recent is the Falsified Medicine Directive (FMD) of 2019, this directive looks closely at the supply chain and how to regulate each step in the process.

The regulations surrounding medicines, pharmacies and counterfeits are discussed further in Chapter Five with more details about the new FMD 2019 and the authorities that govern them.

1.8 Rationale

The counterfeiting of medicines is a global threat that requires stringent monitoring. As shown earlier, antimicrobials are the primary counterfeited medicinal product with 38%. Within that category are antibiotics and antimalarials, both of which are covered within a vast array of literature.

For the antibiotics the classes that are often regarded and analysed are antituberculotic agents, penicillin and antifolates, for antimalarials quinine and malarone (mixture of atovaquone and proguanil) are often the categories analysed.

Antimalarials are often administered with an antibiotic acting as a secondary agent, with this being the case antibiotics will be the focus of this research. It is not often that a subclass of antibiotics or other medicine is analysed as proven by the studies that are available to explore.

Ciprofloxacin is an ideal choice for this purpose, the reason being that as shown previously it has varied and broad applications, whereas other antibiotics target specific aliments.

By having such a range of uses it can be suggested that it would be more likely to be counterfeited as more profit can be gained from its production and use, as it would have a wider consumer base.

This research investigates the chain of supply that the counterfeits are a part of. The next following chapters follow the next steps that the medicines themselves undergo.

First is the creation of the counterfeits and how they can be chemically evolved. This is important to understand as a society, so that individuals can better arm themselves with the knowledge that the counterfeits on the market today, can be sophisticated, and only differ from the genuine medicinal products via their chemical properties.

Most analytical techniques that are used for the detection of counterfeit medicines are destructive of the sample, and require extensive sample preparation, thereby causing the cost and time spent on the research to increase. To prevent this eventuality occurring a FT-NIR Spectrometer will be used as the analytical instrument for this research.

The reason for choosing to use the FT-NIR is that it can be portable in most forms and it also processes the data quickly, allowing further analysis to be completed in-situ. Thus, the use of a FT-NIR is beneficial in respect of finding a quick and inexpensive technique for the analysis of the chosen materials.

The validation for using FT-NIR is that previous studies with similar parameters used has been successful in determining if counterfeit medicines are present.

For more accurate results the use of multiple batches of ciprofloxacin is paramount, this gives more accuracy to what is classed as a counterfeit product and having a variety of country's supplies opens the analysis to include various counterfeit properties that have been discussed in others published work.

The next step would be the laws and regulations surrounding the medicines and the distributors as they are there to protect the public and make sure that the threat of counterfeits entering the supply chain has a minimal disruption to the chain and limited health risk to the end consumer.

The laws and regulations that govern medicines are always changing and adapting to accommodate the changes and evolution of the problem that counterfeit medicines produce.

By understanding the history of the laws, how they came about and what they are protecting against, a picture can be deduced as to what the next logical step will be in our evolution.

Once the laws are in place the distributors are then the next step to be monitored and this is done via the internet and documenting how an online pharmacy functions, the potential risk they can cause, on top of how far their reach is.

With how the law changes and adapts it is also important to understand that the distribution of counterfeits has also changed with the Internet being made accessible to anyone. Online pharmacies are the future as they are convenient and cost efficient, enabling more access points in the supply chain cannot be manipulated and taken advantage of.

It is important to understand the expansion of online pharmacies and how they are monitored. The General Pharmaceutical Council (GPhC) and the MHRA are the two governing bodies for the UK with regards to online pharmacies and their directory of approved pharmacies will be analysed.

Lastly how does the end consumer, the public justify self-prescription. What are the reasons that they use online pharmacies and do they have concerns for counterfeits?

By knowing how society regards counterfeits and the use of online pharmacies, it can open more avenues of manufacturing practice that can help safeguard the consumer more.

It can be used to appeal to the public and give knowledge to protect them to reduce future incidents.

Using public perceptions, counterfeit regulation and the physical properties of counterfeits, this research can help safeguard the future and outline the benefits and the limitations that are present.

1.9 Overall Purpose

The issue of counterfeit medicines is a full circle, from production to consumption. This research is the link between the various steps within that circle

The medicine that is the focal point of the research Ciprofloxacin is widely used for a variety of infections and it is a medicine that is not widely talked about in literature. Most pieces focus on the medicines that target a specific infection.

The various methods implemented in this research follow scientific reasoning alongside legal reasoning with social science as a framework.

By combining each of these distinctive methods in one piece of research a further understanding of the risk of counterfeits can be found. With the combinations of quantification, categorisation and public perception, it is possible to determine the risks posed by counterfeits and what aspects are most effected by them in everyday life.

Currently each of these topics are focused on in a variety of different ways, however it is unlikely if not rare to see the different components that are listed in this research to be combined together to get a full picture of the problems that counterfeit medicines have on society.

From the creation to the consumer following on through the laws and the distributors. This research can help aid in the prevention of counterfeit medicines and support the research that has already been conduct and will be in the future.

By understanding each of the steps along the journey the separate limitations and strength can be uncovered but also the overall strategies that could arise.

1.10 Aims

The purpose behind this research is to further understand and circumnavigate the prevalence, knowledge and regulations associated with counterfeit medicines.

The main focus of this study is ciprofloxacin, why it is used, method of purchase, understanding risk of counterfeit duplication, determining a counterfeits presence and the preventive measures in place for public safety.

This is conducted using exploratory, explanatory, quantitative and qualitative methods, in order to add to the body of literature surrounding counterfeit medicines.

1.11 Objectives

- To identify the most common classes of medicines that are known to be counterfeited with the use of quantitative meta-analysis and cross reference to literature.
- To assess online pharmacies and identify the authenticity of the sites using statistical analysis of internet records.
- To determine the public's reasoning behind purchasing medicines and self-prescribing using quantitative analysis in the form of questionnaires.
- To develop spectroscopic methods for determining the authenticity of some purchased medicines and how to visualised the discrepancies.
- To discuss the new Falsified Medicines Directive and how appropriate it is at regulating medicines in general, with a focus on counterfeit medicines.

Chapter Two: Identification of Counterfeit Medicines Using Spectroscopic Techniques.

After the public perspective and the knowledge of how the medicines are distributed, the identification of counterfeits and authenticating the medicines becomes an important stage of the distribution process.

This chapter investigates the analytical techniques used currently, the authentication of ciprofloxacin batches, what pre-treatment processes are used (chemometric analysis) and the tablet analysis with the aid of PCA and CWS.

Within this chapter a quantitative approach with nominal data was conducted. This research was to determine the presence of counterfeit medicines. Quantitative analysis is a proven methodological process to analyse large sample sizes that contain numerical data.

With this approach FT-NIR was used, as it is an established testing instrument for medicinal products as confirmed in Chapter One and Chapter Five. The reason that this research is important is so that individuals are able to understand and be confident to identify them. This is crucial with regards to understanding if the public are at risk and how to limit that risk (Sun 2009).

2.1 Analytical Techniques

Gas Chromatography (GC), High Performance/Pressure Liquid Chromatography (HPLC) and Mass Spectroscopy (MS) have recently been the most reliable and beneficial techniques available with regard to testing substances, in this case medicines.

Often when coupled together these techniques produce a gold standard of analytical tools for analysis, for example GC – MS (Di Giulio & Bonamore 2008). Despite these techniques being accurate and precise due to high sensitivity, they can at times unfortunately be expensive.

This is due to the extensive preparation the samples must undergo before they can be scanned and measured, this process is time consuming and therefore expensive. However, this has led to more progressive techniques, such as spectroscopy, becoming more popular. Reasons for these techniques rising in popularity includes; they are rapid in producing a result, they require little to no preparation for the sample and they are also inexpensive compared to the other techniques (Manley 2014).

Both qualitative and quantitative information can be obtained from the data collected with spectroscopic techniques. Despite the fact that the whole molecular structure cannot be determined, these techniques can be used to examine the following; determining atomic structure, partial molecular structure, stereo-chemical arrangements as well as the functional groups.

The basis of these techniques is the emission or absorption of electromagnetic ration of a sample which can be either a discrete or a considerable amount (Whiffen 1996). The energy levels/states of the various fluctuations in radiation which are due to either the emission or absorption can be measured and recorded. The representation of such measurements is often in the form of a graph called a spectrum.

Due to a variety of energy changes a range of spectroscopic methods are used for measurements (Cahtwal 2009; Howarth 1973) as seen in table 1.

Table 1:: The comparison of spectroscopic techniques used to define various energy states (Houston 2012).

Type of Energy State	Spectroscopic Techniques Used
Inner Electron Shell	X-Ray
Outer Electron Shell	Florescence
Rational States	Microwaves
States of Magnetic Moment Orientation in a Magnetic Field	Electron Resonance & Nuclear Magnetic Resonance
Sub-nuclear	Gamma Ray
Vibrational States	Infrared & Raman

Spectroscopy techniques can be conducted in tandem with other complimentary instruments as is the case of GC-MS, whereas others are better when they function on their own. It is important to note that for this study NIR will be used in conjunction with a Fourier-Transform (FT) instrument. (FT-NIR) will be used as the spectroscopic technique to analyse the medicines, to determine their authenticity.

FT-NIR systems have the advantages of possessing higher resolutions and higher signal energy, are more stable, are easily repeatable and have better wavelength accuracy. They are not affected by stray light that is known to cause sampling challenges for dispersive systems such as individual NIR (Terrell 2019).

By using the FT-NIR in this study, the data sets produced from analysing the medicines can be counted on to be accurate, reliable and less deficient that if solo NIR was used.

2.2 Principles of Near Infrared Spectroscopy

Since the early 1940s Infrared (IR) spectroscopy has been in use. This was later adapted with the aid of interferometers to create advancements in measurements and analysis.

The basis IR spectroscopy is the interaction between a sample material and the electromagnetic radiation emitted from the instrument as seen in figure 3 (Stuart 2004).

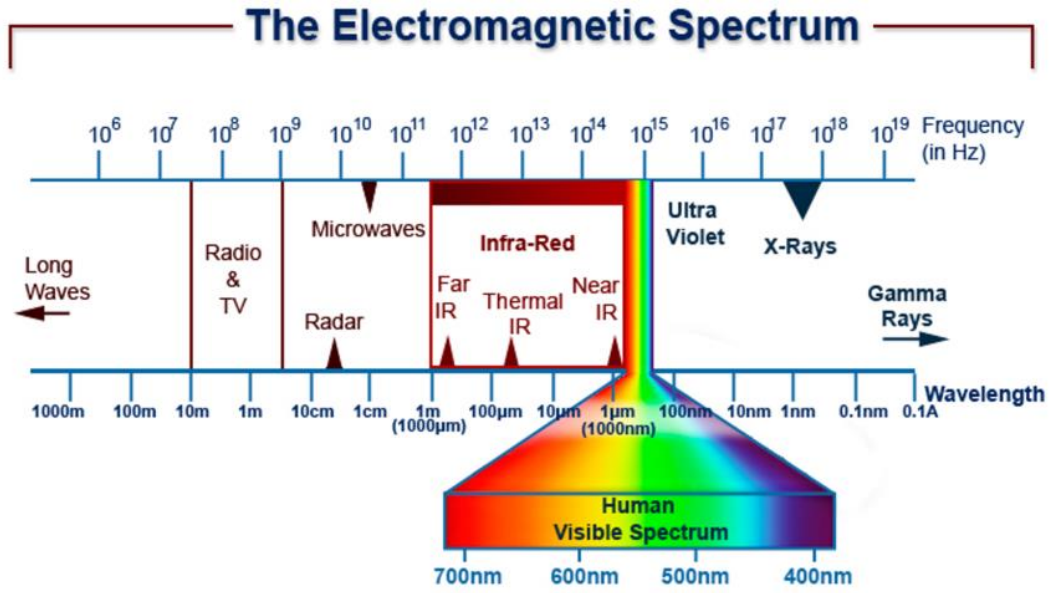


Figure 3: Visual representation of the electromagnetic spectrum and wavelength seperation (Haynes 2016).

The interaction between a sample and the IR radiation, can be classed into one of four categories, depending on the way in which a sample reacts with the IR radiation; ie absorbed, transmitted, scattered or reflected.

Excited vibrations occur within a sample when IR radiation interacts with it, thus causing the molecules inside to be placed in a higher state of vibrational energy (Jee 2016).

One type of IR spectroscopy would be that of NIR, which is composed between the red end and the Mid- Infrared (Mid-IR) region of the visible light on the electromagnetic spectrum.

This particular region lies in the location of 780 – 2,500 nm, which is then further divided into two more subsections; the longer wavelength is represented in the range

of 1,100 – 2,500 nm and the Hershel region which houses the shorter wavelengths 780 – 1,100 nm.

In the last 35 years NIR has been the majority usage, regardless of being discovered over 200 years ago. This is mainly due to the recent advancements made in analysis, such as chemometrics, that allows spectral interpretation to be much easier as well as being to a high quality.

A benefit of using NIR for sample analysis is that it is non-destructive and requires little to no sample preparation (Salganicoff 1998; Lennard 2004; Jee 2016).

NIR instruments collect data that are the result of the molecular vibrations, by examining the vibrational characterises of a sample that is being measured. This is based on the principal theory of 'ideal' diatomic harmonic oscillation.

The basis of the theory is that due to bonds between two atoms (for example H_2) stretching, vibrational energy is experienced. When atoms stretch within a molecule, they obey Hooke's Law (Equation 1) and as a result fundamental frequency are produced (Figure 4).

$$v = \frac{1}{2\pi c}\sqrt{\frac{k}{m}}$$

Equation 1: Stretching Frequencies, the combination of Hooke's Law and fundamental frequencies.

Where 'k' is the classical force constant, 'c' is the speed of light (is not always necessary to use in practice), 'm' is the reduced mass of the atoms and 'v' is the vibrational frequency.

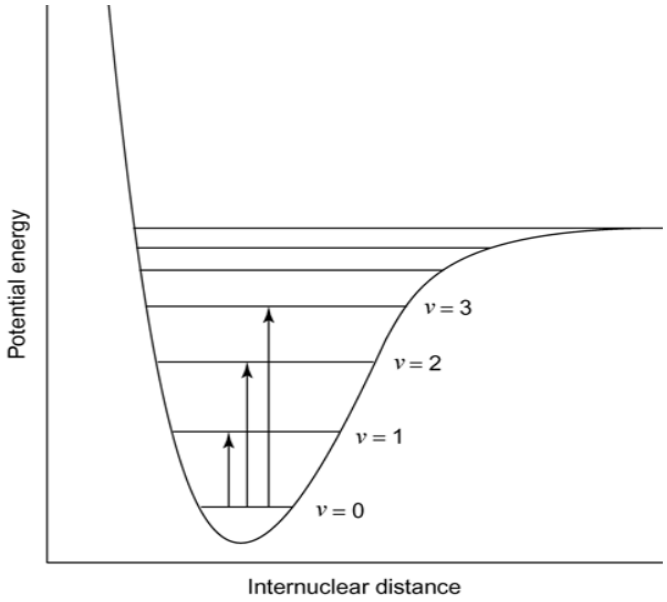


Figure 4: Diatomic molecules obeying Hooke's law. Transitions of the varying overtones and fundamental frequency (v = 0 → v = 1). (v = 0 → v = 2)the 1st overtone and (v = 0 → v = 3) the 2nd overtone and so forth, (Jee 2016).

It is a known fact that overtones are more common within the NIR region, whereas fundamental frequencies are more used in Mid-IR regions (Figure 5).

The difference of individual frequencies or the sum will be calculated when two or more vibrational modes occur simultaneously, this is typical with molecules such as polyatomic molecules when they exhibit energy changes.

These energy changes produce subtraction and combination bands, which are weak bands. Subtraction bands are rarely observed to occur at room temperature even though it is possible, whereas combination bands also have a low probability for occurring (10-1,000 times smaller) compared to that of the Mid-IR fundamental frequencies.

With this being the case there is a high chance of weak absorbance to occur. Despite this, it is classed as an advantage as a sample can be measured without any preparation.

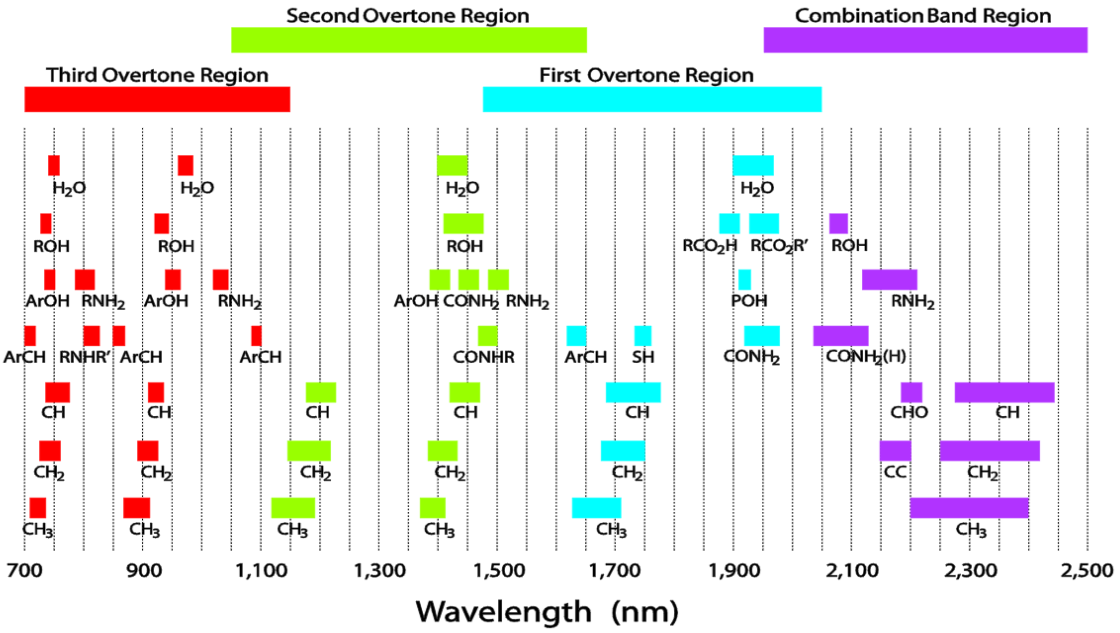


Figure 5: Range of overtone markers created by the bonds between atoms in a molecule (Badr 2011).

The values that are often found to be high value tend to be anharmonic constants. This is because they are encountered in bonds containing hydrogen such as; C-H, N-H, S-H, and O-H therefore they are the most dominating overtones (Figure 5 & 6).

The anharmonic oscillator potential energy level 'E' is defined by the equation:

Equation 2: Anharmonic Oscillator Frequency

$$E \approx hfw\left(v+\frac{1}{2}\right) - hfwx\left(v+\frac{1}{2}\right)^2$$

Where 'h' is Planck's constant, 'v' is the vibrational frequency, 'w' is the spacing between energy levels, 'f' is equilibrium constant, and 'X' is the anharmonicity constant.

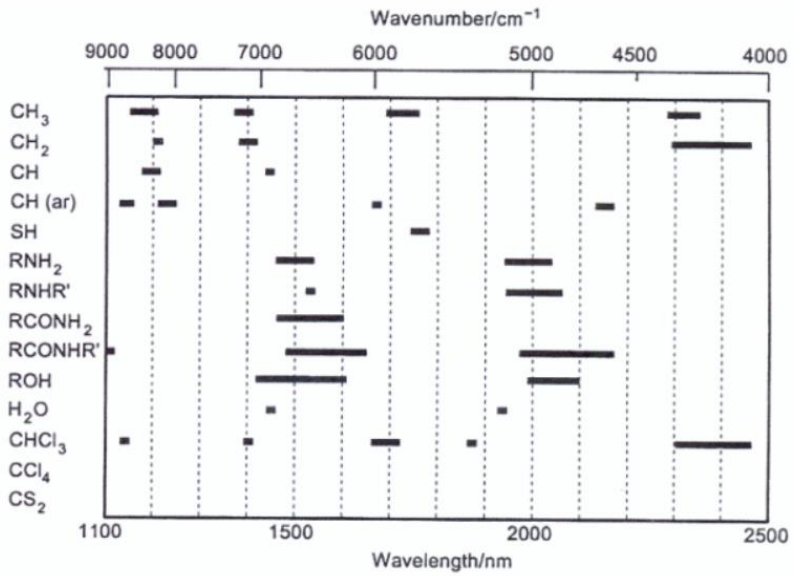


Figure 6: Hydrogen containing bonds in NIR and their respective overtone classes (Stationary Office, 2017).

NIR is capable of multiple measurements from different source types. The two main types that are categorically measured are transmittance (TR) and reflectance (R).

Transmittance measures the degree in which absorption of the wavelength occurs, once the radiation has passed through the sample.

Reflectance however is when the radiation does not pass through the sample and instead reflects off the substance and that is then measured.

Absorption alone is not measured as the result would be zero as no wavelength passes through the sample or reflects off (illustrated in figure 7).

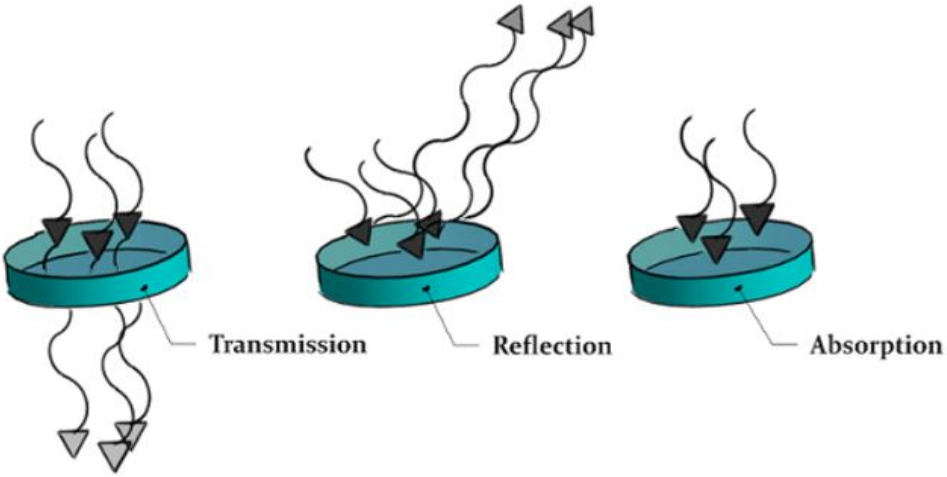


Figure 7: The differences between reflection, absorption and transmission and the basic scale of how the materials effect the radiation (Stationary Office 2017).

When inside the material the radiation reacts in different ways as illustrated in figure 8. The difference between the types of interaction within the sample and the radiation is the basis of the measurements that occur.

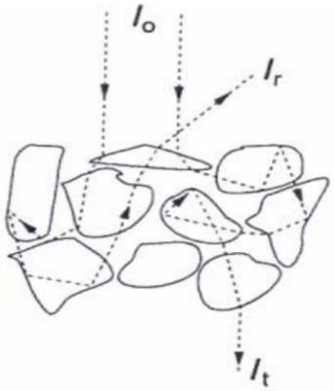


Figure 8: The interaction between the radiation and the inside of the sample (Rinnan 2014).

Transmittance is the ratio between the incident radiations (I_0) to the transmitted radiation (I_t):

Equation 3: Transmittance

$$TR = \frac{I_t}{I_o}$$

Whereas Reflectance can be defined as the ratio between the reflected radiation (I_r) and the incident radiation (I_0):

Equation 4: Reflectance

$$R = \frac{I_r}{I_o}$$

There are two main categories of reflection: specular and diffuse as seen in figure 9

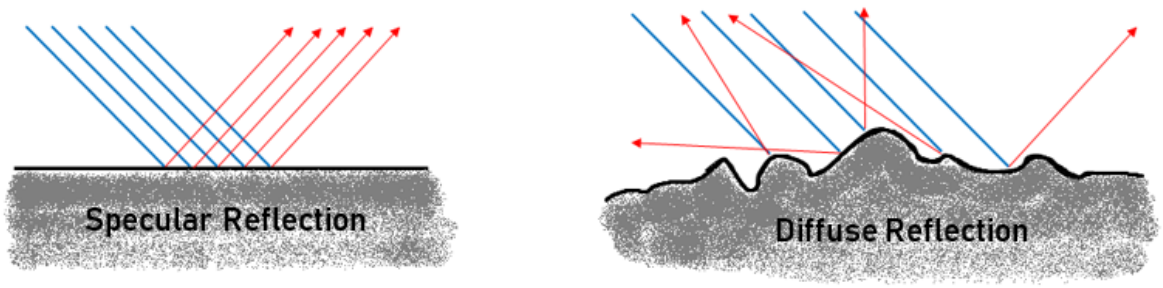


Figure 9: Comparison between diffuse and specular reflection with regards to the radiation within a sample: where (-) is the incident light, (-) is the reflected light.

Specular radiation is when the radiation that is focused on a sample is simply reflected off in a uniform degree when it encounters the surface of a material, unfortunately very little information is gathered from this type of reflectance.

Diffuse reflection however is when unabsorbed radiation is reflected at various angles, this is often caused by the sample often having an uneven surface so the radiation may enter uniformly but will not reflect just so (Jolliffe 2010).

There are multiple variants of vibrational/spectroscopy tools that are based within the electromagnetic spectrum. Working within the range of 400 – 4,000cm^{-1} is Fourier-Transform Near Infrared (FT-NIR) spectroscopy.

The analysis of organic compounds and materials is the main use of the FT-NIR. The difference between the dispersive NIR techniques and the FT-NIR is that instead of prisms and gratings that the former relies on, FTIR uses a Michaelson interferometer as seen in figure 10.

The main components of an interferometer are the two mirrors, one of which is stationary while the other moves in a parallel line to the light beam, and the beam splitter. The distance between the mirrors and the beam splitter can be controlled to utilise certain characteristics of the Infrared light beam.

Polychromatic light (from the source) is split into two beamlets with the use of the aptly named beam splitter; one moves towards the stationary mirror while the other towards the mirror that I was able to move. Once reflected off their corresponding mirrors the beamlets are then combined once again at the beam splitter.

Once combined they successively pass through the detector, depending on the combination phase, constructive or destructive, that the beams are experiencing this will affect the light intensity that is monitored as illustrated in figure 10.

The subsequently detected intensity of the light when applied with the function of the offset mirror, which is measured with the use of a laser, is called an interferogram. After this the interferograms are mathematically transformed with the use of a FT to eventually obtain a spectrum that can be analysed further.

Due to the polychromatic light, not being mono-chromicised all wavelengths can be measured (Hariharan 2007).

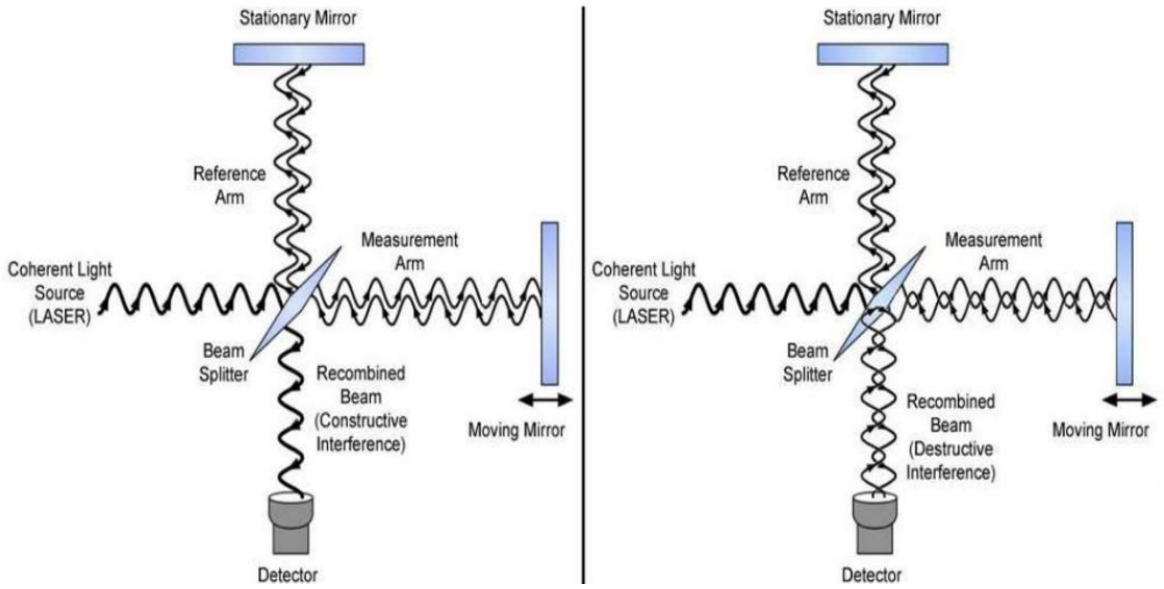


Figure 10: The inside working mechanism of the Michaelson interferometer (Shaw 1999).

Either with the aid of a FT or not, any NIR can obtain both chemical and physical information about a sample. This can then be used equally for qualitative and quantitative analysis. Measurements of a sample can be accomplished in-situ due to little or no preparation being needed.

Whereas the spectral collection method is considered simple, the interpretation of such spectra is more complex as before it can finally be used for chemometric modelling PCA it requires in depth mathematical transformation and editing (Data Pre-treatment).

The data pre-treatment is important on the basis that it corrects the offset baseline shift of a spectrum that is often caused by the scattering of light, known as diffuse reflection (Rinnan 2009; Jee 2016; Stationary Office 2012).

2.3 Data Pre-treatment

When spectra data is in its rawest form, untreated, an effect called spectral offset and overlapping can occur among the different spectra. Multiple factors can contribute towards this phenomenon: moisture content, temperature, sample thickness, optical properties of the sample, age of the sample (expiry date) and how the instrument performs (Einax 1995; Salaganicoff 1998).

Spectral pre-treatment methods are typically used to avoid these spectral quality deviations, these various types of spectral treatment are used to correct spectral noise, which is often the resulting factor of light scattering, it also removes any unwanted data variations/anomalies that are not caused by light scattering.

Light scattering, in respect of a sample, can often be the main carrier of information ascertaining to that sample. Both the chemical properties of the sample and structural information (such as scattering and relative absorbance of light reacting with the sample) can be contained within the diffusively scattered light, which can be analysed with NIR spectroscopy techniques.

There are two different forms of light scattering that avoid interaction with the energy that is contained within the molecules; Rayleigh, which is common with Raman spectroscopy, and Lorentz-Mie. Where Lorentz-Mie is used with particles of a larger size, Rayleigh is used with small sized particles.

Both Lorentz-Mie and Rayleigh are processes which involve electromagnetic scattering; for example, some of these are; bubbles, cells, small particulates, crystalline defects, fibres and droplets, to name but a few of the variants.

Where Rayleigh is wavelength dependent Lorentz-Mie is anisotropic and relies on the shape of the particles. There are two main types of data pre-treatment techniques used for NIR spectroscopy, scatter methods and spectral derivatisation (Rinnan 2009; Rinnan 2014).

2.4 Scatter - Correction Methods

There are various types of scatter correction methods, the most common being Standard Normal Variate (SNV) and Multiplicative Scatter/Signal Correction (MSC). With regard to MSC there are many variations that can occur; Inverse MSC (IMSC), Extended Inverse MSC (EIMSC) and Extended MSC (EMSC). Others, such as de-trending and normalization, also are effective in certain circumstances (Rinnan 2009).

The interferences that can be caused by the light scattering as well at the particle size within the samples, can be corrected with the use of SNV. SNV scales the absorbance values that are found within the NIR spectra automatically (Van Bambeke 2017), thus enabling a result to occur more quickly without manually entering the constraints of the pre-treatment process. The equation below illustrates the correction process for SNV.

$$x_{corr} = \frac{x_{org} - a_0}{a_1}$$

Equation 5: SNV Pre-treatment

Where 'a_0' is the average value from the sample spectrums that are to be adjusted and 'a1' is the standard deviation of those sample spectrum values, 'Xorg' is the original spectra sample that was measured, and 'Xcorr' is the corrected spectra.

With regard to 'a1', multiple vector-norms such as the positive length of the vector, or the square root of the sum of the squares, even the overall sum of the absolute values of the vector elements being the most commonly used.

For SNV it is not necessary for a reference signal to be obtained, in its place each observation of the data is isolated for the remainder. Due to not using the least squares regression parameters for any estimations it is believed that this makes the SNV more sensitive to the entries in the spectrum that identify as noisy entrees (Guo 1999).

Both spectral offset and absorbance scale that are caused by the scattered light, can be corrected with the use of MSC (Einax 1995; Lennard 2004). The scattered light that is shown is relative to the reference sample, meaning that when the same reference sample is used the same scatter pattern will be seen.

With MSC, artefacts (undesirable scatter effects) or other imperfections are removed prior to any data modelling, resulting in a more pronounced result. Unlike with SNV, MSC consists of two steps (Brereton 2006).

Step (1): Coefficient's correction (multiplicative and additive contributions) estimations.

$$x_{org} = b_0 + b_{ref,1} \cdot x_{ref} + e$$ *Equation 6: Step 1 in MSC*

Step (2): Recorded spectrum that has been corrected.

$$x_{corr} = \frac{x_{org} - b_0}{b_{ref,1}} = x_{ref} + \frac{e}{b_{ref,1}}$$ *Equation 7: Step 2 in MSC*

Where 'e' is the un-modelled part of 'X_{org}', 'X_{org}' is the original spectra sample that was measured, b_0 and $b_{ref,1}$ are the scalar parameters, that are different for each sample 'X_{ref}' is the reference spectra used for pre-processing the data and 'X_{corr}' is the corrected spectra.

2.5 Spectral Derivatisation Methods

Norris-Williams (NW) derivatives and Savitzky-Golay (SG) polynomial derivatives filters are main representatives for the spectral derivatisation methods. Both methods for full optimisation require smoothing the spectra prior to the derivatives being calculated.

This reduces the damaging effect on the Signal/Noise ratio (S/N ratio) that other conventional methods would create. For the correction of NIR spectra 1st and 2nd derivatives (D1 and D2 respectively) are used, due to their innate ability to correct the baseline shifts and offsets within the NIR spectra (Lennard 2004).

Whereas the 2nd derivative removes the offset, the 1st derivative reduces the offset effectively to a much similar one that can be understood more clearly.

The more popularised method of the two is SG derivatisation as is uses a vector that includes a smoothing step (Savitszky 1964). It is based on orthogonal projections that alter and reshape spectrums using either the D1 or D2 derivatives.

More commonly a polynomial of the orders 2 – 4 are fitted by least squares to the data using a certain amount of data points that range between 3 and 10 to make it more accurate in correlating the data.

To limit the errors that could occur this process is applied to the complete spectrum rather than individual sections (Barnes 1989; Rinnan 2014). Polynomials are added within a symmetric window of raw data for a derivative to be found at the centre points.

However, this is accomplished after the parameters have been calculated. Once this is achieved the derivatives of any order can then be identified more easily in the future.

The degree of polynomial is directly proportional to the derivative that can be found e.g., a 4th order polynomial can be used to estimate up to the 4th order derivative.

The NW method on the other hand was developed to reduce if not completely avoid the noise inflation that can occur on a spectrum between finite differences. NW is a twostep method (Standcliffe 1991) as follows:

Step (1): An average over several given points with the aim to smooth the spectra is performed using the equation below:

$$x_{smooth,\ i} = \frac{\sum_{j=-m}^{m} x_{org,\ i+j}}{2m+1}$$

Equation 8: 1st step in NW derivatisation

With 'm' being the number of points that are contained within the window of smoothing, which are centred on the current measurement points within the data.

Step (2): For the 1st order derivative to occur the difference between two smoothed values is calculated with the difference being greater than zero. For the 2nd order derivatisation at point 'i' the smoothed value is multiplied by two which is then compared to the value that is smoothed either side. Which is illustrated in equations below:

$$x_i' = x_{smooth,\ i+gap} - x_{smooth,\ i-gap}$$

$$x_i'' = x_{smooth,\ i-gap} - 2 \cdot x_{smooth,i} + x_{smooth,\ i+gap}$$

Equation 9 + 9a: Step 2 in NW

Within this project Savitzky-Golay Derivative 1 and Multiplicative Scatter/Signal Correction are the data pre-treatment methods used for this study. This is because when the data is constructed with these data pre-treatment methods it is more readily readable and can be understood more clearly.

2.6 Chemometric Qualitative Data Analysis

A fundamental part of the analysis for NIR spectra is chemometrics due to it being difficult to interpret. Chemometrics is when statistical and mathematical methods are used in tandem for data selection and optimal experimental analysis.

> *"Chemometrics is a chemical discipline that uses mathematics, statistics and formal logic (a) to design or select optimal experimental procedures; (b) to provide maximum relevant chemical information by analysing chemical data; and (c) to obtain knowledge about chemical systems" (Westad 2005).*

Test assumptions, modelling and the design of the experiment are some of the several (information extraction methods) aspects that chemometric group together (Komsta 2018).

A variety of different qualitative analysis methods including: PCA, Mahalanobis Distance in PCA (MDPCA), Soft Independent Modelling of Class Analogy (SIMCA), Principal Component Regression (PCR), Principle Least Squares Regression (PLSR), Correlation in Wavelength Space (CWS) and lastly Maximum Distance in CWS (MDCWS).

PCA is a multivariable analytical technique which evaluates the variation within a data set collected by the uncorrelated components that endeavours to analyse the structure inside the data set (Parsale 2015).

The expression of orthogonal values – principal components (PCs) – after being extracted from within a matrix table (data set) is the aim of PCA. Using mathematical arguments, which can optimise several algebraic criterions the PCs can be identified (Jolliffe 2010).

PCA is also used to help explain the variations that are found within the data that is collected. For this reason, significantly smaller data sets can be analysed by linear transformation of the original data variables. This is common in the use of PCR and PLSR (Dunteman 2016).

Score vectors and loading arrays are the two pieces of information that are the basis for PCs to be fully functional (Wold 1987). The scores illustrate the dominant matrix patterns whereas the loading arrays demonstrate the variable patterns (Andalo 2004)

For PCA to work the number of PCs for a matrix should be equal to the number of the matrix components. The PC variability is directly proportional to the PC order.

For instance, the first PC, known as PC1, will contain the highest set of variances within the models whereas PC2, the second PC, will contain the second highest set of variables (Zou 2006).

Therefore, PCA can be determined by:

$$M = L \cdot S + E$$

Equation 10: The equation for PCA

Where 'M' is the data table of the matrix, 'L' is the loading arrays within the matrix which has an equal value to the matrix columns, 'S' is the score vectors which also has an equal value to the matrix columns, and finally 'E' is the error rate identified within the matrix.

Simple PCA is the method used in this study for chemometric analysis. The reason being, it can identify trends and clusters within the data, visually thus making the analysis clearer and more accurate.

CWS is a mathematical technique that compares the coefficient of the correlation between the sample spectrum (A) and the reference spectrum (B) (Lennard 2004).

It can be estimated by using the dot product 'rd' produced by the calculated product momentum 'rp' between A and B.

This can be seen in the following equations:

$$r_d = \frac{\sum A_i B_i}{\sqrt{\sum A_i^2 \sum B_i^2}}$$

Equation 11: Dot Product of CWS

$$r_p = \frac{\sum (A_i - \bar{A})(B_i - \bar{B})}{\sqrt{\sum (A_i - \bar{A})^2 \sum (B_i - \bar{B})^2}}$$

Equation 12: Momentum Product of CWS

The resultant correlation coefficient can be either positive or negative. If the result is positive then that suggests that the spectra being compared have similarities, with a result of +1 meaning that the spectra that are compared are practically identical in properties.

However, the reverse also stands true, if a negative value is present, it suggests that the spectra compared are dissimilar, the closer the value is to -1 the more dissimilarities between the spectra are occurring.

Unfortunately, due to noise interference being present in NIR spectra it is rare that a correlation coefficient would have a result of +1. As a result of this rarity occurring, the value 'r' of 0.95 is used as a threshold for two or more pharmaceutical products being classed as being the same, due to the spectra being the match.

If a result of 'r' being lower than 0.95 is found, it is said that the products being compared are not the same as the spectra are not a match, even if they have strong similarities (Brereton 2006).

2.7 Tablet Components

2.7.1 Ciprofloxacin

In the past 35 years, clinical practices have struggled to properly integrate the antimicrobial agents that have been introduced to the market at an inflated rate (Lee & Ronald 1987; Dax 1997)

Like many of their predecessors, fluoroquinolones, since their introduction to society, have become a pillar of treatment for some serious bacterial infections (Patrick 2017). Fluroquinolones are synthetic agents that are related structurally to nalidixic acid (Pandeya 2006).

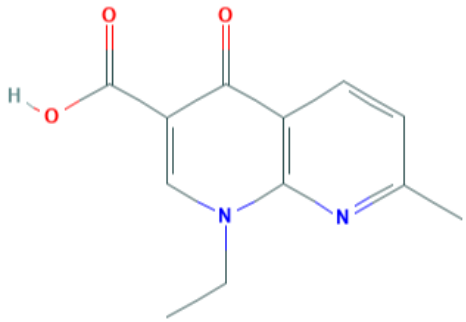


Figure 11: The structural illustration of Nalidixic Acid.

The reason they are so favourable for treatment is due to some of their ideal properties such as; relatively low incidence of toxic and adverse effects, good tissue penetrability and lastly an excellent bioavailability. Which together makes a model medicine for use (Ruizdiaz et al. 2006).

Ciprofloxacin, which was patented in 1983 by Bayer A.G (company based in the Germany - rank 17th in the world), is one of the most successful and widely used compounds of the fluroquinolones class (Appelbaum & Hunter 2000).

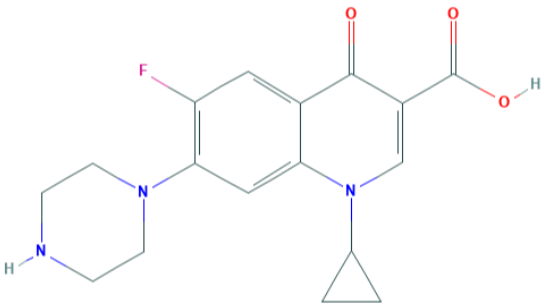


Figure 12: The structural illustration of Nalidixic Acid.

Bayer A.G is also responsible for the creation and patent for Aspirin [1963], Heroin (diacetylmorphine), Phenobarbital, Prontosil (the first antibiotic to be widely used - which won them the Nobel Prize in Medicine in 1939) and finally Yaz - drospirenone (birth control pills).

With a range of over 300 brands to its name, ciprofloxacin is a marketed medicine worldline. Since the introduction to the world market, the value of fluroquinolones has been recognised for their respective uses (de Almeida et al. 2007).

One of the reasons behind this is due to the broad uses of ciprofloxacin and the wide range of activity and pharmacokinetic properties.

With such a wide success, ciprofloxacin has become a high money maker for Bayer A.G, gaining over a billion (American) dollars in additional revenue and a respectable reputation.

Turn of the century ciprofloxacin based on new prescriptions ranked number 11 in the United States, and ranked 20th in total for sales in the United States. In total the gross sales of ciprofloxacin gained Bayer's a total of $1.04 billion in revenue.

Whereas after just five years levofloxacin and ciprofloxacin together controlled 65% of global sales, proving that the purchase of antibiotics particularly fluroquinolones were on the rise.

After being a steady profit with marginal increase over the year, it can be seen that after the anthrax scare that was recorded in 2001, there was a dramatic increase in ciprofloxacin sales.

The recorded sales included the deal that was made between the Us government and Bayer Pharmaceuticals for the purchase of over 100 million tablets of ciprofloxacin.

This deal in turn gave Bayer a foothold on the global share market for pharmaceuticals and to be known as one of the top players in the industry. The deal also regained the company a respectable reputation after losing the patent of Aspirin after WW1 due to the companies' origins.

The reason that the U.S is a one of the pillars of this research is due to who the key players are in the pharmaceutical industry.

Below is a list of the top 20 ranked companies based on their revenues/share holds in the pharmaceutical industry

[Key: Company Name – Revenue - % Change (Decrease) / % Change (Increase) – Location of HQ]

1. Johnson & Johnson - $372.2 bn – 7.5% from Q4 2018 – America [New Jersey]
2. Roche - $239.6 bn – 12.7% from Q4 2018 – Switzerland [Basel]
3. Pfizer - $235.8 bn – 6.9% from Q4 2018 – America [New York]
4. Novartis - $226.3 bn - 14% from Q4 2018 - Switzerland [Basel]
5. Merck & Co. - $213.3 bn – 7.3% from Q4 2018 - America [New Jersey]
6. Eli Lilly - $133.6 bn – 9.0% from Q4 2018 - America [Indiana]
7. Novo Nordisk - $132.1 bn - 17% from Q4 2018 – Denmark [Bagsværd]
8. AbbVie - $119.1 bn - 14.7% from Q4 2018 - America [Illinois]
9. Amgen - $116.8 bn – 5.9% from Q4 2018 - America [California]
10. Sanofi - $115.7 bn – 3.9% from Q4 2018 – France [Paris]
11. GlaxoSmithKline - $105.7 bn – 7.2% from Q4 2018 – United Kingdom [Brentford]
12. AstraZeneca - $103.7 bn – 4.5% from Q4 2018 - United Kingdom [Cambridge]
13. Gilead Sciences – $81.2 bn – 0.3% from Q4 2018 - America [California]
14. Bristol-Meyers Squibb - $78.1 bn – 7.9% from Q4 2018 - America [New York]
15. CSL - $65.9 bn – 5.4% from Q4 2018 – Australia [Melbourne]
16. Takeda Pharmaceuticals - $53.4 bn – 141.8% from Q4 2018 – Japan [Tokyo]
17. Bayer A.G - $63.4 bn – 4.9% from Q4 2018 – Germany [Leverkusen]
18. Celgene - $61.4 bn – 37.1% from Q4 2018 - America [New Jersey]
19. Merck KGaA - $52.2 bn – 13% from Q4 2018 – Germany [Darmstadt]
20. Allergan - $48.7 bn – 8.1% from Q4 2018 – Ireland [Dublin]

(Note these ranks were collected on Q1 of 2019 – BioSpace 2019)

Together these 20 companies reported a collective market cap of $2.63 trillion in Q1 2019, which was an increase of 6.2% from 31st December 2018.

As shown nine of the top 20 pharmaceutical companies in the world are based in the United States (U.S), Meaning that they have an important influence on market trends, what medicines are produced and also more importantly they are more likely to be a country that is a target of counterfeit medicines.

Below in table 2, is just some of the representations of ciprofloxacin medicines that are branded in each country.

Table 2:The comparison between the different brands that are associates with paticular countries.

Name of Country	Brand Name of Ciprofloxacin
Australia	C-Flox, Ciloquin, Ciloxan, Ciprol, Ciproxin, Profloxin, Proquin
Canada	Ciloxan, Cipro
Ireland	Biofloxcin, Cifloxager, Ciproxin, Profloxin, Truoxin
New Zealand	Ciloxan, Cipflox, Ciproxin, Topistin, Ufexil
South Africa	Adco-Ciprin, Biocip, Cifloc, Cifran, Ciloxan, Ciploxx, Cipro-Hexal, Ciprobay, Ciprogen, Dynafloc, Orpic, Spec-Topistin
United Kingdom	Ciloxan, Ciproxin
United States	Ciloxan, Cipro
India	Ciloxan, Cipro, Cifran, Ciplox

2.7.2 Classification

The reason behind the classification of fluroquinolones is due to their wide range of activity and the chemical composition or sometimes known as the pharmacokinetic profile. Ciprofloxacin is a second-generation fluroquinolone.

Out of the fluroquinolone class ciprofloxacin is the most potent. It can be used against a wide range of bacteria. The most vulnerable bacteria against ciprofloxacin are

Neisseria and Enterobacteriaceae, which are aerobic gram-negative bacilli (Farhi et al. 2009).

It is a very successful, capable and effective drug due to its well-established safety aspects and alongside the widely acclaimed potency against a vast number of bacteria.

With more than 250 million patients treated ciprofloxacin is a worldwide success that has been extensively studied, part of that research was into its safety profile that has been documented in numerous publications over the years (Brunner et al. 2004).

Children with cystic fibrosis have been treated with ciprofloxacin as an alternative for antimicrobial therapy. Over 1500 patients treated with ciprofloxacin has identified a safety profile for adults, adolescents and children (Kubin 1993).

The minimum inhibitory concentration (MIC) of ciprofloxacin compared to the other fluroquinolones used commonly for in vitro susceptibility illustrated a distinct superiority when tested against multiple Gram-negative bacterial strains.

Due to ciprofloxacin's broad-spectrums antibiotic properties is used for treatment in cancer patients. It is mainly used because of its apoptotic and antiproliferative activities that are present in several cancer cell lines.

It was detected that the dose-dependent and time – dependent growths caused in a variety of leukaemia cell lines, osteosarcoma and carcinoma were inhibited by ciprofloxacin (Herold et al. 2002).

2.7.3 Mode of action

Fluroquinolones inhibit the bacterial enzyme Deoxyribonucleic acid (DNA) gyrase by nicking/slicing the double stranded DNA introducing the negative supercoils then finally reseals the nicked end of the DNA strand.

This process is necessary to avoid excessive build-up of positive supercoiling strands, when they are separated to allow transcription and replication of the DNA (Cozzarelli 1980; Schmitz 1998).

An enzyme called helicase is used in the process for transcription and replication to unwind the double helix DNA strand. Whilst uncoiling the DNA tension builds due to the surplus supercoiling of the outstanding DNA double helix.

For the overall process to continue and be successful the tension needs to be relieved. The release comes in the form of topoisomerase II enzyme which allows the supercoiled DNA. It breaks both strands of the DNA, overlaps them reforming the double helix structure then reseals them (Patrick 2017).

Ciprofloxacin impedes the activation of DNA gyrase (which is an essential adenosine triphosphate-hydrolysing topoisomerase II enzyme) or ciprofloxacin can prevent the detachment of gyrase from the DNA strand.

When the topoisomerases interact with the DNA it uses its bactericidal ability (Walters et al. 1999).

2.7.4 Current synthetic developments

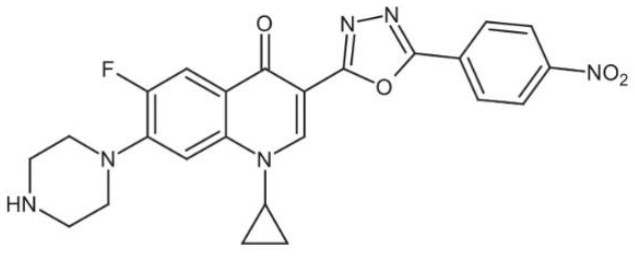
As ciprofloxacin is a commonly used antibiotic that's used to treat a wide range of infections there has been extensive efforts to modify and optimise its potency and activity. Synthetic developments were used to derive an array of a variety of potent analogue candidates of this drug.

The molecular modifications were created by a variety of useful techniques such as branching of the side chain, homologation of the side chain, bio isosteric replacements or stereochemistry to name a few (Abraham & Burger 2003).

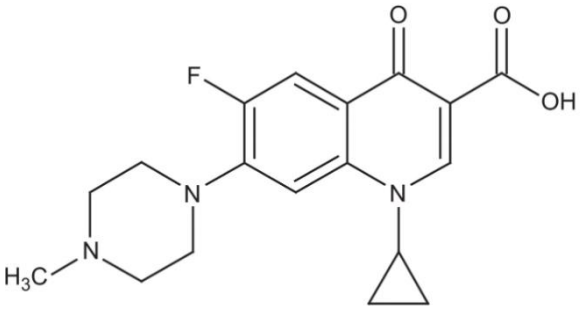
A collective of derivatives of ciprofloxacin have been illustrated to have a successful improvement for potency and activity.

A list of derivatives include:

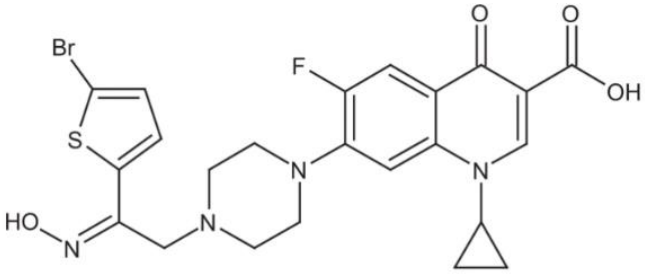
(A) 1-cyclopropyl-6-fluoro-3-(5-(4-nitrophenyl)1,3,4-oxadiazol-2-yl)-7-(piperazin-1-yl) quinolin-4(1H)-one



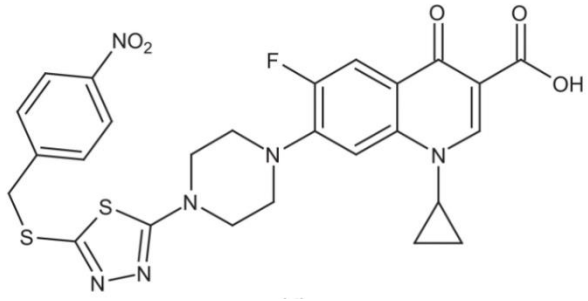
(B) 4-methyl-7-piperazine ciprofloxacin



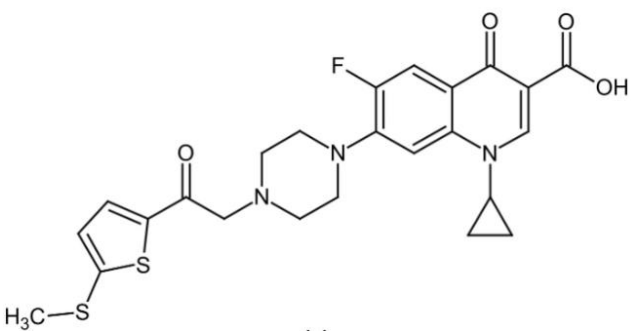
(C) 7-(4-(2-(5-bromothiophen-2-yl)-2-(hydroxyamino) ethyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



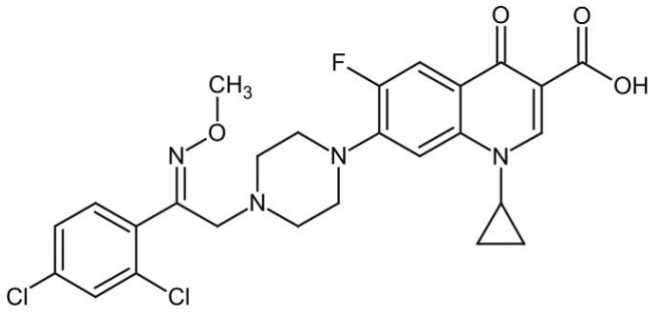
(D) -(4-(5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-yl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



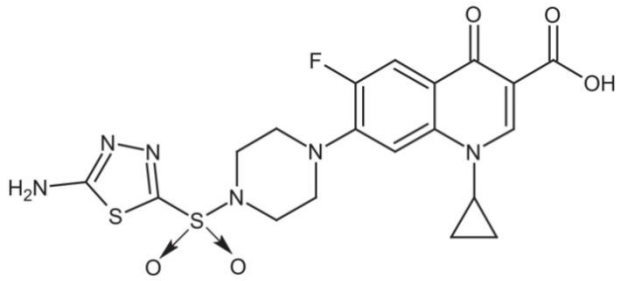
(E) 1-cyclopropyl-6-fluoro-7-(4-(2-(5-(methyl thio) thiophen-2-yl)-2-oxoethyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



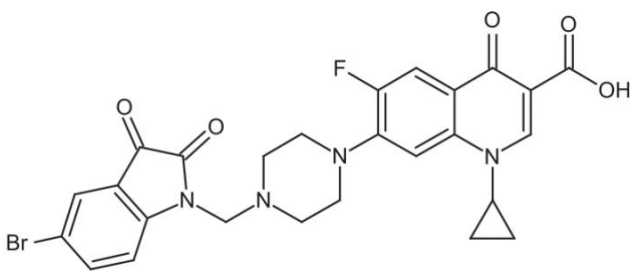
(F) 1-cyclopropyl-7-(4-(2-(2,4-dichlorophenyl)-2-(methoxyimino) ethyl) piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



(G) 7-(4-(5-amino-1,3,4 thiadiazole-2-ylsulfonyl) piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



(H) 7-[4-{(5-bromo-2,3-dioxoindolin-1-yl) methyl} piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



2.7.11 Analytical aspects

Following on from the introduction of Quinolones, the research and development thus far has been rapid in progress and has resulted in a variety or important fluroquinolones.

These fluroquinolones have been under immense scrutiny to understand their physiochemical properties, the uses those particular dosages of ciprofloxacin in certain forms and biological fluids.

Due to this many analytical and assay methods have been used to determine such features of ciprofloxacin and similar compounds.

2.7.12 Physical properties

In its purest form ciprofloxacin arises as a white powder that is thought to have a bitter taste. To minimize the potential for photolytically induced degradation ciprofloxacin should be stored in a dark cool place at ~4°C. the melting point of ciprofloxacin is between 313–315°C. one of the benefits of ciprofloxacin is how freely soluble it is, it can be dissolved in methanol, ethanol, acetone and acetic acid, but partially soluble in water.

The coefficient for the octanol/water partition for ciprofloxacin is known to be less that one (Hirai et al. 1986).

pI = 7.14 (isoelectric point, which is the average of pKa_1 and pKa_2)., pKa_1 = 6.09 and pKa_2 = 8.62 are some of the pH-solubility profile dissociation and isoelectric constants for ciprofloxacin.

These levels suggest that the N-4 of the piperazine substituent and the 6-carboxylic group are the two ionizable functional groups.

Since the ammonium group tends to be the weaker of the two groups, the second ionization constant pKa_2 (8.62) corresponds to the N-4 in the piperazinyl group

proton dissociation, whereas the 6-carboxylic group is represented by pKa_1 (6.09) which is the first ionization constant (Varanda et al. 2006).

pKa_2 value is 8.25 when the ciprofloxacin is at its most physiologically relevant pH, significant dissociation occurs for both the ammonium and carboxylic groups, thus causing substantial fractions of zwitterionic species.

2.7.13 Pharmacokinetic aspects

The pharmacokinetic characteristics of ciprofloxacin are the main reasons why it is commonly used as treatment today.

The primary factors are described in more detail below are as follows; the absorption, distribution, metabolism and finally the elimination of such compound.

2.7.14 Absorption

Even though ciprofloxacin is normally readily absorbed, when administered orally, its complete absorption is typically not achieved via this method.

First pass metabolism does not cause a considerable loss of bioavailability of ciprofloxacin when administered orally. Via oral consumption the complete bioavailability is within the range of 70% - 80% (Morgan 1997).

When intravenously administered (IV) it had a higher bioavailability similar to other medicines. As seen the IV dosage required is less than the equivalent dosage of oral to have a similar effect.

For example, a 500mg tablet given every 12 hours produces an area under the serum concentration-time curve (AUC) equivalent to a 400mg IV infusion given over 60-minute period every 12 hours. Other such comparisons are illustrated in table 3 (Morgan 1997).

Table 3: Examples of how oral dosages compare to the equivanlent IV dosages.

Equivalent AUC Dosing Regimens

Oral Dosage	Equivalent IV Dosage
250mg Tablet every 12 hours	200mg intravenous every 12 hours
500mg Tablet every 12 hours	400mg intravenous every 12 hours
700mg Tablet every 12 hours	400mg intravenous every 8 hours

The pharmacokinetics of Ciprofloxacin within cerebrospinal fluid (CSF) has been described in many studies, it has been found that the penetration when compared to the corresponding serum concentrations was exceptional.

However, the absolute CSF concentration was often at times thought to be subtherapeutic (Leone 2002).

Within the blood-brain barrier there is a slow flux of ciprofloxacin which is suggested by the relative consistency of the CSF level (Lipman et al. 2000).

It is believed that even though a drug-food interaction is known to prolong amount of time needed for the maximum plasma concentration (t_{max}) to be reached, it does not however affect the bioavailability of the drug substantially (Blandeau 1999).

Ciprofloxacin's pharmacokinetic are expected in table 4

Table 4: Comparison between the value and the pharmacokinetic charachteristics/parameters.

Pharmacokinetic Parameter	Value
Elimination half-life (h)	4.16
Oral bioavailability	70-80%
Maximum drug concentration in plasma (mg/L)	0.56
Area under the curve (µg h/mL)	2.56
Primary route of excretion	Renal
Time to peak (h)	1.1
Plasma protein binding (%)	20-40%
Renal clearance (L/h)	21.4
Disposition (% of dose)	
Renal	40-60%
Faecal/biliary	15
Metabolized	10-15%

2.7.15 Distribution

One of the reasons ciprofloxacin is superior to that of other fluroquinolones is because there is little to no binding to plasma proteins.

After oral administration and except for the central nervous system (CNS) it has a good amount of penetration in numerous tissues and fluid of the body.

Except when the meninges are inflamed there is a poor penetration into the cerebrospinal fluid. The liver, kidney, lung and prostate show a substantial drug level that has been achieved.

One of the primary reasons it is used for urinary tract infections is due to the urinary drug concentration which is higher than the minimal inhibitory concentration (Appelbaum & Hunter 2000).

As only a very small fraction of ciprofloxacin passes from mother to unborn child it is suggested that there is a barrier within the human placenta which slows down if not inhibits the transport of fluroquinolones (Polachek et al. 2005).

The bioavailability within the interstitial target site for ciprofloxacin is considered to be a determinant for the efficiency and successfulness of the antimicrobial therapy.

2.7.16 Metabolism and elimination

There is a variety in which the degree of metabolism and elimination of ciprofloxacin via the liver or renal excretion occurs within patients treated.

Even though the primary route for elimination of ciprofloxacin is via the glomerulus filtration and tubular secretion renal route (Davis 2007), eliminations occur both via renal and non-renal routes.

Therefore, if a patient was to have renal impairment their second path of elimination would be via the liver and the dosage would be changed accordingly (Morgan 1997). Unfortunate ciprofloxacin is not cleared from the bodies system substantially well especially by both haemodialysis and peritoneal dialysis.

There is also known to be a reduction in from the metabolism of ciprofloxacin to oxo-ciprofloxacin by hepatic cirrhosis (Wolfson & Hooper 1991).

2.7.17 Adverse effects

When compared to the benefits you gain from using ciprofloxacin the adverse effects are no too severe. At therapeutic doses ciprofloxacin has a mild toxicity, and the adverse effects are generally limited to gastrointestinal incidents such as vomiting, nausea and diarrhoea (Sárközy 2001).

However, skin photosensitivity has also been proven to be a reaction to the use of ciprofloxacin (Appelbaum & Hunter 2000).

Over the years there has been an increasing amount of resistance in pneumococci even though usually that is quite rare (Ho et al. 1999).

Aseptic meningitis (Kepa et al. 2005) and arthritis damage (Mao et al. 2005) are just some of the consequences of ciprofloxacin being used to treat anthrax (Liu et al. 2008).

Due to the higher dosage required to pass through the blood-brain barrier (BBB), therefore there is now a need to increase the managed uptake to the brain for successful treatment (Feliciano et al. 2008).

As with resistance in pneumococci, there has been a growing resistance and infective complications when ciprofloxacin is used as an antibiotic prophylaxis for prostate biopsies (Feliciano et al. 2008).

2.7.18 Drug interactions

Antacids containing sucralfate, aluminium and other agents such magnesium have been known to reduce the absorption of ciprofloxacin after being digested (Sárközy 2001).

For this reason, it might be hazardous to use together whilst treating a serious infection (Dollery 1999).

The interaction between methylxanthines such as caffeine and ciprofloxacin have a disturbing if not more fatal interaction with each other than the interaction with antacids.

During this interaction there is a rise in serum theophylline concentration to a significant amount, which involves the isoenzyme 1A2 of the cytochrome P-450 pathway becoming more pronounced the more it is used. Consequently, the monitoring of the xanthine's is needed along with required dose reduction (Efthymiopoulos et al. 1997)

The use of ciprofloxacin has also been associated with the elevation in serum levels of cyclosporine.

However, an increase in the serum concentration along with a significant decline in the clearance of ciprofloxacin throughout the system when an interaction is observed when it is paired with cimetidine, azlocillin and probenecid.

On the other end of the spectrum due to the interaction with the ciprofloxacin the serum concentration of antineoplastic drugs lowers significantly (Lubasch et al. 2000)

Citrates, carbonic anhydrase inhibitors and sodium bicarbonate, impede the solubility of ciprofloxacin thus causing the urine to become alkaline and consequently leading to crystalluria (Efthymiopoulos et al. 1997; Dollery 1999; Boy et al. 2004).

2.7.19 Clinical indications

As suggested earlier Ciprofloxacin is effective against a broad range of bacterial infections, even those that are often deems difficult to treat.

Due to the wide-spectrum nature of ciprofloxacin oral efficacy, bactericidal and the general good tolerability, it is being used widely for blind therapy infections. However, if a Gram-positive organism is suspected to be the cause of infection. It should also not be used for minor cases (Efthymiopoulos et al. 1997; Dollery 1999; Boy et al. 2004).

Table 5: Comparison between the Clinical indications and the Infection causing organisms.

Clinical indication	Infection-causing organisms
Urinary Tract Infections	Escherichia Coli, Klebsiella Pneumoniae, Enterobacter Cloacae, Serratia Marcescens, Proteus Mirabilis, Providencia Rettgeri, Morganella Morganii, Citrobacter Diversus, Citrobacter Freundii, Pseudomonas Aeruginosa, Staphylococcus Epidermidis, Staphylococcus saprophyticus, or Enterococcus faecalis
Acute Uncomplicated Cystitis in Females	Escherichia Coli or Staphylococcus Saprophyticus
Chronic Bacterial Prostatitis	Escherichia Coli or Proteus Mirabilis
Lower Respiratory Tract Infections	Escherichia Coli, Klebsiella Pneumoniae, Enterobacter Cloacae, Proteus Mirabilis, Pseudomonas Aeruginosa, Haemophilus Influenzae, Haemophilus Parainfluenza, or Streptococcus Pneumoniae
Acute Sinusitis	Haemophilus Influenzae, Streptococcus Pneumoniae, or Moraxella Catarrhalis
Skin and Skin Structure Infections	Escherichia Coli, Klebsiella Pneumoniae, Enterobacter Cloacae, Proteus Mirabilis, Proteus Vulgaris, Providencia Stuartii, Morganella Morganii, Citrobacter Freundii, Pseudomonas Aeruginosa, Staphylococcus Aureus (Methicillin-susceptible), Staphylococcus epidermidis, or Streptococcus pyogenes
Bone and Joint Infections	Enterobacter Cloacae, Serratia Marcescens, or Pseudomonas Aeruginosa
Infectious Diarrhoea	Escherichia Coli (enterotoxigenic strains), Campylobacter Jejuni, Shigella Boydiia, Shigella Dysenteries, Shigella Flexera, or Shigella Sonnei
Typhoid Fever	Salmonella Typhi
Uncomplicated Cervical and Urethral Gonorrhoea	Neisseria Gonorrhoeae
Pyelonephritis	Escherichia Coli

2.8 Excipients:

2.8.1 Medicine Dosage Forms & Excipients

Ever since medicine was first discovered and used to ease the wounded or cure illness, the route it has been administered has always been evolving. The evolution of this pathway is to find the optimal dosage and environment for the drug to be given (Williams 1996; Rowe et al. 2003; O'Shaughnessy 2015; Abrantes et al. 2016).

There are two main factors that determine if a drug will or will not reach the intended site of action within the body and if it has an impact.

1. The bioavailability of the drug – the extent at which the drug/metabolites become completely available to its intended biological destinations e.g. the site of action within the body.
2. How the drug is given to the patient – the route of administration

Combining these factors are vital in determining the correct treatment for the patient.

The way a person reacts to a drug entering the body impacts whether they can effectively use the medicine. By understanding the different routes and what the medicine is made of can help determine what the best course of treatment is.

This section focuses on the medicines themselves, how they are administered, the forms of administration and what they are comprised of.

All of these points together form a picture of how society can be deceived into buying a counterfeit which seems genuine, over its real counterpart.

2.8.2 Route of Administration

There are various routes of administration that each have their own advantages and disadvantages. The reason being that once the drug enters the body it is metabolised in different sections of the body. This causes different speeds of action within the patient e.g some medicines are known to have slow-release mechanisms allowing for the medicine to work over a few hours rather than a quick release which has an almost immediate and short effect.

The routes of administration are as follows (Williams 1996; Rowe et al. 2003; O'Shaughnessy 2015; Abrantes et al. 2016):

- Oral – via the mouth
- Injection
    - Intravenously, IV – into the vein
    - Intramuscularly, IM – into the muscle
    - Intrathecally – into the space around the spinal cord
    - Subcutaneously, SC – beneath the skin
    - Implantation – inserted into the body
- Sublingual – under the tongue
- Buccal – between the cheek and gums
    - Inserted
        - Rectally – into the rectum
        - Vaginally – into the vagina
    - Placed
        - Ocular – into the eye
        - Otic – into the ear
- Nasal – sprayed or absorbed through the nasal channel in the nose
- Nebulization – breathed into the lungs
    - Inhalation - usually through the mouth
- Cutaneous – applied to the skin

- Topical – local effect
- Systematic – body wide effect
    - Transdermal – normally a patch on the skin

2.8.3 Types Dosage Forms

The term dosage relates not only to the strength of medicine given but also the physical form by which the drug molecules are delivered to the desired site of action.

There are four categories which the forms are split into similar to everyday life (Williams 1996; Rowe et al. 2003; O'Shaughnessy 2015; Abrantes et al. 2016):

Solid Dosage Forms

1. Semi – Solid Dosage Forms
2. Liquid Dosage Forms
3. Gas Dosage Forms

The most common dosage form is that of the solid variety.

There are two sections in which drugs are categories in when focusing on the strength and volume of the dosage.

1. Unit Dose
2. Bulk Dose

2.8.4 Solid Dosage Forms

Solid Dosage Forms are aptly names as they occur in a solid state, they are often used for the therapeutic effect either via and oral or nebulization/ inhalation route.

Examples of Solid Dosage Forms (O'Shaughnessy 2015):

- Tablets/Pills – Are compressed solid dosage forms that contain the excipients and active ingredients. (Unit Dose).
- Capsules – Unlike tablets where the particles are compressed, the particles are placed into a soft or hard soluble shell. (Unit Dose).

- Granules – An agglomeration of much smaller particles of powders. (Unit Dose).
- Sachets – A small bag or pouch packet that contains small sized spherical granules. (Unit Dose).
- Lozenges – A solid dosage form that when placed in the mouth dissolves slowly. (Unit Dose).
- Powders – Are the base forms of all solid dosage forms. (Bulk Dose).
- Dry Powder Inhalers – Small powder particles that are delivered to the lungs by making a similar characteristic to gas. (Unit Dose).
- Chewables – Are solid forms that are similar to tablets and capsules but needed to be chewed for the desired effect. (Unit Dose).

Advantages:

- More stable than other dosage forms.
- Easy to handle.
- Most accurate over the other dosage forms.
- No preservation required.

Disadvantages:

- Expensive Machines used in their creation.
- Hard for kids and patients to swallow if unconscious or nil by mouth

2.8.5 Semi – Solid Dosage Forms

Semi – solid dosage forms are solids that can act like a liquid, they are mainly used for topical treatment via the skin, nasal, vaginal and rectal cavities (Rowe et al. 2003).

Examples of Semi - Solid Dosage Forms (Williams 1996; Rowe et al. 2003; O'Shaughnessy 2015; Abrantes et al. 2016):

- Ointments – A smooth Oily substance created from a mixture of ingredients. (Unit Dose).

- Pastes – Either a hard or smooth thick mixture that can be spread over treatment area. (Unit Dose).
- Cream – Emulsions of oil and water, either oil-in-water (O/W) or water-in-oil (W/O). (Unit Dose).
- Plasters (treatment within) – A relatively thick smooth mass that has a strong adhesive that becomes solid over time. (Unit Dose).
- Gels – They range from being soft and weak to hard and tough, they are dilute cross-linked system that exhibits no flow when in a steady state, otherwise it acts like a liquid. (Unit Dose).

Advantages:

- Suitable dosage form for bitter drugs
- It is used externally
- Local action and Site-specific action of the drug on the affected area.
- The probability of side effects can be reduced
- First, pass gut and hepatic metabolism is avoided.
- More stable than a liquid dosage form
- Convenient for unconscious patients or patients to have difficulty in oral administration.

Disadvantages:

- May cause staining.
- Physicochemical is less stable than a solid dosage form.
- The accuracy can't be measured, for the semisolid dosage form.
- Application with a finger may cause contamination.
- They are bulky to handle.
- May cause irritation or allergy to some patients

Ideal Properties:

- Non-gritty
- Smooth texture

- Non-greasy and non-staining
- Elegant in appearance
- Non-hygroscopic
- Non-dehydrating

2.8.6 Liquid Dosage Forms

Liquid Dosage Forms occur in a liquid state, they are often used via oral, subcutaneous, intravenous, intramuscular, cutaneous (topical and systematic), Ocular and Otic.

Liquid dosage forms can be divided into two sections according to their phases and both have either external or internal use (Rowe et al. 2003):

1. Monophasic – Only one phase that is liquid.
    a. Internal Use:
        i. Syrup – Either a thick or runny sweet liquid made from boiling sugar and other constituents in water.
        ii. Mixture – One or more liquids that blend together smoothly to form a solution.
        iii. Linctus – A syrup or sticky preparation that is used for a local therapeutic action on the mucous membrane within the throat.
        iv. Elixirs – A hydro-alcoholic solutions that contains at least one active ingredient.
        v. Parenteral preparations – Solutions, suspension and emulsions that are prepared for injection.

    b. External Use:
        i. Gargle – The action of using a non-digestible liquid used as an intraoral wash.
        ii. Mouthwash - A non-digestible liquid used as an intraoral wash
        iii. Lotions – A thick, smooth or gritty liquid preparation.

iv. Nasal Drops – A solution of ingredients that are used in the nasal passage, they can be converted into a spray for inhalation and local effect.

v. Ear Drops – A mixed solution of excipients that are used in the ear cavity.

vi. Eye Drops - A blended solution of ingredients that are used in the eye cavities.

2. Biphasic – Two phases one liquid and one solid.
    a. Internal Use:
        i. Suspension – Two or more substances one the solvent and the others solid particles that do not mix with each other and the particles are left suspended in the solution.
    b. External Use:
        i. Emulsion – Similar to creams they are made of two or more (liquid) substances that do not cohesively mix without forced effort e.g., oil and water.

Advantages:

- The rate of absorption of the liquid dosage form is so faster than the solid dosage form.
- Very useful for those patients who have trouble swallowing.
- Liquid dosage forms are flexible to take a proper those than solid dose

Disadvantages:

- The problem of container breakage.
- Affected by microorganisms: Due to the presence of sweetening and flavouring agents.
- It needs a lot of special storage conditions.

- Less stable than other doses.

2.8.7 Gas Dosage Forms

Gas Dosage forms are particles that are in a gaseous state. They are stored in containers and are released upon applying pressure. The containers have valve systems that allow for limited or continuous delivery.

Examples of Gas Dosage Forms (Rowe et al. 2003):

- Vaporizer – A device that vaporizes the liquid based into it to create a gas so that it can be inhaled.
- Sprays – Liquid droplets that are dispersed in a large surface area, usual for local topical effect.
- Aerosols – A colloidal suspension of a particles dispersed in the air via a gas.
- Nebulizer – A device used to create a gaseous spray from a liquid by means of compression, oxygen or ultrasonic vibrations (it is sometimes referred to as an atomizer).
- Atomizer – An instrument that reduces a liquid into a spray (disinfecting, cooling, medicinal use or perfumes).
- Inhalers – Solutions, suspensions or emulsions of drugs in mixtures of inert propellants held under pressure in a gaseous dispenser such as inhalers and aerosols.

There are no advantages or disadvantages that specifically apply to gas dosage forms but apply to the medicines they carry such as the liquids that are pressurised.

2.9 Pharmaceutical Excipients

Within a medicine there is a variety of components to make sure it functions correctly, each of the components has a specific job. In this section the different types of excipients will be explored; the category, properties and examples of chemicals within the category.

An Excipient is:

"An excipient is any constituent of a medicinal product that is not an active substance used in the creation of pharmaceutical products. The desired effect of an excipients is to guarantee physiochemical and biopharmaceutical success" – (British Pharmacopeia 2017)

2.9.1 Excipient Classification

Excipients are broken into three classifications; Standard, Mixed and Co-processed.

Standard Excipients: Either compendial or non-compendial inactive substances (Compendial means that the substances are indexed in the pharmacopeia.

Mixed Excipients: A mixture of two or more compendial or non-compendial substances, this mixture can be either in a liquid or solid form.

Co-processed Excipients: A combination of two or more compendial or non-compendial substances, in a variety of methods such as melt extrusion, granulation, milling and spray drying.

Following on excipients are separated into four source points; animal, vegetable, mineral and synthetic.

Animal Sources: Extracted from animals such as Lactose, Beeswax and Gelatine

Vegetable Sources: Extracted from plants and vegetables such as Peppermint, Starch and Guar Gum.

Mineral Sources: Extracted from the earth such as Silica, Talc and Calcium Phosphate.

Synthetic Sources: Man-made (via combination methods) such as Lactic Acid, Polyethylene Glycols and Saccharin.

2.9.2 Characteristics of Excipients

For an excipient to be successful in use it must have the following characteristics (Abrantes et al. 2016):

1. It must be physiologically inert.
2. Stable both physically and chemically - either by themselves or in combination with other excipients or drugs.
3. Available commercially within an acceptable physical and chemical grade.
4. Accepted by the FDA/ regulatory agencies and non-toxic.
5. Compatible with drugs.
6. Have organoleptic properties that are accepted such as odourless and colourless.
7. Impurity and microbial hazard free.
8. Aid not hamper the bioavailability of the overall drug.
9. Economical
10. The quality must not be put into question.

2.9.3 Excipient Functionality

Along with the characteristics the excipients also have a purpose e.g., the functionality. These functions together combine to make the medicines we know as a society.

Pharmaceutical Excipient Functions are as follows; Fillers, Binders, Disintegrants, Glidants, Organoleptic Additives - Colouring Agents, Flavouring Agents and

Sweetening Agents, Anti-adherent, Lubricants, Coatings, Preservatives, Antioxidants, Sorbents, Solvent & Co-Solvent, Buffering Agents, Chelating Agents, Viscosity Imparting Agents and Humectants.

Filler/Dilutants: Also known as fillers or bulking agents, dilutants are components within a solid dosage form to increase the volume or weight of the medicine (O'Shaughnessy 2015).

Examples of Dilutants are as follows:

- Microcrystalline Cellulose
- Powdered Cellulose
- Anhydrous Lactose
- Lactose Monohydrate
- Spray-Dried Lactose,
- Mannitol [preferable for chewable tablet]
- Starch
- Pregelatinized Starch
- Maize Starch
- Corn Starch
- Sorbitol
- Sucrose
- Compressible Sugar (20–60% for chewable tablets)
- Confectioner's Sugar (10–50%)
- Sugar Spheres
- Dextrates
- Dextrin
- Dextrose
- Calcium Phosphate, Dibasic, Anhydrous
- Calcium Carbonate
- Maltose
- Maltodextrin
- Kaolin
- Calcium Phosphate, Dibasic, Dihydrate
- Tribasic Calcium Phosphate,
- Calcium Sulphate
- Cellaburate
- Calcium Lactate
- Cellulose Acetate
- Silicified Microcrystalline Cellulose,
- Cellulose Acetate
- Corn Syrup
- Pregelatinized Starch and Corn Starch
- Corn Syrup Solids
- Erythritol (30.0–90.0%)
- Ethyl- cellulose (1.0–3.0%)
- Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion
- Fructose
- Isomaltose
- Alpha-Lactalbumin
- Lactitol
- Magnesium Carbonate (direct compression ≤45)
- Magnesium Oxide
- Methacrylic Acid and Ethyl Acrylate Copolymer
- Methacrylic Acid and Methyl Methacrylate Copolymer
- Polydextrose
- Sodium Chloride (Capsule diluent 10–80%)
- Simethicone
- Pregelatinized Modified Starch
- Starch, Pea
- Hydroxypropyl Pea Starch
- Starch, Pregelatinized Hydroxypropyl Pea
- Potato Starch
- Starch, Hydroxypropyl Potato
- Pregelatinized Hydroxypropyl Potato Starch,
- Starch, Tapioca
- Wheat Starch
- Starch Hydrolysate, Hydrogenated
- Pullulan
- Talc (Tablet and capsule diluent 5.0–30.0%)
- Amino Methacrylate Copolymer
- Trehalose
- Xylitol

Binders: Also known as granulators, binders are substances that are used in formulations to facilitate the agglomeration of loose powder to clustered granules This often occurs in the presence of a granulating liquid such as hydroalcoholic mixtures, dihydrogen monoxide (water) and other solvents (Williams 1996).

Examples of Blinders are as follows:

- Polyvinylpyrrolidone is also known as Povidone,
- Copovidone
- Carbomer
- Corn Starch and Pregelatinized Starch
- Pregelatinised starch
- Carboxymethylcellulose Sodium, Carmellose Sodium
- Hypromellose/ hydroxypropyl methylcellulose (HPMC)
- PEG (Polyethylene Glycol)
- Hydroxyethyl Cellulose
- Hydroxypropyl Cellulose
- Hydroxyethyl methyl Cellulose
- Calcium carboxymethylcellulose/ Calcium cellulose glycolate
- Guar Galactomannan/ Guar Gum
- Ethyl-cellulose
- Chitosan Hydrochloride
- Dextrin
- Low-Substituted Hydroxypropyl Cellulose
- Hydroxypropyl Starch
- Ceratonia
- Inulin
- Magnesium Aluminium Silicate
- Maltodextrin
- Methylcellulose
- Dextrates
- Polyethylene Oxide
- Povidone
- Sodium Alginate
- Starch
- Sucrose
- Compressible sugar
- Zein
- Gelatine
- Polymethacrylates
- Sorbitol
- Glucose
- Zein
- Acacia

Disintegrants: A substant or a mixture of multiple substances that are added to a formula to facilitate the breakdown/ disintegration of the medicine into smaller fragments allowing for faster dissolution (Abrantes et al. 2016).

When a disintegrants interacts with a liquid such as water, intestinal or stomach acid, they can absorb said liquid causing them to dissolve, swell of even form gel like substances. Consequently, the medicine form (often a tablet) will disintegrate or rupture thus increasing the surface area of the drug substance for improved dissolution (Rowe et al. 2003).

Examples of Blinders are as follows:

- Crospovidone
- Croscarmellose Sodium Low-Substituted Hydroxypropyl Cellulose
- Sodium Starch Glycolate
- Chitosan Hydrochloride
- Corn Starch and Pregelatinized Starch
- Calcium Alginate & Calcium Sodium Alginate
- Docusate Sodium
- Microcrystalline Cellulose
- Hydroxypropyl Starch
- Magnesium Aluminium Silicate
- Methylcellulose
- Sodium Alginate
- Starch
- Pregelatinised Starch
- Calcium Carboxymethylcellulose
- Powdered Cellulose

Coatings: Are Substances that coat a medicine in the form of a tablet, capsule and other particles. Not all tablets need coatings (O'Shaughnessy 2015).

A successful coating formula most commonly consists of:

- Colourants
- Solvents
- Opaquant – Extenders
- Plasticizers
- Film Formers – Enteric or Non-Enteric
- Miscellaneous coating solution components

Solvent & Co-Solvent: A solvent is the base of a solution formed by combining with a solute. A co-solvent is a substance that is added to the primary solvent in a solution to aid in increasing the solubility of a poorly-soluble compound (Rowe et al. 2003).

Examples of Solvent include:

- Acetone
- Alcohol
- Amylene Hydrate
- Benzyl Benzoate
- Butyl Alcohol
- Canola Oil
- Capryl Caproyl Polyoxylglycerides
- Corn Oil
- Cottonseed Oil
- Diethylene Glycol Monomethyl Ether
- Ethyl Acetate
- Glycerine
- Hexylene Glycol
- Isopropyl Alcohol
- Lauroyl Polyoxylglycerides
- Linoleoyl Polyoxylglycerides
- Methyl alcohol
- Methylene Chloride
- Methyl Isobutyl Ketone
- Mineral Oil
- Oleoyl Polyoxylglycerides
- Peanut Oil
- Polyethylene Glycol
- Polyethylene Glycol Monomethyl ether
- Propylene glycol
- Sesame Oil
- Stearoyl Polyoxylglycerides
- Water

Examples of Co- Solvent include:

- Ethanol
- Propylene Glycol
- Glycerine
- Glycofural
- Polyethylene Glycols

Polymers: A substance that consists of very large molecules or macromolecules comprised of many repeating subunits (Abrantes et al. 2016).

Examples of Polymers include:

- Chitosan
- Carrageenan
- Ispaghula
- Acacia
- Gelatine
- Agar
- Shellac
- Guar Gum

Plasticizers: A substance that is added to compound to increase its plasticity, decrease its viscosity and friction to ultimately make the compound softer and more flexible (Williams 1996).

Examples of Plasticizers include:

- Citrate Esters
  - Triethyl Citrate
  - Tributyl Citrate
  - Acetyl Triethyl Citrate
  - Acetyl Tributyl Citrate
- Fatty Acids Esters
  - Butyl Stearate
  - Glycerol Mono Stearate
  - Stearyl Alcohol
- Sebacate Esters
  - Dibutyl Sebacate
- Phthalate Esters
  - Diethyl Phthalate
  - Dibutyl Phthalate
  - Dioctyl Phthalate
- Glycol Derivatives
  - Polyethylene Glycol
  - Propylene Glycol
- Others
  - Triacetin
  - Mineral Oil
  - Castor Oil
- Vitamin E TPGS
  - D-α-tocopheryl Polyethylene Glycol 1000 Succinate

Film Formers: They are used as protection against environmental factors such as the air, light and moisture. The layer coating the drug helps to increase the mechanical strength, aids the patient in swallowing the drug, helps in product identification e.g., a bright or unique colour, texture and taste (O'Shaughnessy 2015).

The coating also enables to mask the taste and smell, furthermore it can be used to modify the release of the active ingredient.

There are four types of Film Coating:

1. Conventional Film Coating
2. Modified Release Film Coating
3. Sustained Release Film Coating
4. Enteric Film Coating & Non-Enteric Film Coating

Examples of Enteric Film Coating:

- Hydroxyl Propyl Methyl Cellulose
- Sodium Carboxy Cellulose
- Ethyl Cellulose
- Acrylate Polymer EudragitE
- Povidone
- Propyl Ethylene Glycol

Examples of Non-Enteric Film Coating:

- Cellulose Acetate Phthalate
- Acrylate Polymer EudragitL, S
- Hydroxyl Propyl Methyl Cellulose Phthalate
- Polyvinyl Acetate

Anti-adherent: Used to prevent the tablets/pills from sticking to the insides of the dies and to the punches during the compression process. They also go by the name of anti-sticking agents (Williams 1996).

Examples of Anti-adherent include:

- Starch (Corn-starch)
- Talc
- DL – Leucine
- Sodium Lauryl Sulphate
- Magnesium Stearate (Stearates)
- Colloidal Silicate

Emollients: They are used to adjust the texture of the products, such as ointments, creams and lotions. They are also used to aid in the smoothness and softness of the skin. Typically, they are used in conjunction with emulsifying agents for far better results (O'Shaughnessy 2015).

Examples of Emollients include:

- Glycerine
- Glyceryl Mono Stearate
- Polyethylene Glycol
- Petrolatum
- Isopropyl Myristate

Emulsifying Agents: Used to reduce the surface tension between immiscible liquids or in a mixture between solids and liquids. It is a biphasic preparation that is a combination of two or more liquids that's are forced to mix and remain together, it is successful when the kinetic energy in the mixture is decreased (Abrantes et al. 2016).

The agents that are used are surface active, meaning that they absorb to the freshly made oil-water combo interface during the emulsion process. This absorption characteristic enables the formula to remain a emulsion and not recoalesce or cream.

Examples of Emulsifying Agents include:

- Carbomer
- Carrageenan
- Lanolin
- Lecithin
- Mineral Oil
- Oleic Acid
- Oleyl Alcohol
- Pectin
- Poloxamer
- Polyethylene Sorbitan
- Fatty Acid esters
- Triethanolamine

Humectants: They are used in the prevention of product drying such as creams and gels, this is successful due to the ability to attract and retain water vapour (Rowe et al. 2003).

Humectants can be categorised into three sections:

1. Organic – Carbon based compounds occurring in natural environments.
2. Metal Organic – An organic-inorganic hybrid crystalline porous material.
3. Inorganic – Compounds that contain no carbon elements. However elementary carbon (graphite or diamonds) is considered inorganic alongside Nitrogen, Oxygen and Silicon.

Examples of Humectants include:

- Propylene Glycol
- Glycerine
- Sorbitol
- Triethanolamine
- Glycerol
- Ethylene Glycol
- Polyethylene Glycol (PEG)
- Diethylene Glycol
- Dipropylene Glycol
- Mannitol
- Glucose

Preservatives: a substance that is added to prevent decomposition of the product by undesirable chemical changes or unwanted microbial growth. Consequently, they improve/ amplify the shelf life of the products (Abrantes et al. 2016).

Examples of Preservatives include:

- Methyl Paraben
- Ethyl Paraben
- Propyl Paraben
- Butyl Paraben
- Benzyl Alcohol
- Chlorobutanol
- Phenol
- Meta Cresol
- Chloro Cresol
- Benzoic Acid
- Potassium Benzoate
- Sodium Benzoate
- Phenoxyethanol
- Phenylethyl Alcohol
- Ethanol
- Sorbic Acid
- Thiomersal
- Phenylmercuric Nitrate
- Bronopol
- Propylene Glycol
- Benzalkonium Chloride
- Benzethonium Chloride

Antioxidants: Are substances that protect the Active Pharmaceutical Ingredients (APIs) that would normally degrade in the presence of either oxygen or peroxides (Rowe et al. 2003).

Examples of Antioxidants include:

- Butylated Hydroxy anisole
- Butylated Hydroxytoluene

- Sodium Metabisulphite
- Citric Acid

Sorbents: Are an insoluble substance used to absorb gases and liquids.

There are four types of pharmaceutical sorbents:

1. Activated Alumina
2. Activated Carbon
3. Polymeric Adsorbent
4. Silica Gel

Buffering Agents: Used to adjust the pH of the drug to optimise its stability, they are also used to keep a constant hydrogen ion concentration (Williams 1996).

There are three types of buffers available:

1. Acidic Buffers / Acidifying Agent– Buffers that contain a weak acid and one of its salts. They are used to increase the metabolic acidosis of the patient and the gastric hydrochloric acid.
2. Basic Buffers / Alkalizing Agent - Buffers that contain a weak base and one of its salts. They are used to increase the pH within the body.
3. Double Salt Buffers - Buffers that comprises of two salts.

Examples of Buffers include:

- Acetic Acid
- Citric Acid
- Fumaric Acid
- Hydrochloric Acid
- Malic Acid
- Nitric Acid
- Phosphoric Acid
- Propionic Acid
- Sulfuric Acid
- Tartaric Acid
- Ammonia Solution
- Ammonium Carbonate
- Diethanolamine
- Potassium Hydroxide
- Sodium Bicarbonate
- Sodium Borate
- Sodium Carbonate
- Sodium Hydroxide
- Trolamine
- Boric Acid
- Lactic Acid
- Potassium Citrate
- Sodium Acetate
- Sodium Citrate
- Sodium Lactate Solution
- Sodium Phosphate
- Succinic Acid

Examples of Double Salt Buffers include:

- Monobasic Potassium Phosphate
- Dibasic Potassium Phosphate

Chelating Agents: A chemical compound that reacts with the metal ions in the body to forma a stable water-soluble complex. The reason they are successful is that they have a ring-like centre structure which allows it to form at least two bonds with the metal ions flowing in the body, allowing for it to be excreted (O'Shaughnessy 2015).

- Succimer
- Deferoxamine
- Penicillamine
- Edetic Acid
- Deferasirox
- Ditiocarb

Viscosity Imparting Agents: A substance that is added to a mixture to increase the viscosity without modifying a compounds characteristic. These types of agents improve the suspension of added ingredients, provide a body and increase stability (Abrantes et al. 2016).

Examples of Viscosity Imparting Agents include:

- Hydroxy Ethyl cellulose
- Hydroxy Propyl Methyl Cellulose
- Methyl Cellulose
- Polyvinyl Alcohol

Lubricants: Are non-toxic and are pharmacologically inactive substances that are usually added to formulas to reduce if not prevent frictional forces between particles to each other and between particles and (metal contact surfaces) manufacturing equipment such as dies and punches (Williams 1996).

Liquid lubricants are used before compaction as they are absorbed by the solid dosage forms. Lubricants are also known to improve the flow rate of granulation.

Examples of Lubricants are as follows:

- Magnesium Stearate
- Magnesium Silicate
- Calcium Stearate
- Sodium Lauryl Sulphate
- Sodium Stearyl Fumarate
- Magnesium Lauryl Sulphate
- Stearic Acid
- Calcium Stearate
- Glyceryl Behenate
- Behenoyl Polyoxylglycerides
- Glyceryl Dibehenate
- Lauric Acid
- Glyceryl Monostearate
- Glyceryl Tristearate
- Myristic Acid
- Palmitic Acid
- Poloxamer
- Polyethylene Glycol
- Polyethylene Glycol 3350
- Polysorbate 20
- Polyoxyl 10 Oleyl Ether
- Polyoxyl 15 Hydroxy Stearate
- Polysorbate 40
- Polyoxyl 20 Cetostearyl Ether
- Polyoxyl 40 Stearate
- Polysorbate 60
- Polysorbate 80
- Potassium Benzoate
- Sodium Benzoate
- Sorbitan Monolaurate
- Sorbitan Monooleate
- Sodium Stearate
- Sorbitan Monopalmitate
- Sorbitan Monostearate
- Zinc Stearate
- Sorbitan Sesquioleate
- Sorbitan Trioleate
- Talc

Glidants: Also known as anticaking agents are similar to lubricants in the way that they are non-toxic and are pharmacologically inactive substances used to promote the flow rate of granulation (Rowe et al. 2003).

It also decreases particle friction and unity when powders in particular are stored in bulk. Glidants are added during lubrication but in the dry stages before compaction (Rowe et al. 2003).

Examples of Glidants are as follows:

- Colloidal Silicon Dioxide
- Talc
- Tribasic Calcium Phosphate
- Calcium Silicate
- Cellulose, Powdered
- Magnesium Oxide
- Sodium Stearate
- Magnesium Silicate
- Magnesium Trisilicate
- Silica

Surfactant: Have well defined polar and non-polar regions on the substances that allow for aggregation in the solution that forms micelles. The non-polarised drugs can eventually be partitioned into micelles that can ultimately be solubilised. It acts similar to a lubricant and decrease the interaction/ surface tension occurring between a solid and liquid, a liquid and gas or even between two liquids (Rowe et al. 2003).

Examples of Surfactants are as follows:

- Behenoyl Polyoxylglycerides
- Polysorbate 20
- Polysorbate 40
- Docusate Sodium
- Polysorbate 60
- Polysorbate 80
- Benzalkonium Chloride
- Capryl Caproyl Polyoxylglycerides
- Cetylpyridinium Chloride
- Lauroyl Polyoxylglycerides
- Linoleoyl Polyoxylglycerides
- Octoxynol 9
- Oleoyl Polyoxylglycerides
- Poloxamer
- Polyoxyl 10 Oleyl Ether
- Polyoxyl 15 Hydroxy Stearate
- Nonoxynol 9
- Polyoxyl 20 Cetostearyl Ether
- Polyoxyl 40 Stearate
- Pullulan
- Polyoxyl Lauryl Ether
- Polyoxyl Stearyl Ether
- Sodium Lauryl Sulphate
- Sorbitan Monolaurate
- Sorbitan Monooleate
- Polyoxyl Stearate
- Sorbitan Monopalmitate
- Sorbitan Monostearate
- Stearoyl Polyoxylglycerides
- Sorbitan Sesquioleate
- Sorbitan Trioleate
- Tyloxapol

Colouring Agents: An inactive substance which are added to produce a significant appearance to help differentiate products from each other that would otherwise may have similar physical appearances (Abrantes et al. 2016).

Colouring agents are placed into four categories:

1. Lakes: Insoluble forms of dyes that are a consequence of its irreversible adsorption onto a hydrous metal oxide.
2. Natural Colourants: Colouring Substances that are not considered to be dyes.
3. Dyes: Water – Soluble Colouring substances
4. Inorganic Pigments: Compounds such as metal oxides e.g., Iron Oxide and Titanium Oxide.

Examples of Colouring Agents are as follows:

- Caramel
- Ferric Oxide
- Titanium Dioxide
- Ferrosoferric Oxide
- Aluminium Oxide
- FD & C Red #40 /Allura Red AC
- Amaranth
- FD & C Blue #1 /Brilliant Blue FCF
- Canthaxanthin
- Carmine
- Carmoisine (Azorubine)
- Curcumin (Turmeric)
- FD & C Red #3 /Erythrosine
- Fast Green FCF
- Green S (Lissamine Green)
- D & C Red #30 /Helendon Pink
- FD & C Blue #2 /Indigo Carmine
- Iron Oxide Black
- Iron Oxide Red
- D & C Red #7 / Lithol Rubin BK
- Patent Blue V
- D & C Red #28 / Phloxine B
- Iron Oxide Yellow
- D & C Red #27 / Phloxine O
- Ponceau 4R (Cochineal Red A)
- Quinoline Yellow WS
- D & C Yellow #10
- Riboflavin (Lactoflavin)
- FD & C Yellow #5 /Tartrazine
- FD & C Yellow #6 / Sunset Yellow FCF

Flavouring Agents: Can be a single or combination of chemicals be it natural or synthetic in origin that help make the medicine more palatable for the patient thus increasing their compliance. They produce an aroma or a taste when orally smelled or consumed (Williams 1996).

Examples of Flavouring Agents are as follows:

- Vanillin
- Peppermint flavour powder
- Berry flavour powder
- Strawberry flavour powder
- Orange flavour powder
- Lemon flavour powder
- Orange essence
- Ethyl Maltol (It has a flavour and odour 4–6 times as intense as maltol)
- Eucalyptus Oil
- Isobutyl Alcohol
- Sodium Succinate
- Adipic Acid
- Almond Oil
- Anethole
- Benzaldehyde
- Denatonium Benzoate
- Ethyl Acetate
- Ethyl Vanillin
- Ethyl Cellulose
- Fructose
- Fumaric Acid
- l-Glutamic Acid, Hydrochloride
- Lactitol
- Leucine
- Malic Acid
- Maltol
- Menthol / Racementhol
- Methionine
- Methyl Salicylate
- Monosodium Glutamate
- Peppermint Oil
- Strawberry flavour, liquid
- Peppermint Spirit
- Race Methionine
- Rose Oil
- Rose Water, Stronger
- Sodium Acetate
- Sodium Lactate Solution
- Tartaric Acid
- Thymol
- Fumaric Acid
- Inulin
- Isomaltose
- Neo Hesperidin Dihydrochalcone

Sweetening Agents: They are used to also mask the usual unpleasant taste and flavours that medicines have. The sweeteners bind to the receptors on the tongue that are responsible for the sweet tastes that the body experiences (O'Shaughnessy 2015).

Examples of Sweeteners are as follows:

- Sucralose
- Saccharin Sodium
- Neotame
- Sucrose
- Acesulfame Potassium
- Aspartame
- Aspartame Acesulfame
- Corn Syrup
- Dextrates
- Dextrose
- Erythritol
- Fructose
- Galactose
- Glucose,
- Glycerine
- Inulin
- Invert Sugar
- Isomaltose
- Lactitol
- Maltitol
- Maltose
- Mannitol
- Saccharin
- Saccharin Calcium
- Sorbitol
- Starch Hydrolysate, Hydrogenated
- Sugar, Compressible
- Sugar, Confectioner's
- Tagatose
- Trehalose
- Xylitol

Release Modifying Agents: Are substances that are used to control the speed at which the dosage is released. The most common is a prolonged release or a controlled release (Rowe et al. 2003).

Examples of Release Modifiers are as follows:

- Carbomer Copolymer
- Shellac
- Carbomer Homopolymer
- Hypromellose
- Carbomer Interpolymer
- Carboxymethylcellulose Sodium
- Carrageenan
- Cellaburate
- Ethyl Cellulose
- Glyceryl Monooleate
- Starch, Pregelatinized Modified
- Glyceryl Monostearate
- Guar Gum
- Hydroxypropyl Betadex
- Hydroxypropyl Cellulose
- Polyethylene Oxide
- Polyvinyl Acetate Dispersion
- Sodium Alginate
- Starch, Pregelatinized
- Xanthan Gum
- Alginic Acid

2.10 Instrument – Fourier Transform Near Infrared Spectrometer

The instrumentation that was the basis on the work in identifying the counterfeit medicines was the PerkinElmer Spectrum Two N Fourier-Transform Near Infrared Spectrometer (figure 13).

The PerkinElmer Spectrum Two N FT-NIR fully equipped with a highly sensitive temperature stabilized In GaAs detector for quantitative use and low light applications as well as a $LiTaO_3$ (lithium tantalite) NIR Detector.

Alongside this it is also equipped with, for more repeatable and accurate results, standard Atmospheric Vapour Compensation (AVC), Absolute Virtual Instrument (AVI) and Automatic Performance Verification (APV). It also has OpticsGuard for humidity protection and Dynascan interferometer design.

Figure 13: PerkinElmer Spectrum Two N Fourier-Transform Near Infrared Spectrometer in the process of scanning a ciprofloxacin tablet. As shown in on the computer screen the Spectrum 10 ES IR operating software illustrating the spectra as the sample is scanned.

The collected spectra contained, at intervals around $1cm^{-1}$, over the wavenumber range of 4000 - $10{,}000cm^{-1}$, roughly 6,000 different data points.

The spectra graphs were produced by the Spectrum 10 ES IR operating software that was fitted on the computer whilst it was attached to the instrument.

Spectrum 10 ES IR software was only used when the sample was tested, this was due to it showing the raw data and observations of the sample set could be seen.

Therefore, if a sample was tested but did not follow the pattern of the same sample from previous scans it would be tested again.

2.11 Materials Used for Analysis:

For this research, 40 different materials/excipients were used for analysis. 296 ciprofloxacin tablets were inclusively used from a combination of 28 various batches.

All the batches were purchased and acquired from various countries, from different sources, most of which are deemed reliable. The source of purchase sources includes online pharmacies and brick and mortar versions.

42 raw materials were scanned and analysed in this project, are listed below, three of which are combined as they are commonly found together in medicines. These are the Amoxicillin + Clavulanic Acid as well as the Amoxicillin + Potassium Clavulate.

The raw materials were chosen as the majority of them are found to be excipients in the antibiotic tablets scanned and others show similar properties and were scanned for comparison.

These materials are used in the PCA comparisons of the antibiotics and the binary mixtures and the CWS comparisons containing the raw materials and antibiotics as illustrated further on in this chapter.

Within the APPENDIX illustrates all the details of the various ciprofloxacin batch samples, including product name, average weight of the tablet with the m/m%, batch number, the API that was involved, the manufacturer and the place of purchase (country) were recorded.

The medicines collectively were gathered in a variety of ways, some were remaining tablets from various individuals' treatments. Some were purchased over the counter in multiple abroad countries, some were purchased via the internet and delivered, where others needed to be collected.

By having multiple collection methods, it greatly improves the validity of the tests conducted as not just one area in the supply chain was focused on.

The information gathered as highlighted in the APPENDIX such as different Manufactures, Country of Source, Excipients, and volume of API were tested and recorded. This overall method of approach means that the exploration of counterfeit medicines can be expanded and separated for future in depth analysis.

A list of the raw materials that were used for this study all of which were contained in 4ml clear vials:

- Amoxicillin
- Amoxicillin + Clavulanic Acid
- Amoxicillin Trihydrate + Potassium Clavulate
- Azithromycin
- Ciprofloxacin
- Doxycycline
- Clarithromycin
- Lamivudine
- Cephalexin
- Ofloxacin
- Metronidazole
- Telithromycin
- Erythromycin
- Amoxicillin Hydrates
- Calcium Hydrogen Phosphate
- Ciprofloxacin Hydrochloride
- Citric Acid
- Clindamycin
- Croscarmellose Sodium
- Crospovidone
- Gelatine
- Glucose
- Glyceric Acid
- Glycerine
- Ibuprofen
- Lactose
- Maize starch
- Neomycin Sulphate
- Paracetamol
- Salicylic Acid
- Sodium chloride
- Sodium Citrate Monobasic
- Sodium Stearate
- Stearic Acid
- Sucrose
- Talc
- Magnesium Stearate
- Microcrystalline Cellulose
- Titanium Dioxide
- Sodium Stearyl Fumate

2.12 Method

2.12.1 pre-scanned:

All materials that were measured were in a variety of states, these included; tablets, solutions, crushed powders and liquids. To enable an accurate measurement to be taken each state had a different process that it underwent.

The solutions and liquids were placed into a 4mL water glass vial (transparent). These vials protect the samples from environmental influence such as humidity. The empty vials (E_{V0}) mass was measured first and recorded. The vials were then filled with the various materials using pipette due to the varying viscosity of the solutions, and the mass was re-measured and recorded (E_{V1}).

The measurement originally recorded, E_{vo}, was subtracted from E_{V1} to calculate the mass of the material itself. The properties of the materials found within the vials, such as the name, manufacturer and batch number, were recorded and attached to the vials for future indication of what lay inside.

For the powders the same 4mL water glass vials were used, the empty vials were weighed, and the measurement recorded. Once the vial was filled with the correct material mass using a spatula they were re-weighed, and the measurement was once again recorded. The mass from the empty glass vial was deducted from the overall mass.

The antibiotic tablets (all 296 ciprofloxacin and the comparative antibiotics) however were individually weighed, their mass' were recorded, and then placed into a clear zip bag, which were then labelled with the tablet's properties including the mass, name of tablet, the API, expiration date, batch number, manufacturer and the tablet number within the batch.

2.12.2 Weight Validation

For the powders and solutions, an optimum volume of material within the vials needed to be calculated. The reason being that a uniform mass could then be used with all materials and a clear result could then be examined further.

For this to happen the top five excipients, discovered in literature to be within the tablet categories that were researched in this project, were scanned at various volumes.

The excipients measured were; Magnesium Stearate, Microcrystalline Cellulose, Maize Starch, Talc and Lactose, the volumes measured ranged between 0g – 1g at intervals of approximately 100mg.

Once scanned the spectra from each of the excipients were pre-treated with SG D1 and treated with MSC. The spectra were then examined, and the main seven peaks were identified and the wavenumber corresponding to the peaks was recorded as illustrated in figure 14.

For Microcrystalline Cellulose there were seven main peaks that were discovered; 4298cm^{-1}, 4342cm^{-1}, 4800cm^{-1}, 5216cm^{-1}, 5628cm^{-1}, 6664cm^{-1} and 8192cm^{-1} as seen to be identified in figure 15. The Signal/Noise Ratio for each of the wavenumbers for each of the volumes were grouped for further analysis.

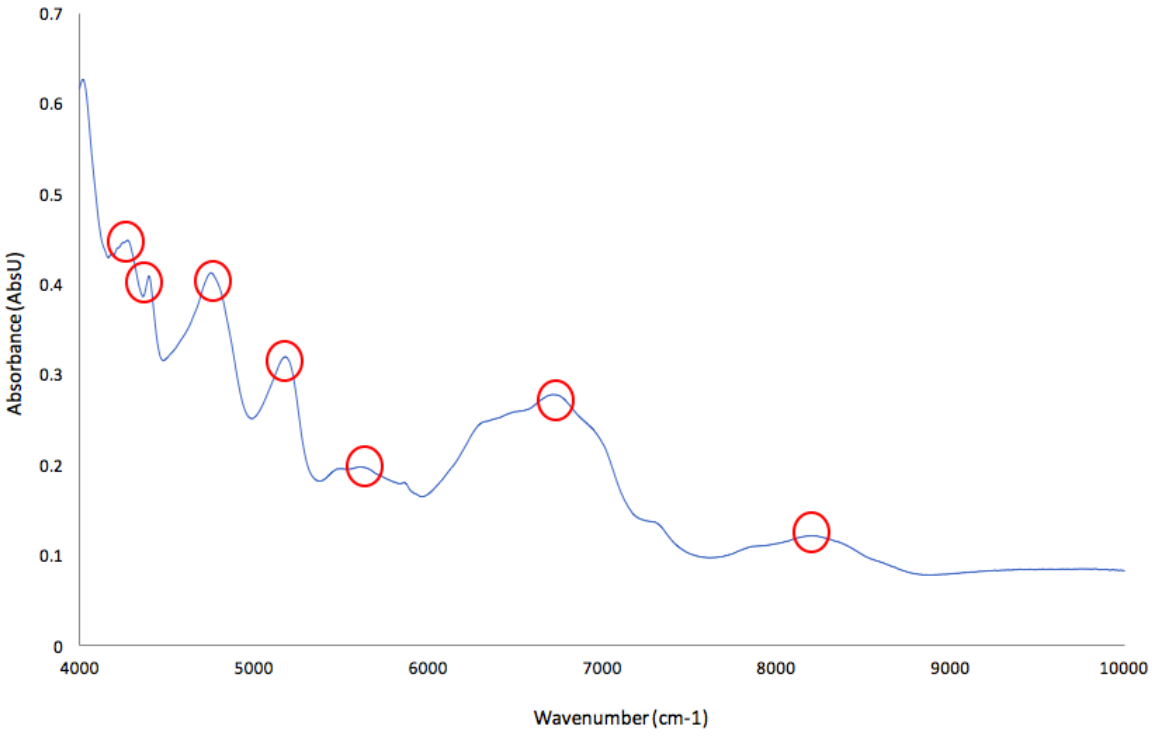


Figure 14: Seven main peaks of Microcrystalline Cellulose (MCC) highlighted by a red circle for illustration.

Visual aids were then created to help in the comparison between the Signal/Noise Ratio and the volume of excipients for each of the wavenumbers that the main peaks identified. Most commonly the data represented in the visual aids were of a normal distribution characteristic making it easier to identify the optimum volume needed as seen in figure 15

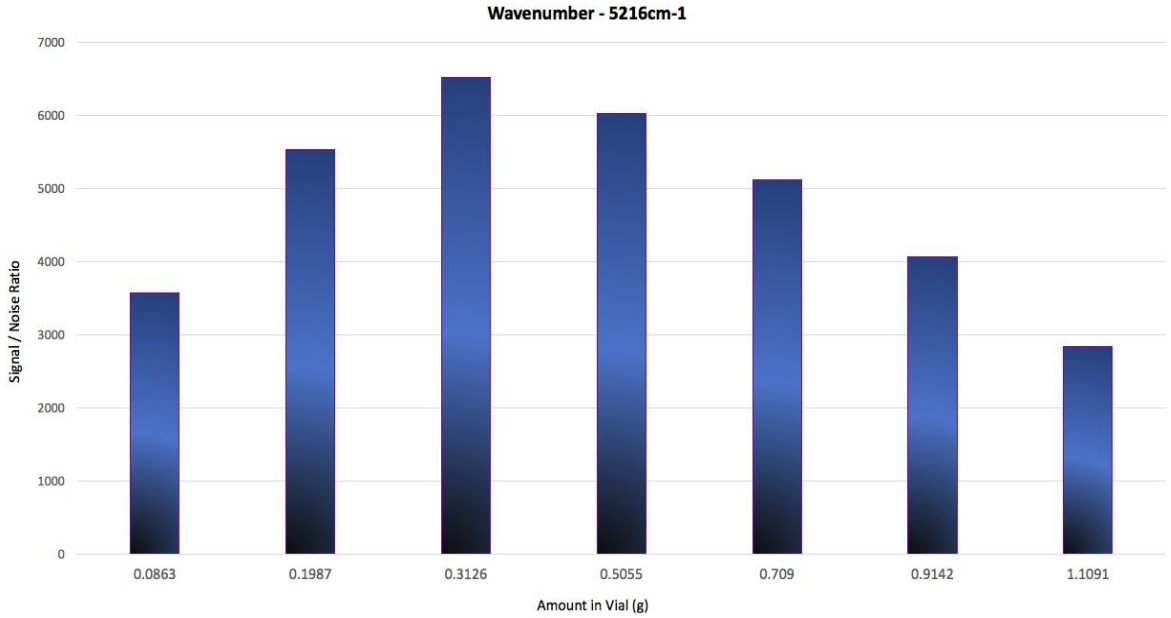


Figure 15: Visual Representation of one Wavenumber for MCC with its corresponding Signal / Noise Ratio when scanned at various volumes.

All wavenumbers that were found to be a main peak were examined and the results recorded for each to identify which volume gave the maximum Signal/Noise ratio for that wavenumber.

The overall volume that produced the optimum Signal/Noise ratio for all excipients was 300mg. Therefore, 300mg was the volume that the powders (excipients) and mixtures (binary mixtures) were measured to throughout this project.

2.12.3 Pilot Study:

Originally the tablets that were to be scanned were contained within glass vials, however when the spectra collected from those tablets were analysed it illustrated a variety of noise present.

To correct this, adjustments were made to limit the noise impacts, the tablets were removed from the vials, with the use of gloves/ tongs, and placed directly on the FT-NIR for scanning.

As a result, the spectra showed defined peaks. Accordingly, the tablets throughout the project were placed directly onto the NIR plate during the scanning process. After each tablet was scanned the plate was wiped carefully with solution and dried with a soft tissue to help prevent contamination.

The tablets orientation was the next to be tested to further validate the method that would be used. A variety of tablets were scanned in multiple ways; each side was scanned and rotated 90° and re-scanned, a total of four scans were taken for each tablet two on each side.

When the results were examined, it was shown that the side scanned caused variation within the spectra, however, the rotation did not cause any variations to occur. It was concluded that the minimum number of scans that were needed for the project was two.

However, with the powders and solutions not being compacted like the tablets two methods for validation ensued. The first being when the samples were stagnant and scanned, the second being when the powders and solutions were placed in a vortex mixer and scanned.

When the data collected was examined and compared it was seen that when placed in the vortex various readings would occur. This illustrated how a powder, or a solution is formed with regard to the particulates within it.

By using the vortex throughout the project more accurate results were gained. For each powder and solution three to four scans were taken to ascertain a more reliable result due to the general properties within the sample.

A benefit from using the Spectrum Two N Fourier-Transform-Near Infrared Spectrometer rather than another NIR, is that is does not require manual background or reference scans as the instrument itself completes those before a scan occurs.

2.24.4 Scanning Process:

For the tablets two scans were taken, one on each side (plain side and then the pharmaceutical side). For more accurate and reliable data collection, multiple samples were taken from a single batch, up to ten tablets from each batch were used and multiple batches were used to show correlations within the data.

For the powders and solutions, now measuring at 300mg, these were scanned three to four times depending if the sample was a pure standard or a mixture created for testing. The solutions and powders were both vortexed between individually scans.

2.12.5 Data Input

When scanned each sample had the spectral wavenumber range of between 4,000 cm^{-1} and 10,000 cm^{-1} which had ~ 6000 data points at scanning intervals of 1cm^{-1}. The data that was collected was saved using three different extensions for further analysis (Sing Point [.sp] , JCAMP-DX [.DX] and Excel [.csv]).

2.12.6 Data Pre-treatment & Analysis

After the data had been saved using the various extensions, it was imported into Unscrambler 10.5.1 for data manipulation (pre-treatment) to take place and then imported into Excel for further spectral analysis.

For this project, the data was derivatised to the first order using SG D1 and treated with MSC for spectral quality to be more accurate. The reason that SNV was not used was that, for the data that was collected, SNV did not show variation within the data points that made further analysis impossible.

2.13 Results & Discussion of Analysis

2.13.1 Spectral Quality

The NIR spectra had to be optimised for the noise present in the spectra to be reduced with the aim of making interpretation of the spectra easier to understand. This is also called curve fitting.

MSC and the D1 of SG were used to treat the spectra with the aim of reducing the noise caused by the scattering. By using this method, the total number of peaks increased, enabling higher discrimination margins when completing further multivariate data analysis as illustrated in in figure 16..

Maximum absorbance, minimum absorbance, wavelength range, signal to noise ratio (S/N) and the number of peaks were some of the many factors that were considered when examining the spectral quality see APPENDIX.

When some of the ciprofloxacin batches are compared - as shown in figure 17 & 18 for some there is a peak at ~ 7100cm-1 which can be converted to 1408.45nm.

The conversion of wavenumber to wavelength is illustrated below:

$$k = \frac{1}{\lambda}$$

Equation 13: The conversion between wavenumber and wavelength

Where 'k' is the wavelength, 'λ' is the wavenumber.

When the 1408nm peak is examined further and compared to the overtones in Chapter Five it represents a CH2 or CH3 bond.

Due to the particulars of the C-H bond it is hard to determine the cause of such a bond appearing in the ciprofloxacin and where the contamination came from.

The reason for calling it a contamination is that the peaks are only found within the 'counterfeit' samples. The authentic and generic samples do not contain the extra peak at 7100cm-1/1408nm.

Due to the comparisons of the raw materials to the ciprofloxacin samples, this bond and the excipients used in the tablets – from the medicine's leaflets - it can be assumed the peak comes from Talc, as it has a strong peak at ~ 1408nm - as shown in figure 16.

For future research the use of other instruments such as gas chromatography can be used to isolate the compound responsible for the C-H bond appearing at ~ 1408mn to confirm the assumption of Talc being the main contributor to this peak being present.

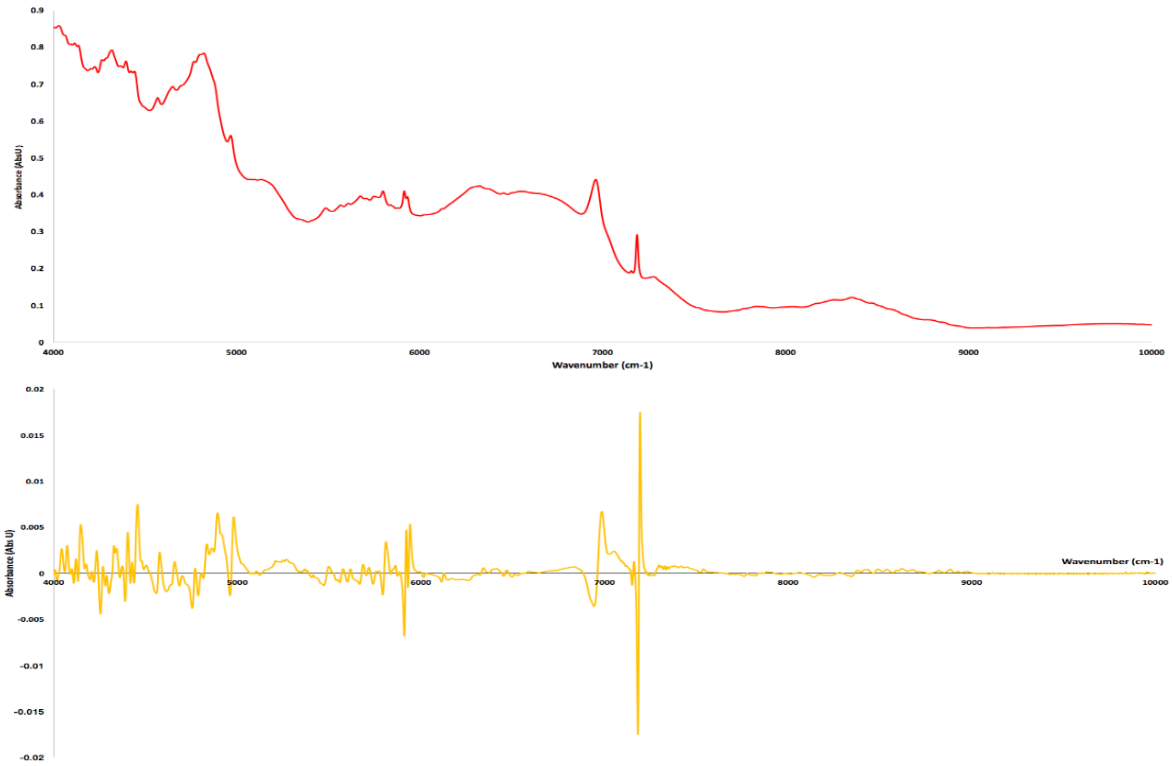


Figure 16: The comparison between an untreated spectra (-) and MSC-D1 treated spectra (-) produced by the PerkinElmer FT-NIR.

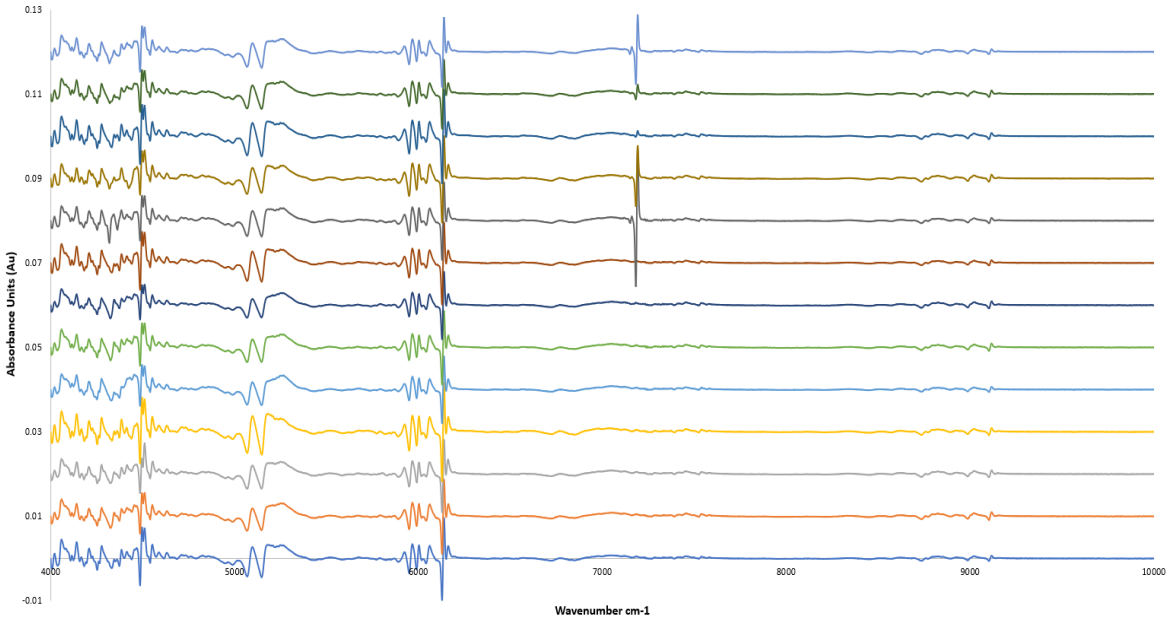


Figure 17: MSCD1 Ciprofloxacin comparison of some of the batches used.

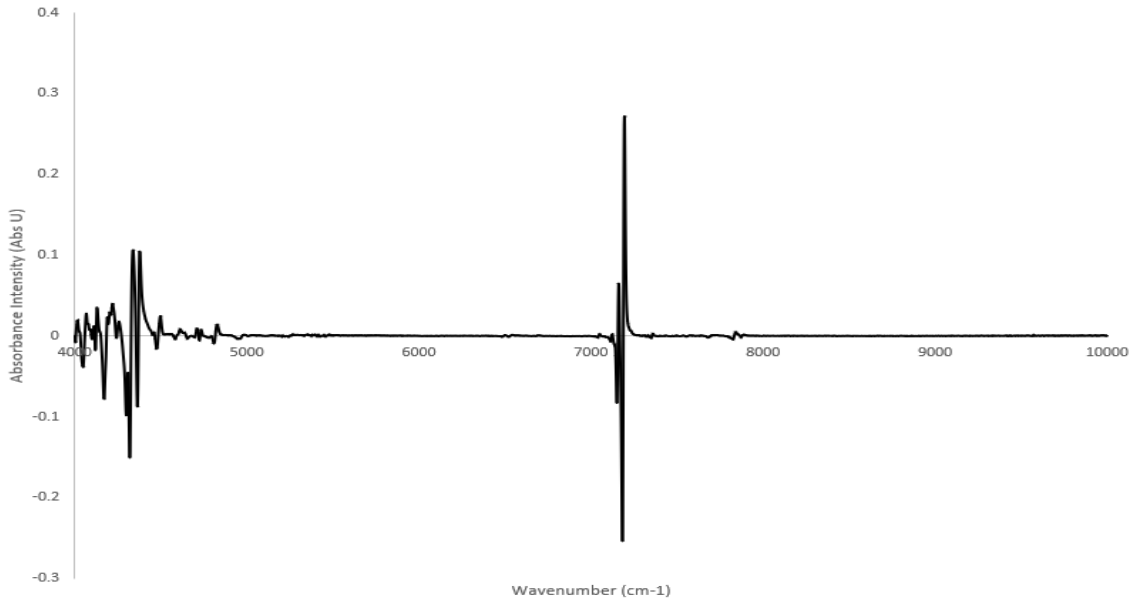


Figure 18: MSCD1 Talc, with a distinguishable peak at ~7100cm-1.

2.14 Binary Mixtures Data Analysis:

Within the pharmaceutical industry the use of powders for the intermediate or final products is widespread practice, and the mixing of those powders is one of the most common pharmaceutical operations.

Most pharmaceutical products have a mixing stage and it would be difficult to find one that does not use this technique at some stage of production.

Mixing can be defined as the process in which one product is created with two or more constituents that are mechanically blended or mixed together. The constituents are chemical substances, either elements or compounds.

When mixed together chemical bonding or other chemical changes do not occur and each constituent of the mixture retains its chemical properties or make up (Atkins et al. 2002).

With regard to pharmaceutical mixing, it often occurs on a large scale, for example:

- The mixing of powders in a variety of proportions prior to tableting or granulation.
- The dry mixing of various materials for direct tablet compression.
- The dry blending of powders within compound powders (insufflations) and capsules.

Solids such as powders can be divided into two types depending on the flow properties of the materials themselves, as illustrated in figure 19; cohesive which have a resistance to flowing through other materials e.g. wet clay or non-cohesive which are materials which flow readily such as sand, grain, even plastic chips (Smalley 1970).

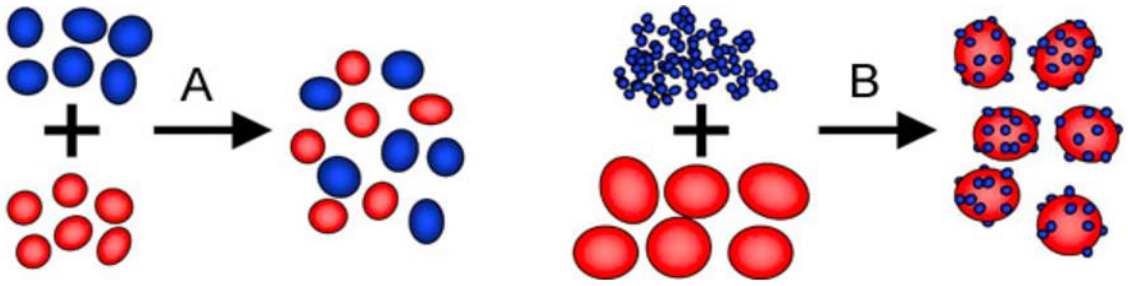


Figure 19: Comparison between (A) cohesive and (B) non-cohesive material mixtures

Flow ability must be mastered such and the understanding of free-flowing particles within powder mixtures must be achieved to enable successful production (Teunou et al. 1999).

The reason for this is that within dry powders van der Waals forces are the main inter-particle force that causes the particulates to adhere to each other. This occurs especially when the contact distance between particles ~ 0.4 nm and the particle distances below that of 50 nm (Krupp 1967).

The reason that van der Waals are so important within powder mixtures is that the size of the van der Waals force is directly proportional to the size of the particle itself (Yang & Evan 2007).

Therefore, it is easier to produce a mixture with powders that have similar density and fineness, than to produce a mixture of a large mass of coarse powder combined with a small proportion of fine powder.

Other than the density and the size of the particle, the adhesive properties of the constituents are also important factors that are taken into consideration when producing pharmaceutical products.

For instance, in one tablet there are a variety of different types of powders/ compounds that when compressed form the tablet. These include but are not limited to the APIs, the bulk components, coating and some components which enable a slow release of the API into the blood stream.

For that reason, in the testing of tablets and other pharmaceutical compositions the knowledge of mixture behaviour is vital.

As explained by Sun (2016) a classification for binary mixtures are theoretical considerations based on tableting behaviours. Using various systems of classification, binary mixtures can be used as a guide for efficient tablet formulation that are developed based on the different mechanical properties of the APIs and the excipients used.

For this reason, the examination of binary mixtures is a key element in the discovery of fraudulent behaviour and counterfeit products being produced and sold around the world.

What should be shown when a binary mixture is subjected to PCA is a parabola effect, for as one excipient increases in volume the other excipient decreases in volume.

To test this theory five excipients will be combined in 10 various combinations and then analysed with FT-NIR. After they are analysed, they will be subjected to both PCA and CWS analysis. This is because the visual representation of the data that both produces is clear and concise.

Table 6: The classification of each binary mixture (BM) model with the various components, where (A) is Magnesium Stearate (MgS) , (B) is Talc (Talc) , (C) is Microcrystalline Cellulose (MCC) , (D) is Maize Starch (MzeS) and lastly (E) is Lactose (Lact) .

Model Number	Excipient Contents
BM - 1	A + B
BM - 2	A + C
BM - 3	A + D
BM - 4	A + E
BM - 5	B + C
BM - 6	B + D
BM - 7	B + E
BM - 8	C + D
BM - 9	C + E
BM - 10	D + E

The excipients that are used for the binary mixtures within this research are as follows; Magnesium Stearate, $Mg(C_{18}H_{35}O_2)_2$, Microcrystalline Cellulose, $C_{18}H_{32}O_{16}$, Maize Starch, $Ca_2H_5O_{12}P_3$, Lactose, $C_{12}H_{22}O_{11,}$ and finally Talc, H2Mg3O12Si4. As shown in figure 20, the various excipients have significantly different signatures.

Each of the models have 13 vials within which there is a varying quantity of excipient. As stated previously, as one excipient increases in volume the other decreases. The ratio of the vials in each model are; 100% + 0%, 90% + 10%, 80% + 20%, 75% + 25%, 70% + 30%, 60% + 40%, 50% + 50%, 40% + 60%, 30% + 70%, 25% +75%, 20% + 80%, 10% + 90% and finally 0% + 100% with excipient 1 and excipient 2 respectively.

2.14.1 Binary Mixtures PCA:

As illustrated in table 7, there are 12 different PCA Binary Mixture models, which when combined illustrate why mixture definition is important. It also has the benefit of understanding the structures of the chemicals themselves.

Table 7: The collection of Binary Mixture (BM) PCA Models and their respective Principle components (PC) on MSC-D1 pre-treated FT-NIR data. Where (A) is Magnesium Stearate (MgS), (B) is Talc (Talc), (C) is Microcrystalline Cellulose (MCC), (D) is Maize Starch (MzeS) and lastly (E) is Lactose (Lact).

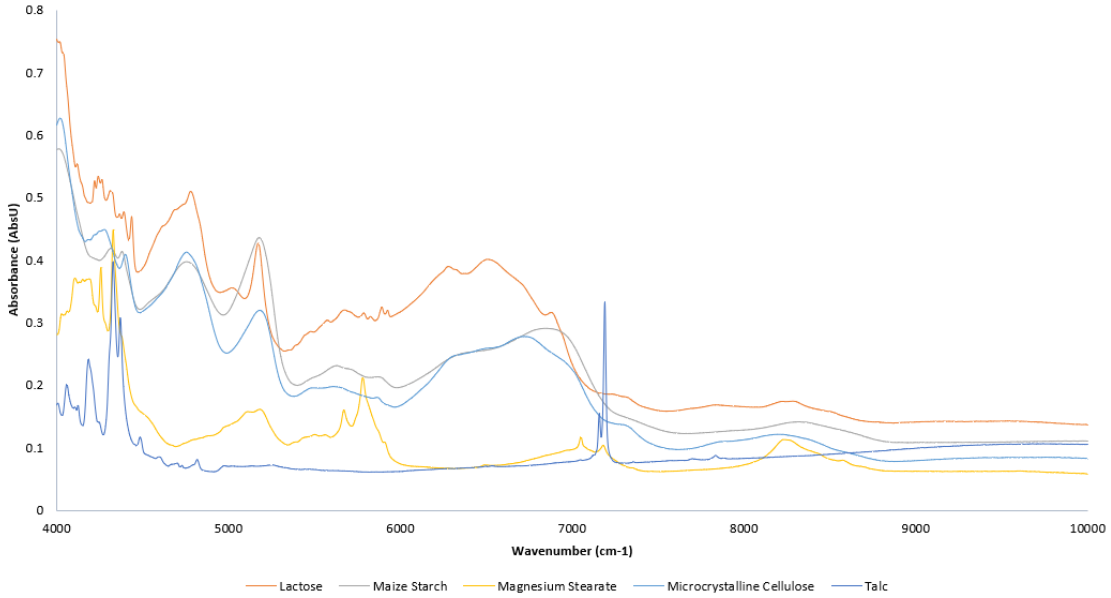
PCA Model	Samples Compared	PC 1 (%)	PC 2 (%)
PCA - BM 1	Binary Mixture - A + B	99	1
PCA - BM 2	Binary Mixture - A + C	99	0
PCA - BM 3	Binary Mixture - A + D	100	0
PCA - BM 4	Binary Mixture - A + E	99	0
PCA - BM 5	Binary Mixture - B + C	100	0
PCA - BM 6	Binary Mixture - B + D	100	0
PCA - BM 7	Binary Mixture - B + E	100	0
PCA - BM 8	Binary Mixture - C + D	97	1
PCA - BM 9	Binary Mixture - C + E	98	1
PCA - BM 10	Binary Mixture - D + E	99	0
PCA - BM 11	Binary Mixture - ALL	98	1
PCA - BM 12	Binary Mixture - Raw Excipients	95	3

Figure 20 illustrates the FTNIR raw spectra of the excipients in the binary mixtures over lapping each other, it aids to illustrate clearly defined peaks and broad bonds shown in each constituent.

Each of the excipients featured in the graph below represent the most common available in the ciprofloxacin tablets. Within the graph it can be seen that there are strong sharp peaks related to the talc excipient, one at ~7100 and one at ~4400. These peaks transfer over to the ciprofloxacin tablet spectra as illustrated in the MSCD1 Ciprofloxacin comparison graph (figure 18)

The magnesium stearate excipient has a defined peak at ~5800. the other excipients in this model illustrate broad peaks overlapping the ~4500-7500 range.

This broad range makes it difficult to certifiably distinguish the different excipients from each other as they behave similarly to each other when place in the infrared



beam.

Figure 20: The raw spectra of Magnesium Stearate, Microcrystalline Cellulose, Maize Starch, Lactose and finally Talc

2.14.2 Binary Mixtures CWS:

As illustrated in table 8, there are 10 different PCA Binary Mixture models, which when combined illustrate why mixture definition is important. It also has the benefit of understanding the structures of the chemicals themselves.

Table 8: The collection of Binary Mixture (BM) Correlation Wavelength Space (CWS) Models on MSC-D1 pre-treated FT-NIR data. Where (A) is Magnesium Stearate (MgS), (B) is Talc (Talc), (C) is Microcrystalline Cellulose (MCC), (D) is Maize Starch (MzeS) and lastly (E) is Lactose (Lact).

CWS Model	Samples Compared	'r' Max	'r' Min
CWS - BM 1	Binary Mixture - A + B	1	0.88
CWS - BM 2	Binary Mixture - A + C	1	0.5
CWS - BM 3	Binary Mixture - A + D	1	0.4
CWS - BM 4	Binary Mixture - A + E	1	0.4
CWS - BM 5	Binary Mixture - B + C	1	0.5
CWS - BM 6	Binary Mixture - B + D	1	0.5
CWS - BM 7	Binary Mixture - B + E	1	0.5
CWS - BM 8	Binary Mixture - C + D	1	0.88
CWS - BM 9	Binary Mixture - C + E	1	0.7
CWS - BM 10	Binary Mixture - D + E	1	0.6

2.14.3 Binary Mixture 1 (A) + (B)

Binary mixture 1 is comprised of (A) Magnesium Stearate and (B) Talc.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

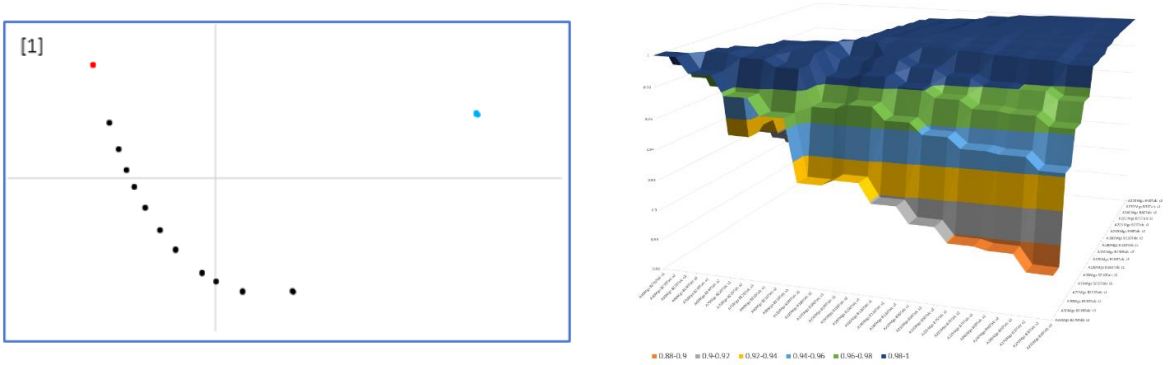


Figure 21: PCA – BM1 & CWS – BM1 respectively comprised of Magnesium Stearate & Talc.

PCA – BM 1 as shown in figure 21 demonstrates a clearly defined relationship between the ratio mix comprised of compound (A) and (B).

This illustrates the sensitivity of the FTNIR instrument used. The reason being that each ratio sample mix within the model is shown to be comparable and the level of ratio able to be determined.

This is supported by the CWS-BM1 model in figure 21. The ratio mix shows to have a strong correlation when the various sample mixtures are compared to themselves as you would expect. When the ratios are compared against each other the level of excipient within the ratios is more noticeable.

The overall 'r' value ranges from 0.88 to 1. This indicates that the binary model for mixtures (A) & (B) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the orange section of the CWS graph represents the 88% ratio mix that has a correlation of 0.88, whereas the light green section indicates 0.96 'r' value for a 96% correlation match.

2.14.4 Binary Mixture 2 (A) + (C)

Binary mixture 2 is comprised of (A) Magnesium Stearate and (C) - MMC - Microcrystalline Cellulose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

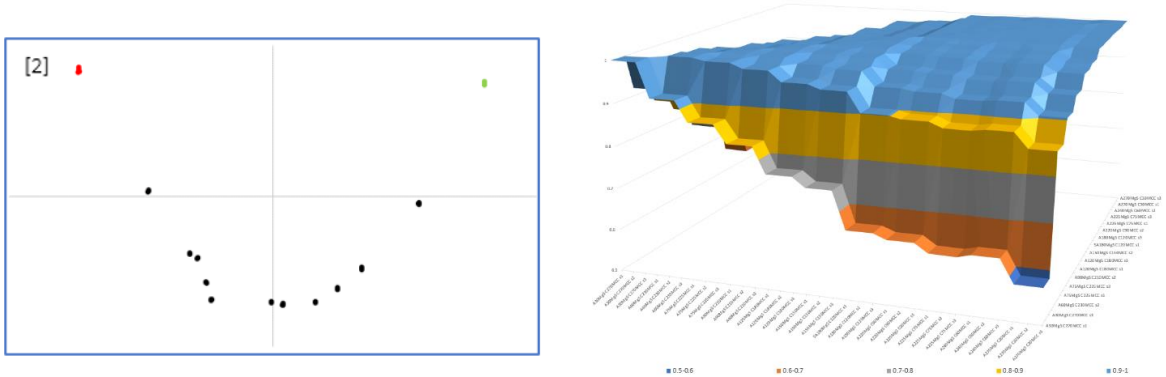


Figure 22: PCA – BM2 & CWS – BM2 respectively comprised of Magnesium Stearate & MCC.

PCA – BM 2 and CWS – BM 2 as shown in figure 22 demonstrates a clearly defined relationship between the ratio mix comprised of compound (A) and (C).

BM2 demonstrates an ideal model for the ratios when analysed as it clearly shows 50% to 100% mixtures which is how the whole binary mixture is comprised of as one excipient increases and the other decrease at a identical rate. It is a directly proportional relationship.

The overall 'r' value for the CWS model ranges from 0.5 to 1. This indicates that the binary model for mixtures (A) & (C) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark blue section of the CWS graph represents the 50% - 60% ratio mix that has a correlation of 0.5, whereas the yellow section indicates 80% - 90%.

2.14.5 Binary Mixture 3 (A) + (D)

Binary mixture 3 is comprised of (A) Magnesium Stearate and (D) Maize Starch.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

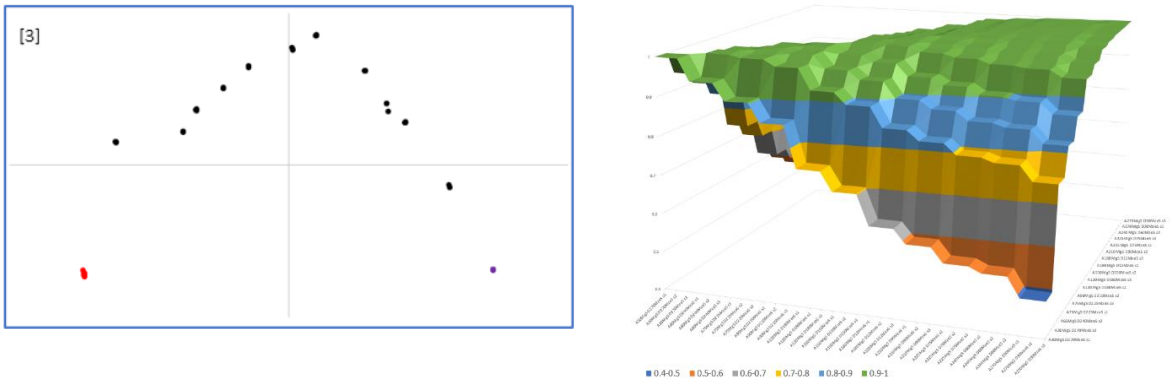


Figure 23: PCA – BM3 & CWS – BM3 respectively comprised of Magnesium Stearate & Maize Starch.

PCA – BM 3 and CWS – BM 3 as shown in figure 23 demonstrates a clearly defined relationship between the ratio mix comprised of compound (A) and (D).

The overall 'r' value ranges from 0.4 to 1. This indicates that the binary model for mixtures (A) & (D) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark blue section of the CWS graph represents the 40% ratio mix that has a correlation of 0.40, whereas the light blue section indicates 0.80 'r' value for an 80% correlation match.

BM3 has the largest 'r' value range within all the binary mixtures this could be and also it is the only model for the binary mixtures that has an inverted parabola, there is no reason that can be determined for this effect as the mixture itself is definable.

More investigation would be needed to understand what could cause this change apart from the possibility of commination or axis reversal.

2.14.6 Binary Mixture 4 (A) + (E)

Binary mixture 4 is comprised of (A) Magnesium Stearate and (E) Lactose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

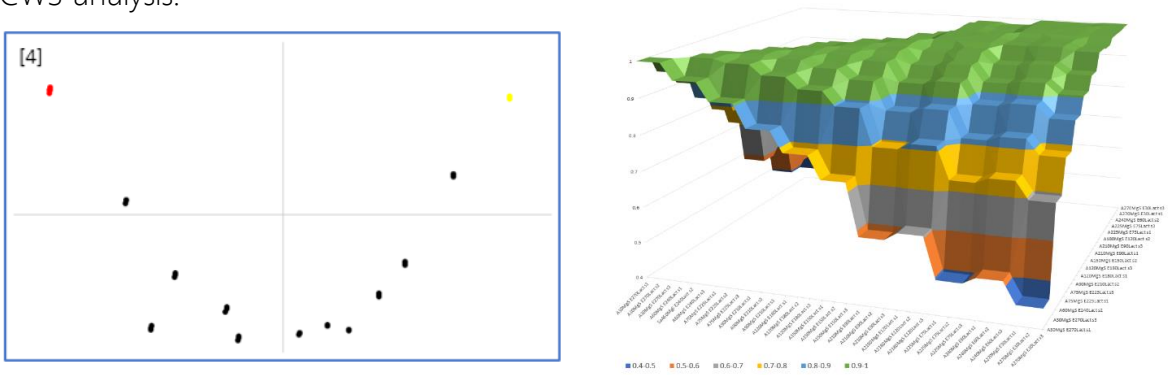


Figure 24: PCA – BM4 & CWS – BM14 respectively comprised of Magnesium Stearate & Lactose..

PCA – BM 4 and CWS – BM 4 as shown in figure 24 demonstrates a clearly defined relationship between the ratio mix comprised of compound (A) and (E).

The overall 'r' value ranges from 0.40 to 1. This indicates that the binary model for mixtures (A) & (E) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the orange section of the CWS graph represents the 50-60% ratio mix that has a correlation of 0.50-0.60, whereas the light green section indicates 0.90-1 'r' value for a 90-100% correlation match.

BM4 is similar to BM3 in how the ratio mixtures are illustrated, only one ratio sample within the model seems to be out of the parabolic trend set for PCA analysis, the CWS illustrates the correlative effect similar to the PCA model.

2.14.7 Binary Mixture 5 (B) + (C)

Binary mixture 5 is comprised of (B) Talc and (C) - MMC -Microcrystalline Cellulose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

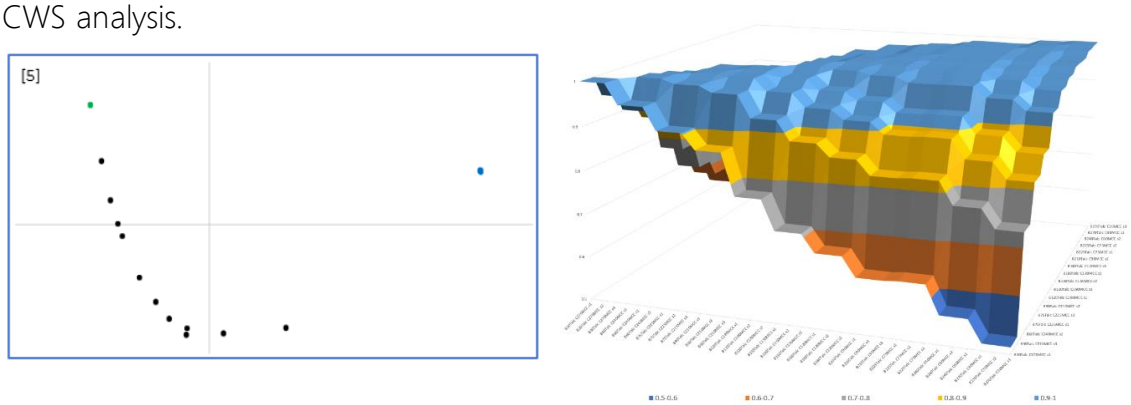


Figure 25: PCA – BM5 & CWS – BM15 respectively comprised of Talc & MCC.

PCA – BM 5 and CWS – BM 5 as shown in figure 25 demonstrates a clearly defined relationship between the ratio mix comprised of compound (B) and (C).

The overall 'r' value for the CWS model ranges from 0.5 to 1. This indicates that the binary model for mixtures (B) & (C) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark blue section of the CWS graph represents the 50% - 60% ratio mix that has a correlation of 0.5, whereas the yellow section indicates 80% - 90%.

The mixture ratios and success rates of identification of excipient amounts, are similar to models BM2, BM6 & BM7, as the parabolic effect of the PCA models show how the ratio of the mixtures change within a model compared to the percentage of the mix.

Similarly, the CWS models show clearly defined bands of correlations between 50% and 100% and the respective 'r' values of 0.5 1.

2.14.8 Binary Mixture 6 (B) + (D)

Binary mixture 6 is comprised of (B) Talc and (D) Maize Starch.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

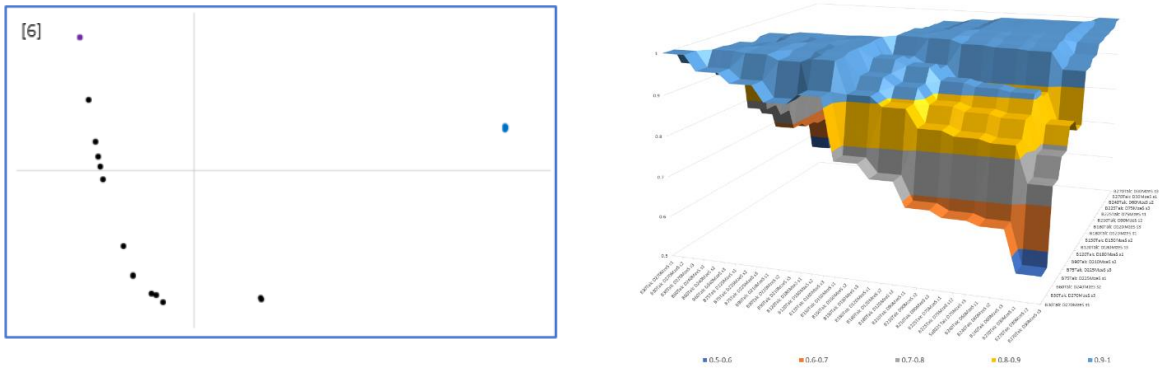


Figure 26: PCA – BM6 & CWS – BM16 respectively comprised of Talc & Maize Starch

PCA – BM 6 and CWS – BM 6 as shown in figure 26 demonstrates a clearly defined relationship between the ratio mix comprised of compound (B) and (D).

The overall 'r' value for the CWS model ranges from 0.5 to 1. This indicates that the binary model for mixtures (B) & (D) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark blue section of the CWS graph represents the 50% - 60% ratio mix that has a correlation of 0.5, whereas the yellow section indicates 80% - 90%.

Just as with BM5 the binary mixture analysis is a success as the PCA illustrates a definitive curve/trend and the CWS demonstrates a clear correlation for each of the ratios within the model.

2.14.9 Binary Mixture 7 (B) + (E)

Binary mixture 7 is comprised of (B) Talc and (E) Lactose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

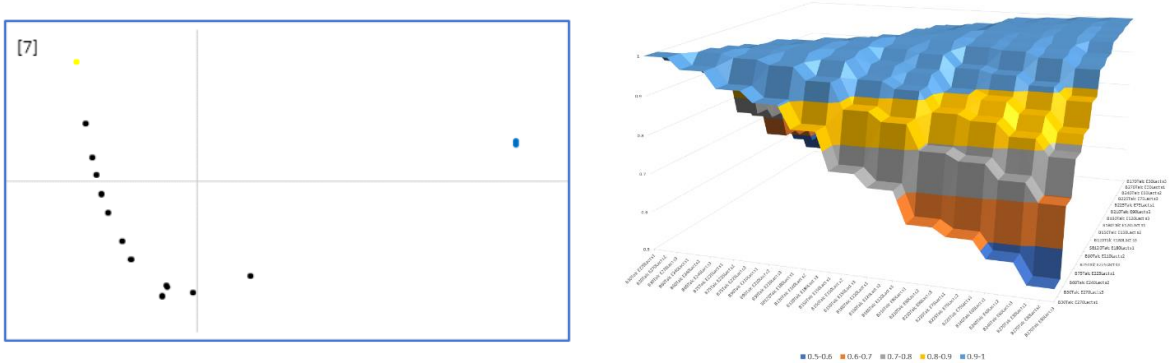


Figure 27: PCA – BM7 & CWS – BM7 respectively comprised of Talc & Lactose

PCA – BM 7 and CWS – BM 7 as shown in figure 27 demonstrates a clearly defined relationship between the ratio mix comprised of compound (B) and (E).

The overall 'r' value for the CWS model ranges from 0.5 to 1. This indicates that the binary model for mixtures (B) & (E) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark blue section of the CWS graph represents the 50% - 60% ratio mix that has a correlation of 0.5, whereas the yellow section indicates 80% - 90%.

BM7 has a similar result to BM2, BM6 and BM8 with regards to how the PCA and CWs has determined the variance and correlative characteristics of the ratios within the models.

2.14.10 Binary Mixture 8 (C) + (D)

Binary mixture 8 is comprised of (C) - MMC -Microcrystalline Cellulose and (D) Maize Starch.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

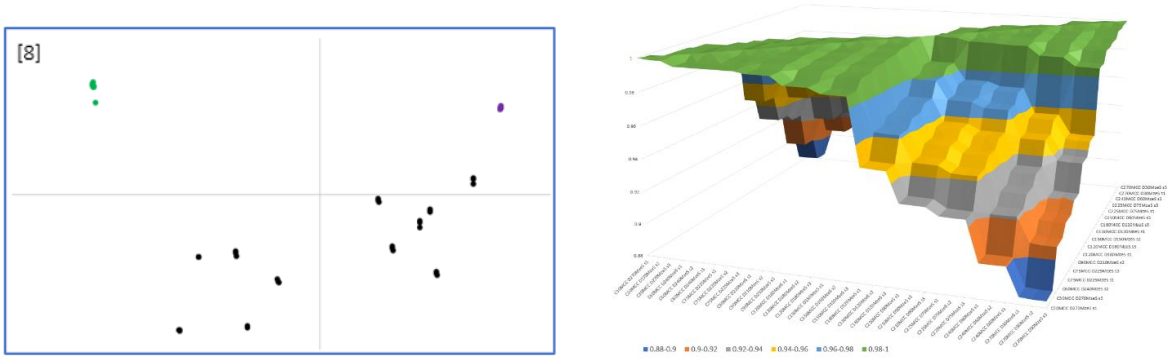


Figure 28: PCA – BM8 & CWS – BM18 respectively comprised of MCC & Maize Starch.

PCA – BM 8 and CWS – BM 8 as shown in figure 28 demonstrates a clearly defined relationship between the ratio mix comprised of compound (C) and (D).

The overall 'r' value ranges from 0.88 to 1. This indicates that the binary model for mixtures (C) & (D) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the orange section of the CWS graph represents the 88%% ratio mix that has a correlation of 0.88, whereas the light green section indicates 0.96 'r' value for a 96% correlation match.

The reason for the interrupted parabola for the mixture of (C) & (D) could be that an error occurred when the vials were filled with and the ratio mix was incorrect and the m/m% were out of proportion.

2.14.11 Binary Mixture 9 (C) + (E)

Binary mixture 9 is comprised of (C) - MMC -Microcrystalline Cellulose (E) Lactose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

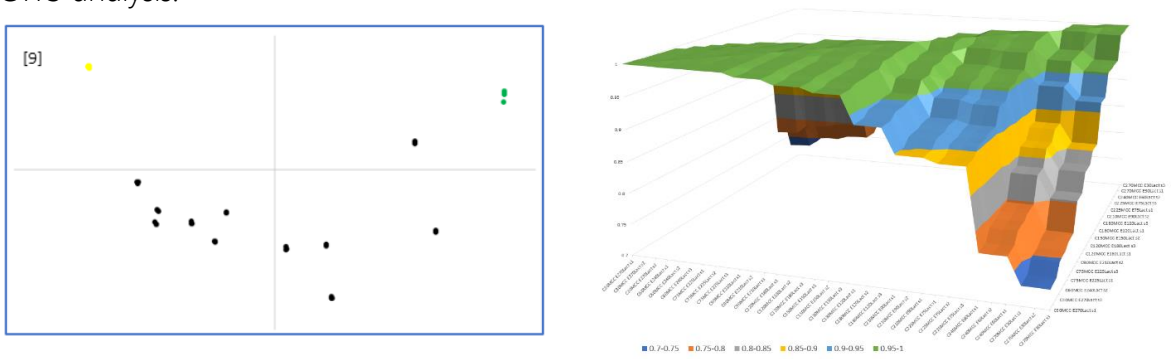


Figure 29: PCA – BM9 & CWS – BM9 respectively comprised of MCC and Lactose

PCA – BM 9 and CWS – BM 9 as shown in figure 29 demonstrates a clearly defined relationship between the ratio mix comprised of compound (C) and (E).

The overall 'r' value ranges from 0.7 to 1. This indicates that the binary model for mixtures (C) & (E) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the grey of the CWS graph represents the 80-85% ratio mix that has a correlation of 0.80-0.85, whereas the dark blue section indicates 0.70-0.75 'r' value for a 70-75% correlation match.

Similarity to BM8 the disruption to the ratio determination could be the result of incorrect m/m% and ratio mix measured or contamination to the sample itself.

2.14.12 Binary Mixture 10 (D) + (E)

Binary mixture 10 is comprised of (D) Maize Starch and (E) Lactose.

Comparison of similarities found within the mixture illustrated both with PCA and CWS analysis.

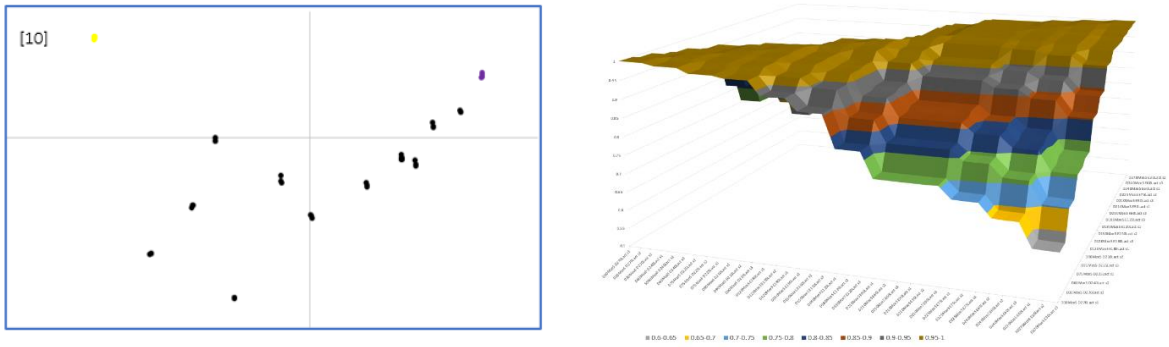


Figure 30: PCA – BM10 and CWS – BM10 respectively comprised of Mazie Starch & Lactose.

PCA – BM 10 and CWS – BM 10 as shown in figure 30 demonstrates a clearly defined relationship between the ratio mix comprised of compound (D) and (E).

The overall 'r' value ranges from 0.6 to 1. This indicates that the binary model for mixtures (D) & (E) are a success, as the percentage of the mixtures are able to be distinguished and calculated.

For instance, the dark grey of the CWS graph represents the 90-95% ratio mix that has a correlation of 0.90-0.95, whereas the light blue section indicates 0.70-0.75 'r' value for a 70-75% correlation match.

As with BM8 & BM9 the binary mixture interruption could again be the result of miscalculation or measurement, contamination of such samples.

2.15 Binary Mixture Comparison:

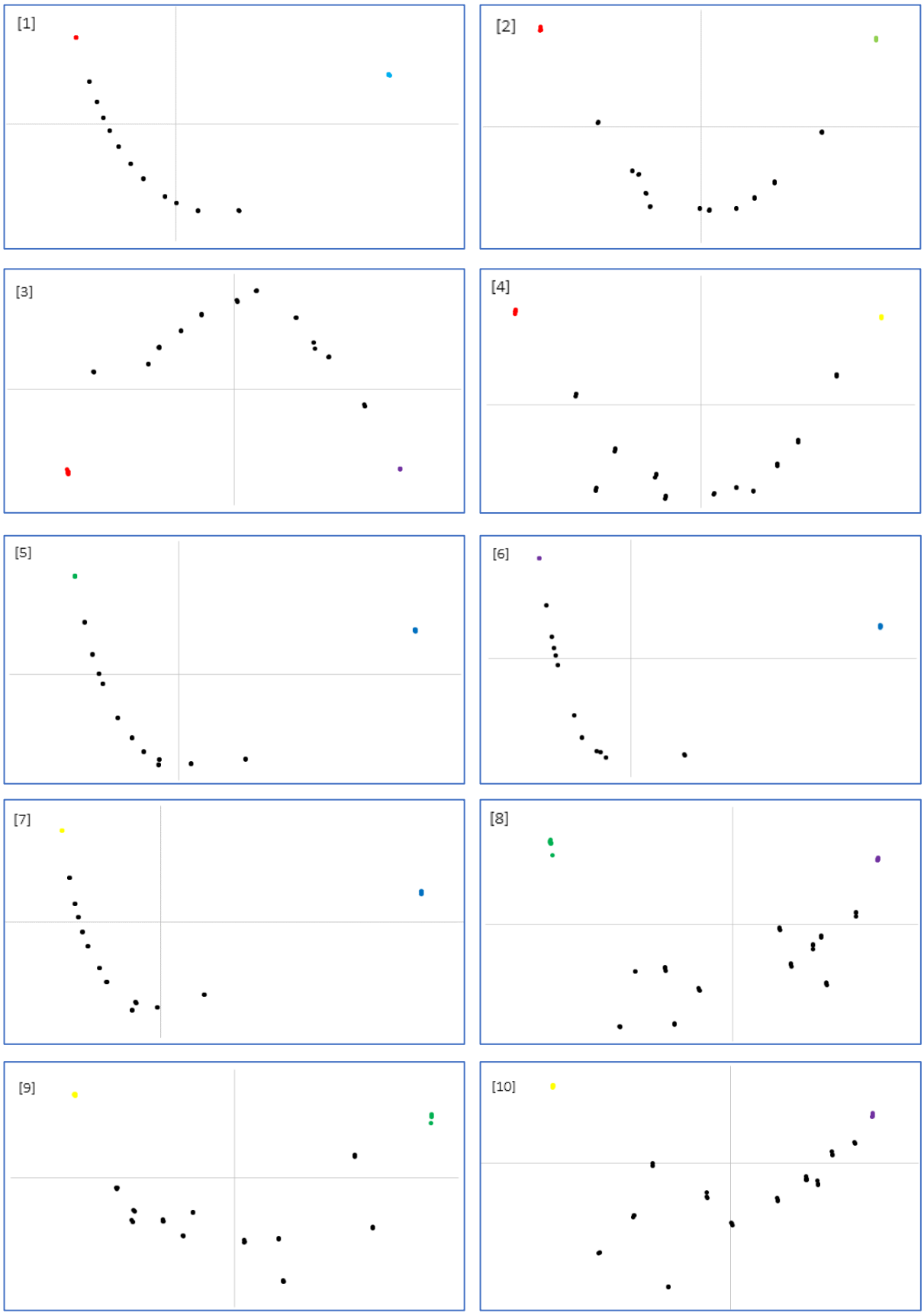


Figure 31: The collection of PCA binary mixture models from 1 - 10. Where [1] is the mixture of A+B, [2] is A+C, [3] is A+D, [4] is A+E, [5] is B+C, [6] is B+D, [7] is B+E, [8] is C+D, [9] is C+E, [10] is D+E. Where (A) is MgS, (B) is Talc, (C) is MCC, (D) is MzeS and lastly (E) is Lact..

As seen in figure 31 PCA – BM 1 - 7 show clear parabola effects between the two main excipients shown in colours and the various ratios within the model in black. By having a clear parabola effect, it can be suggested that volumes of excipients within a sample can be quantified.

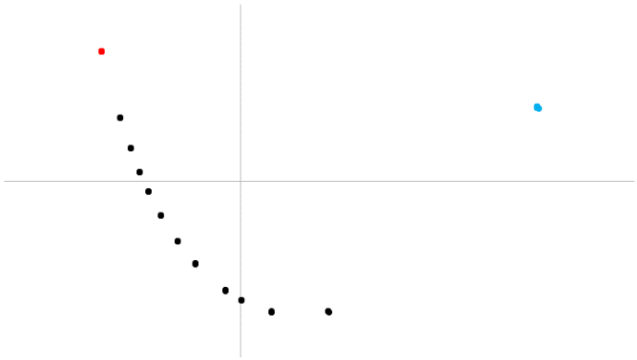


Figure 32: PCA - BM 1, where MgS and Talc are in a comparative ratio mixture. As the MgS volume ratio decreases and the Talc volume increases the data points start to bend towards Talc.

Not all the binary mixtures illustrate a perfect parabolic effect. There are several reasons why this could have happened. The first is that the samples themselves could have been contaminated with other substances if the spatulas were not cleaned thoroughly between mixtures being produced.

Another reason being that the percentages of the samples within the mixture where not accurate enough, thus the percentages of volume where disrupted.

However, PCA – BM 8 – 10 show a scattering of data points rather than a clear parabola effect like the other models. The reason in this case is most likely due to the chemical structures of the excipients in models 8 – 10.

The chemical composition of MCC, MzeS and Lact, could be interfering with the readings as they are similar in structure. Also, it is illustrated that as one excipient's volume increases, the inverse is true for the remaining excipient in the mixture and the volume decreases as seen on closer inspection in figure 25.

As can be seen in figure 34, when the Binary models are combined in one PCA the clusters start to be seen. With the pure excipients being at each end of a model the mixtures of various percentages in volume can be found along a line between the two excipients that contribute to the mixtures.

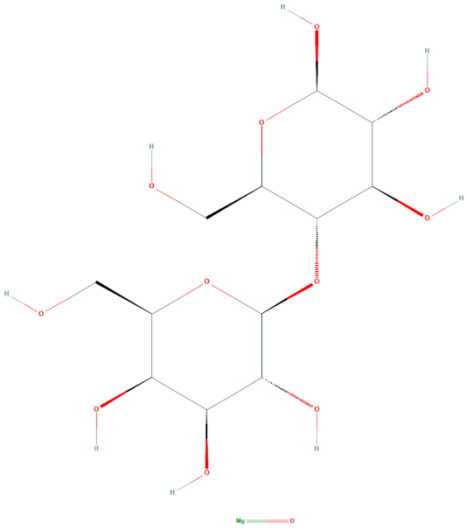
As can been seen in figure 35, between the black dots representing MCC and the purple dots representing MzeS, the two mixtures represented by the orange dots are in a linear line connecting the two. This shows that PCA can distinguish the percentages in the mixtures and which excipients they belong to.

As indicated in the black circle there is a cluster of three models and three excipients, which can be examined further in figure 34. When the cluster is examined more closely it can be seen that a triangle of mixtures form, and each side of the triangle is a batch mix of a binary mixture.

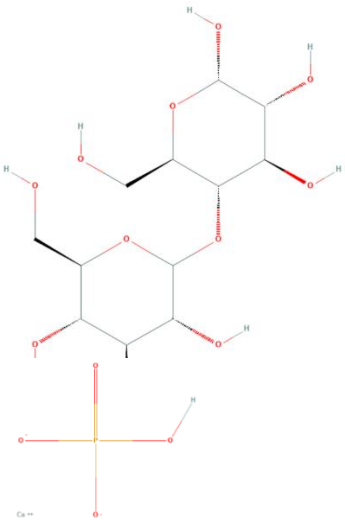
The peaks of the triangle are three of the excipients used. As shown in figure 33 the chemical compounds of C, D and E are of similar structure, whereas A and B are different.

Figure 33: The Chemical Strcuture of the Excipeints found in the binary mixtures. Where (A) is MgS, (B) is Talc, (C) is MCC, (D) is MzeS and lastly (E) is Lact..

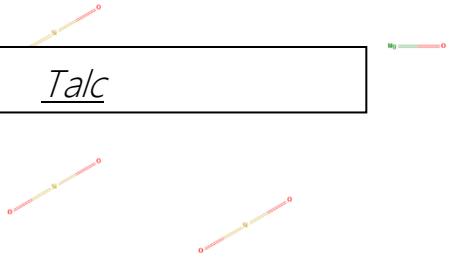
Lactose



Microcrystalline Cellulose

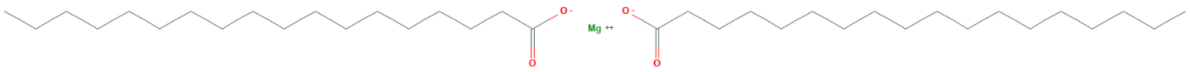


Talc



Maize Starch

Magnesium



This is the cause of the cluster triangle being close together and the larger triangle seen in PCA-BM 1. This triangular cluster is made of the same components that gave the no parabola in the binary mixtures seen in PCA-BM 8-10.

2.16 Binary Mixtures Implications:

The binary mixtures created, demonstrate on a small scale the excipient structure that is found within tablets. By using the various mixtures of the common excipients found, a satisfactorily method of analysis and the correct instrument can be determined.

Not only does the mixtures aid in the spectra analysis, but the ratios between the excipients in the various mixtures also help determine how accurate and sensitive the FTNIR is.

This sensitivity when understood, factors in the effects that the surroundings and other variables have on the instrument and how accurate the spectra is that is produced. Therefore, the FTNIR and PCA are able to distinguish between the various excipients in a mixture and a compacted tablet.

The spectra that were then treated by an illustrative analysis, in this case PCA, can determine if correlation and similarities can be found within the binary mixtures of different ratios and thus determine the same properties in the tablets.

For the CWS analysis only 4/10 models demonstrate the ideal data to be illustrated with 'r' values between the ranges of 05 to 1. Whereas the other models the 'r' values are ranging from as low as 0.4 to 1.

By knowing that similar compound structures group together it can be suggested that overall similar compounds will also group together as the structural integrity is virtually identical if not for a slight variation.

For further analysis to determine the margin of accuracy tertiary mixtures and quandary mixture should be used to pinpoint the variants in the data set.

Figure 34: PCA-BM 11, the comparison for all 10 binary mixtures models with the 13 vial ratios within.

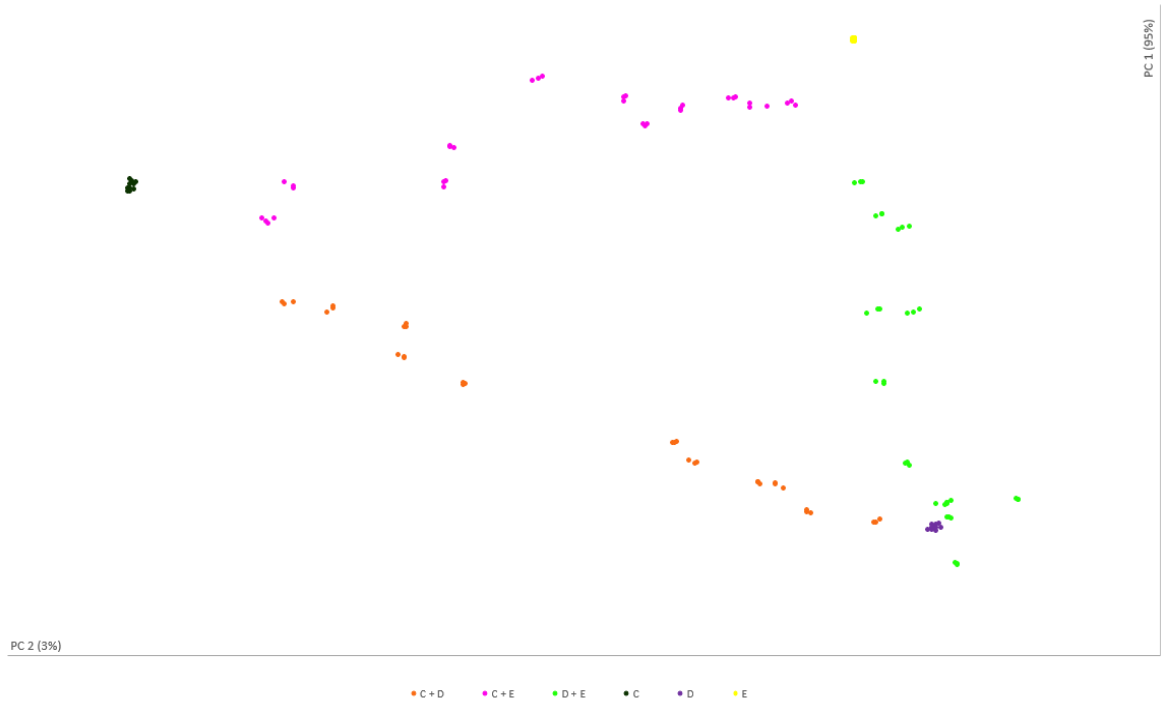


Figure 35: Closer examination of the cluster found in figure 34

2.17 Data Analysis - PCA:

2.17.1 Antibiotics

PCA was the chosen method of analysis with regard to distinguishing groups in the NIR data. The reason for the others mentioned previously, such as SIMCA and CWS, not being used was due to software incompatibilities.

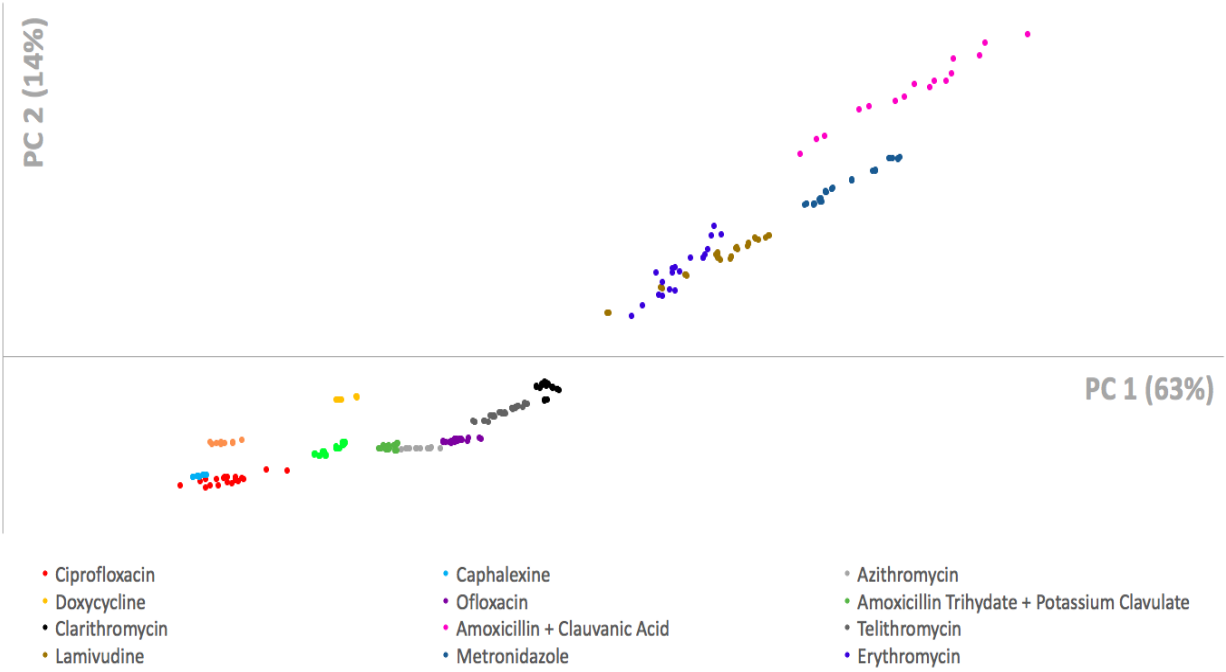
PCA was the chosen analysis tool because it is helpful in distinguishing different groups and can give a visual representation of them.

To gain a more accurate representation of all the data clusters 11 PCA models were created as illustrated in table 9. Of these, 10 focuses on the groupings of ciprofloxacin, whereas the remaining model illustrates the relationship between different classes of antibiotics and the raw excipients that are present in medicines.

Table 9: The collection of PCA Antibiotic (AB) Models and their respective principle components (PC) percentages on MSC - D1 pre-treated FT-NIR data. Where 'A' is authernitic Ciprofloxacin, 'G' is tested generic Ciprofloxacin and 'C' is counterfeit ciprofloxacin.

PCA Model	Samples Compared	PC 1 (%)	PC 2 (%)
PCA - AB 1	Antibiotic Composition (Various)	63	14
PCA - AB 2	All Readings - A	37	28
PCA - AB 3	All Readings - G	87	7
PCA - AB 4	All Readings - C	48	31
PCA - AB 5	Averages - A	60	19
PCA - AB 6	Averages - C	85	8
PCA - AB 7	Averages - G	52	33
PCA - AB 8	Averages - A, C & G	43	38
PCA - AB 9	Averages - C & G	54	30
PCA - AB 10	Averages - G & A	59	24
PCA - AB 11	Averages - A & C	66	14

By having AB 2 –7 it can be seen that the use of the averages rather than the complete data set would have little to no effect on the PCA data. As shown the PC



percentages do vary from the same groups in different models. The discrepancies however are not significant enough to warrant excluding the use of averages.

Figure 36: Illustrates how PCA can correlate and cluster the various MSC - D1 treated antibiotics where PC1 is 63% and PC2 is 14%

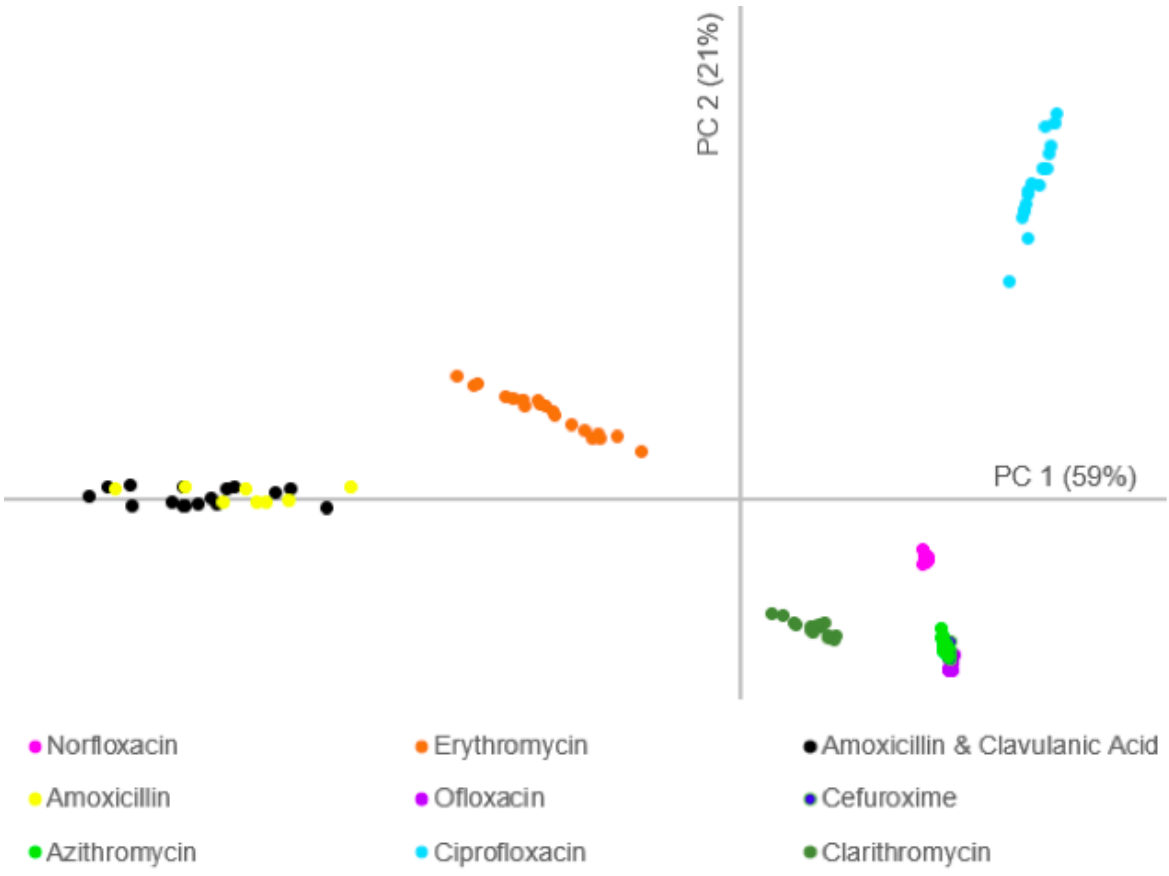


Figure 37: Illustrates PCA - AB1 with a smaller number of various MSC - D1 treated antibiotics with PC1 being 59% and PC2 is 21%.

The groups/ clusters that are shown in figures 36 and 37 are the result of the variations with regard to the intensity of the absorbance at different wavelengths being grouped together due to similarities found.

The reason for the groupings is that the same type of medicines would have the same or similar chemical compositions. When exposed to the NIR radiation the chemicals that have the same type of bonds, such as O=H, N=H and C=H, show the same results.

The bonds present in one type of compound would then respond differently at varying wavelengths, compared to the same type of bonds in a more diverse compound.

PCA is also a valuable tool to use when trying to identify manufacturers as the compounds created with the same chemical makeup cluster together. With the cake scenario, if a group of friends were to cook Victoria sponge cakes, with multiple repeats,

PCA would be able to cluster and identify who made which cake. This being due to the recipes varying from person to person, even though the sponges made are fundamentally the same thing.

When PCA was used to analyse the ciprofloxacin batches it was successful in categorising the variations between A&C, G&C and C&C within the multiple grouped PCA models.

When analysing the PCA models some clusters were found to be distinct, whereas others are broader in appearance (illustrated in figure 38).

Five batches were identified as counterfeit, 9 were identified as generic and 14 were identified as authentic.

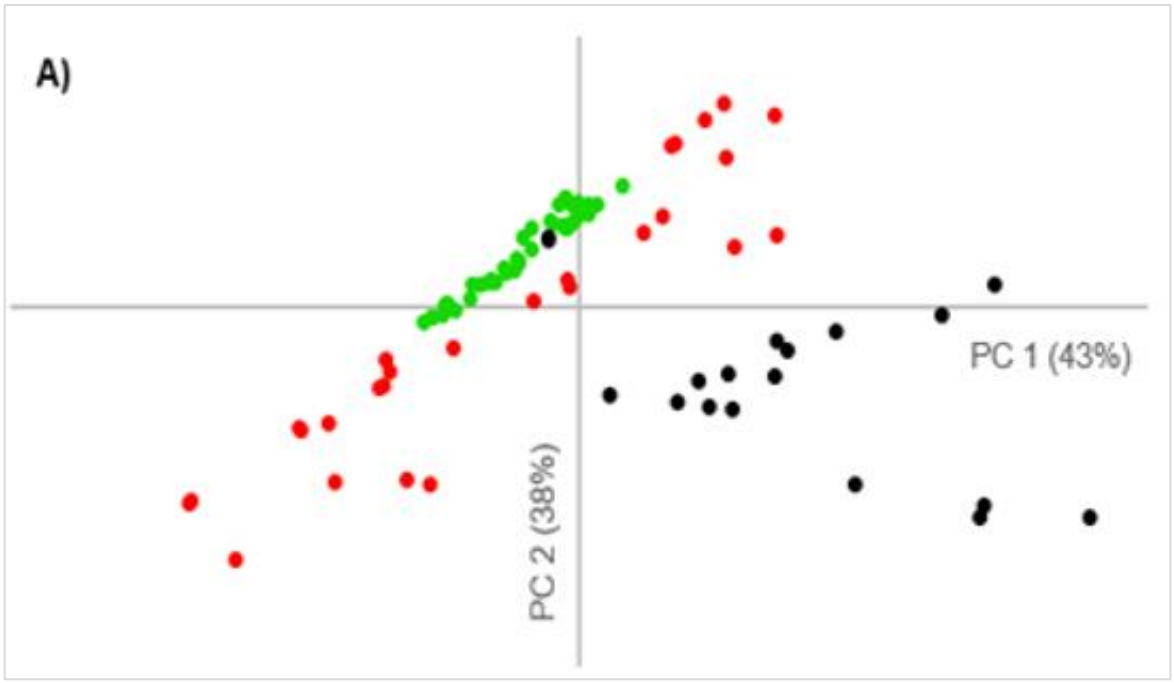


Figure 38: (A) PCA-3 MSC-D1 pre-treated FT-NIR spectra of counterfeit (black), generic (red) and authentic (green) where PC1 is 43% and PC2 is 38%. (B) PCA-6 MSC-D1 pre-treated FT-NIR spectra of counterfeit (black) and authentic (green) where PC1 is 66% and PC2 is 14%.

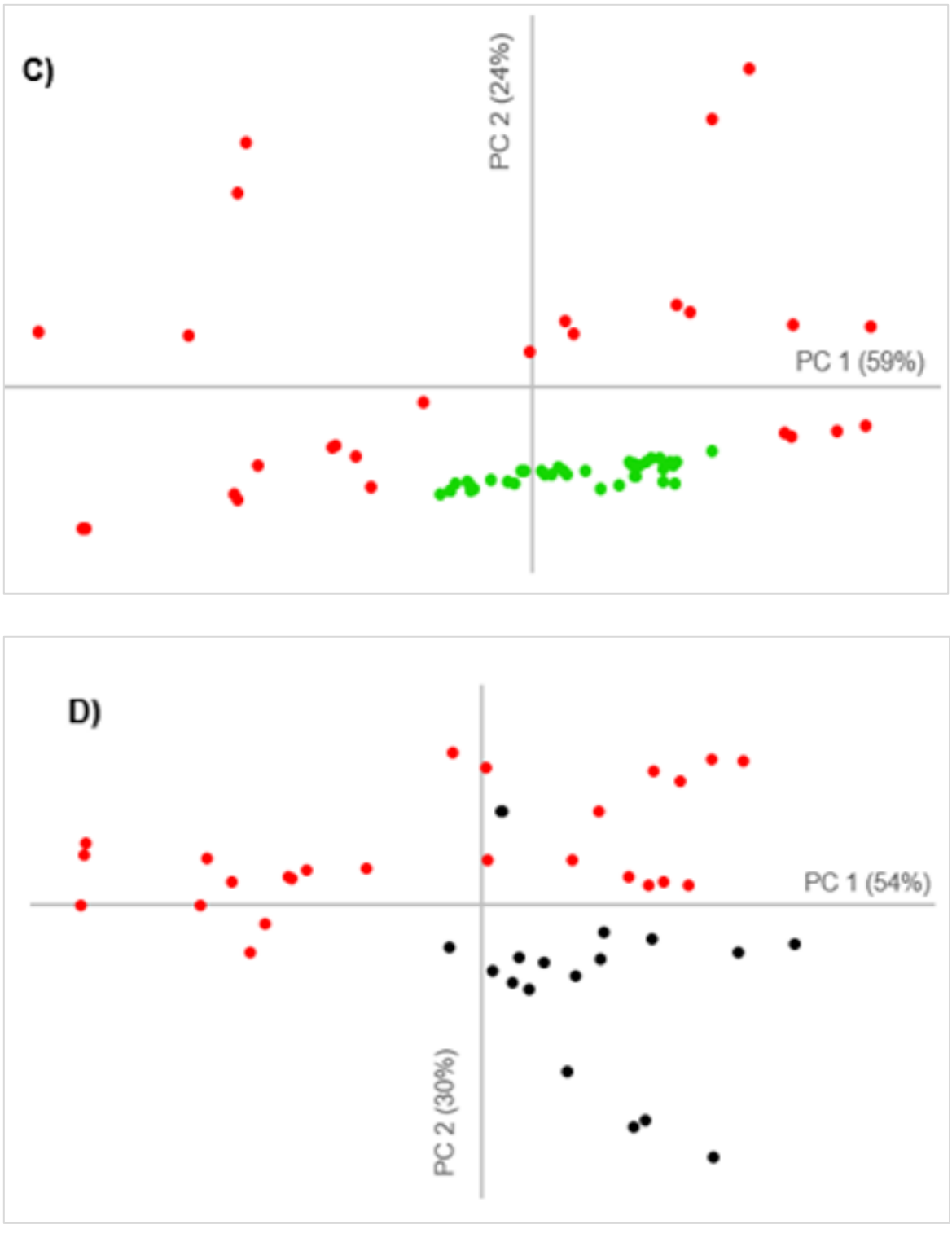


Figure 39. (C) PCA-5 MSC-D1 pre-treated FT-NIR spectra of generic (red) and authentic (green) where PC1 is 59% and PC2 is 24%. (D) PCA-4 MSC-D1 pre-treated FT-NIR spectra of counterfeit (black) and generic (red) where PC1 is 54% and PC2 is 30

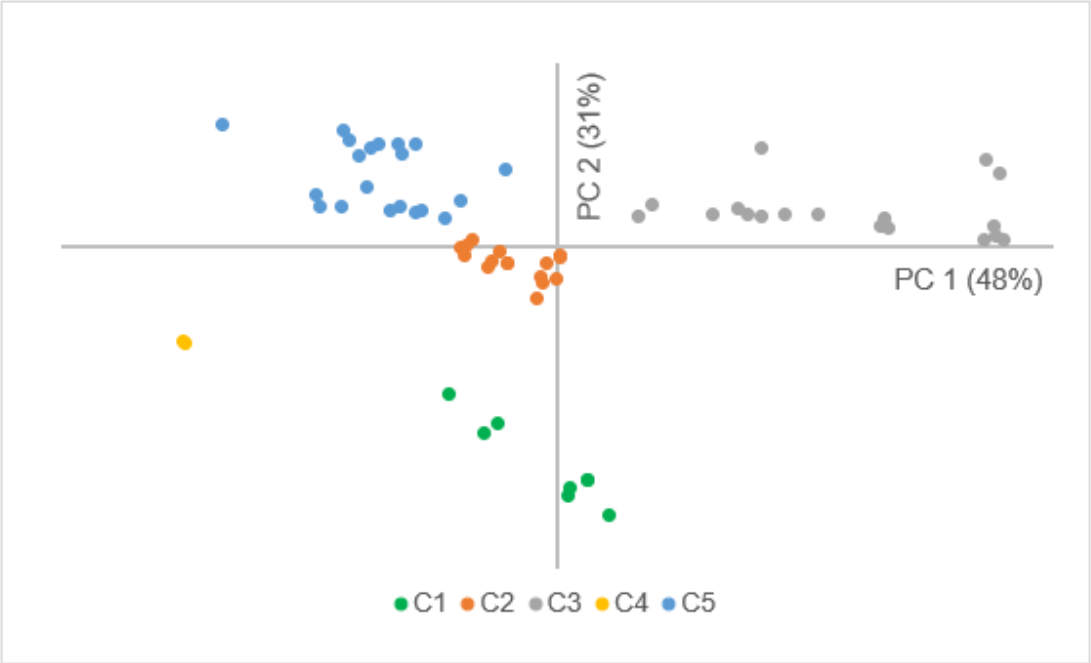


Figure 40: PCA-AB6 MSC-D1 pre-treated counterfeit ciprofloxacin batches where PC1 is 48% and PC2 is 31%.

Unfortunately, as seen figure 39, there are no set clusters, which means that the CC PCA model was unable to distinguish between the sources correctly. Even if they are not from the same manufacturer the countries themselves have different manufacturing restrictions, meaning that countries of origin would be seen on an ideal model.

The three that should be grouped together are C3, C4 and C5 as they are from sources in Lebanon. However, C2, C3 and C5 seem to be groups, whereas C2 is from Ghana.

One of the problems that PCA has is when there is a heavy bias in the sampled date. Due to the way PCA works it 'explains' the cause of most of variation in the data.

Therefore, if most of the samples are deemed to be from one part of the population such as C3, C4 and C5, the PCA will calculate a component that mostly spans this population and will pull the remaining data inline such as C2.

Due to only having five samples there were confirmed to be counterfeit, there is not a sufficient amount of mappable data. Another reason for the samples data being

skewed is that as they are counterfeiting, the regulations that would be in those countries may not be followed completely so similarities could be found where there should be none.

AC and GC were able to separate for the main part the manufacturing sources and cluster them together as demonstrated in figure 41 for AC and figure 42 for GC.

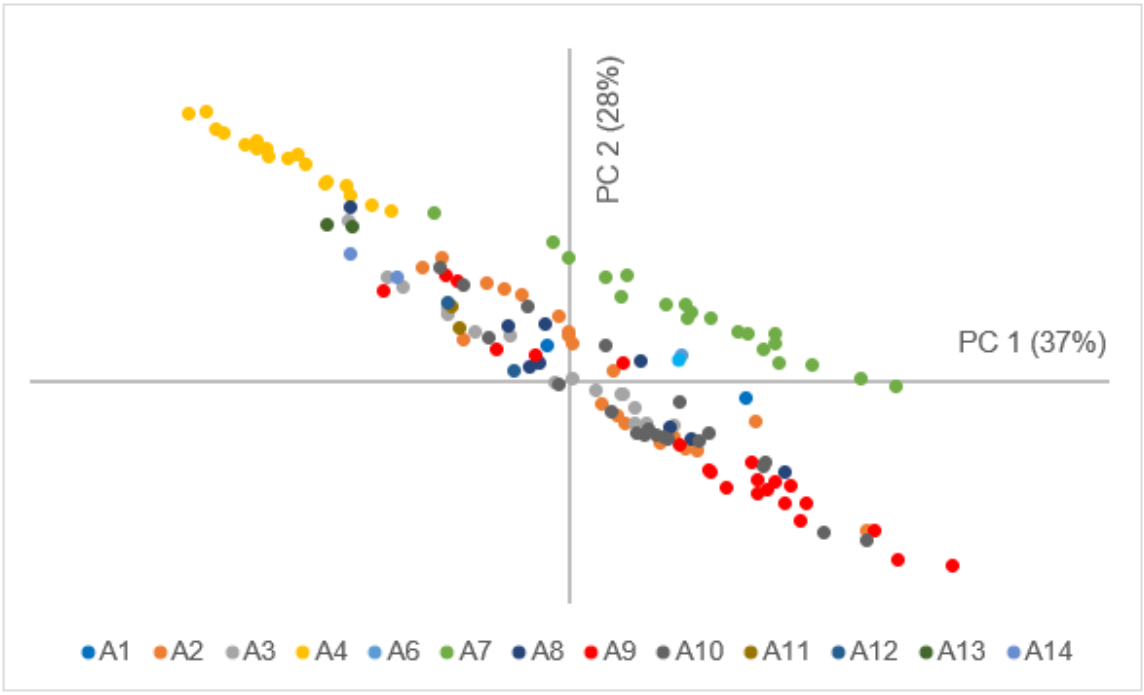


Figure 41:PCA- AB5 MSC-D1 pre-treated authentic ciprofloxacin batches where PC1 is 37% and PC2 is 28%.

PCA-AB5 figure 41 was able to shoe the manufactures in a country but separation of those countries as well, even if the clusters did not seem to be clear and concise. A7 was a product from Lebanon, whereas A14 and A6 were produced in Ghana. The remainder of the ciprofloxacin batches were produced in the UK.

As is with a majority of countries the UK has different manufacturers. This is shown with A4 being for the most part separate to the rest of the batches. A4 was produced by Telanc Pharma, whereas the UK batches were produced by Bayer AG Germany and grouped together.

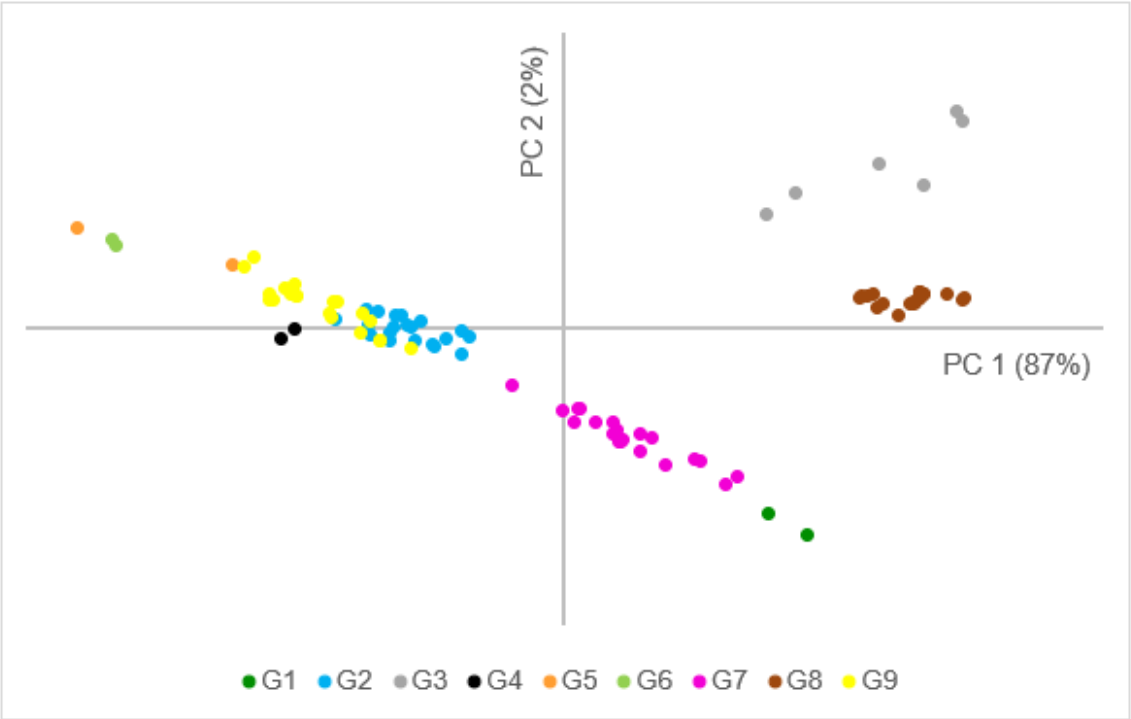


Figure 42:PCA-AB7 MSC-D1 pre-treated generic ciprofloxacin batches where PC1 is 87% and PC2 is 2%.

PCA-AB7 figure 34 also demonstrated the ability of PCA distinguishing countries of origins. Just like with PCA-AB5, PCA-AB7 shows the variations of manufacturers within the countries.

In figure 41, batches G3 and G8 are detached from the main group and from each other. G3 and G8 are from Lebanon, they are however from different manufacturers. The manufacturers of those two batches are Pharma International Co, an unknown source.

G1 was produced in Tanzania and shows separately from the main group that were produced in the UK.

When examining the UK batches, a separation of manufacturers has occurred with G7, which was manufactured by Karib Kemi Pharma compared to Bayer AG Germany that produced the remaining of the batches.

2.18 Data Analysis - CWS

With PCA being successful in determining counterfeit medicines another method that was deployed for analysis was CWS for the comparison between multiple different vectors.

Eight comparison models were created as shown in table 10 for a more accurate representation of the data.

Table 10: Table of correlation models and their respective 'r' values.

CWS Model	Samples Compared	(r) Value Max	(r) Value Min
CWS 1	Antibiotics Vs Antibiotics (one batch of each type)	0.94	0.21
CWS 3	Ciprofloxacin Vs Ciprofloxacin (all batches)	0.99	0.62
CWS 2	Raw Material Vs Raw Material	0.99	-0.47
CWS 4	Raw Material Vs Antibiotics (one batch of each type)	0.99	-0.41
CWS 5	Raw Material Vs Ciprofloxacin (all batches)	0.99	-0.47
CWS 6	Raw Material Vs Authentic Ciprofloxacin	0.99	-0.42
CWS 7	Raw Material Vs Counterfeit Ciprofloxacin	0.99	-0.49
CWS 8	Raw Material Vs Generic Ciprofloxacin	0.99	-0.45

CWS is capable of determining how similar one product is to another, it determines correlation comparison by finding how often a similarity appears throughout a spectra's wavelength range when compared to another sample (Bewick, Cheek and Ball, 2003). Within this project the correlation occurs between the range of 4000cm-1 and 10000cm-1.

The reason for using CWS in this study is that when comparing antibiotic samples to raw materials it can be determined if the material is contained within the medicine.

The reason behind the separate models is to illustrate a broad understanding of similarities found between antibiotics, excipients and other raw materials. A variety of materials were used in these comparisons – for a list of materials used please see

Section 2.23. The comparisons ultimately test how each compound or material compares against themselves, materials of similar properties and the same type of compound.

The value 'r' is used to determine how strong a correlation comparison is between two samples. If it shows 0.65, it suggests that there is a 65% match between the samples compared.

The 'r' value can be used in the case of medicines and raw materials to determine if an API is present in the mixture. For a similarity to be observed it must show an 'r' value of 0.95 and above for a consideration of correlation to occur.

2.18.1. CWS Model 1: Antibiotic Vs Antibiotic

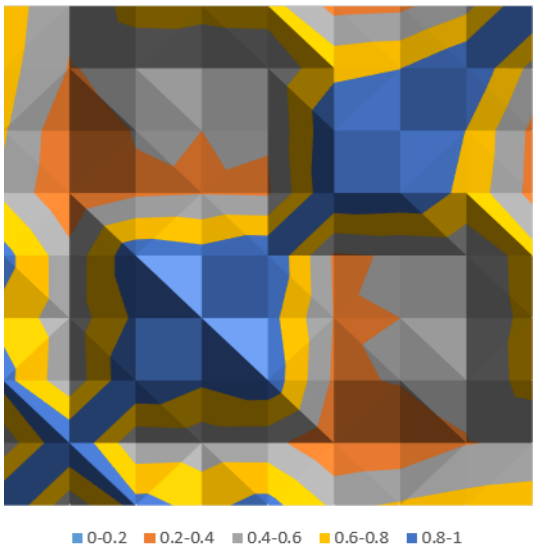


Figure 43: CWS -1 showing MSC-D1 pre-treated Antibiotic FT- NIR data being compared against each other with a max 'r' value of 0.94 and a min 'r' value of 0.21.

CWS-1 illustrated in figure 43, illustrates the similarities found when comparing the antibiotic samples to each other.

The overall 'r' value range for the various antibiotics are compared to themselves ranged from 0.94 to 0.21. When an antibiotic was compared against itself it illustrated a strong correlation as demonstrated by the diagonal dark blue line the 'r' values for the comparisons ranged from 0.8 to 1.

When different types of antibiotics were compared to each other there was not a defined high correlation, but some similarities appeared the 'r' value ranged between 0.4 to 0.8. Certain antibiotics match characteristic of others when they should not. Some of the samples that illustrated a correlation 'r' value of 0.8 or above when there is no reason for a high correlation are azithromycin, cefuroxime and ofloxacin.

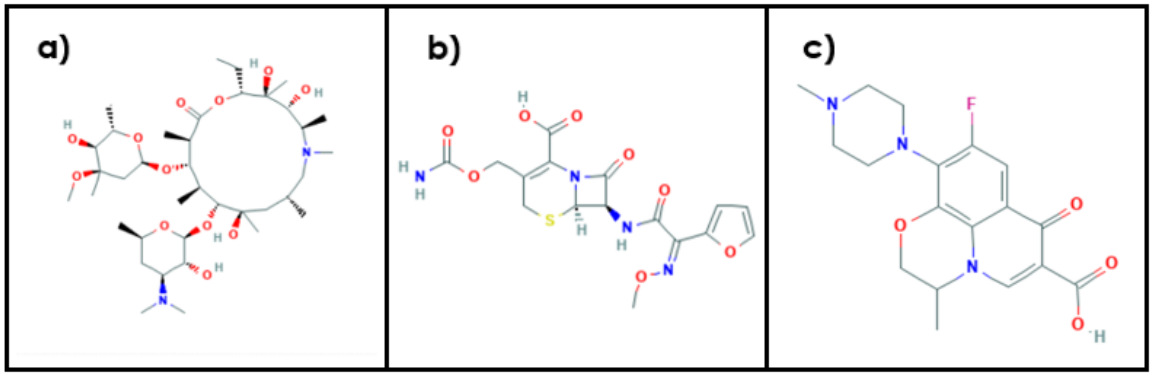


Figure 44: The chemical structures of azithromycin, cefuroxime and ofloxacin.

As illustrated in figure 44 the chemical structures of these three API compounds that show a high correlation, are structurally unsimilar, so the high correlation identified could be due to contamination of the samples.

Another reason for the high correlation is due to the excipients contained within the tablets being the same if not similar as each other. One such excipient that is the same throughout the batches is Talc.

By having Talc in a large quantity as a filler the CWS would not be able to distinguish between the API that was need to be correlated and the small percentages of other materials involved in the tablets.

2.18.2 CWS Model 2: Ciprofloxacin Vs Ciprofloxacin

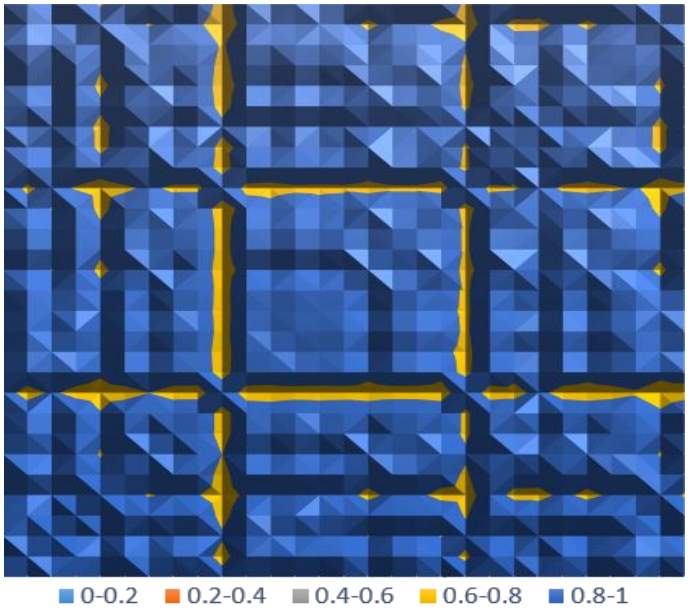


Figure 45: CWS -2 showing MSC-D1 pre-treated Ciprofloxacin FT- NIR data being compared against each other with a max 'r' value of 0.99 and a min 'r' value of 0.21.

CWS-2 illustrated in figure 45, illustrates the similarities found when comparing the ciprofloxacin samples to each other.

The 'r' value range for the authentic ciprofloxacin batches matching against themselves ranged from 0.99 to 0.87. Similarly, the 'r' value range for the counterfeits when compared to each other range from 0.90 to 0.50.

Whereas when the counterfeit medicines are compared to the authentic medicines the overall 'r' value ranges from 0.62 to 0.85. Therefore, the overall 'r' value range for the ciprofloxacin batches compared to themselves ranged from 0.99 to 0.62 on average.

As illustrated in figure 45 there are some 'r' values that are as low as 0 to 0.2, this demonstrates that even though the tablets are all classed as ciprofloxacin, the counterfeits compared to authentic have significant differences to each other. This could be caused by different excipients present or different amounts of APIs.

Unlike the other models there is no clear distinction of correlation when a sample is compared to itself. There are however two ciprofloxacin batches that show clear comparisons for all the other samples (illustrated in yellow).

The grid lines demonstrate that there is a 0.6-0.8 correlation between the two ciprofloxacin samples and the other samples when compared. These batches are the counterfeit 'it502bz' and cf1h0005.

These particular characteristics suggest that there is a component within the tablets that are shared throughout the different batches.

Unfortunately, there is not a way to distinguish the particular characteristic component involved in the correlation.

2.18.3 CWS Model 3: Raw Material Vs Raw Material

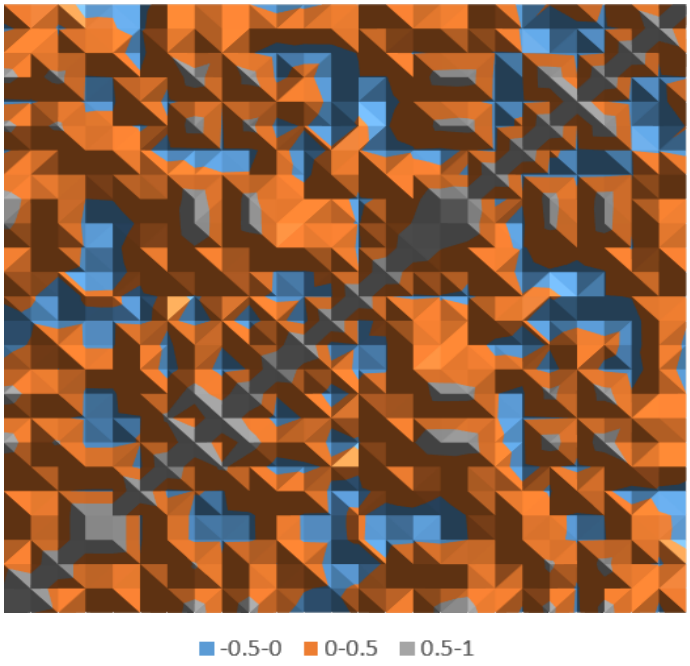


Figure 46: CWS -3 showing MSC-D1 pre-treated Raw Material FT-NIR data being compared against each other with a max 'r' value of 0.99 and a min 'r' value of -0.47

CWS-3 illustrated in figure 46, illustrates the similarities found when comparing the raw materials to each other.

The 'r' value range for the raw materials compared to themselves ranged from 0.99 to -0.47. The 'r' values demonstrated by the grey line range between 0.5 to 1.

The 'r' values are split into such a wide range, for example -0.5 to 0, 0 to 0.5 and 0.5 to 1, is due to how different the materials are structurally in their raw form when compared to each other.

As shown in CWS -1 there is a medium to high correlation demonstrated when a sample is compared to itself. This is illustrated in figure 46 by the clear diagonal line (in grey).

When the raw materials are compared to each other there are a limited number of high correlations, except when the samples are compared to themselves. The main similarities occur between the sodium containing compounds and the sugar-based

compounds. This is mainly due to the similarities in structures and the behaviours they present when the FTNIR is used for analysis.

2.18.4 CWS Model 4: Raw Material Vs Antibiotics

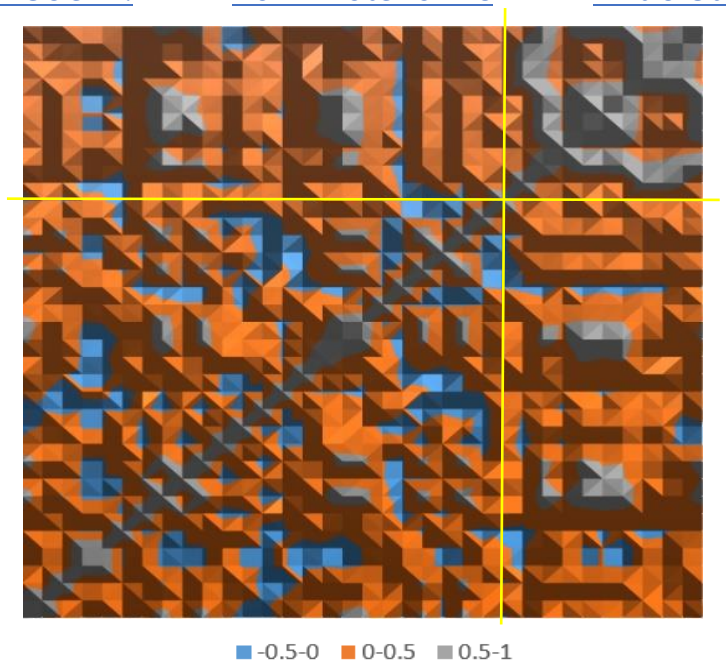


Figure 47: CWS -4 showing MSC-D1 pre-treated Raw Material FT- NIR data being compared against one batch of each type of antibiotics with a max 'r' value of 0.99 and a min 'r' value of -0.41.

CWS-4 illustrated in figure 47, illustrates the similarities found when comparing the raw materials to the antibiotic samples.

The 'r' value range for the raw materials compared to the various antibiotics ranged from 0.99 to -0.41. The sections segregated in figure 47 illustrate the different comparisons, (1) & (4) the raw materials compared to the antibiotic batches, (3) the raw materials compared to themselves and (2) the antibiotics compared to themselves.

Once again as similar to CWS-1 & 3 there is a correlation demonstrated when a sample is compared to itself. This is illustrated in figure 47 by the clear diagonal line (in grey).

Often seen when the sample is compared to themselves. As shown in CWS -1 when the antibiotics are compared together there are high correlations with some

discrepancies illustrated where some of the excipients are not common across the antibiotics.

When the comparisons between the antibiotics and raw materials are examined further it can be seen that there are some high correlations in the groups. The main correlation found are those that represent lactose, talc and titanium dioxide, this is expected as they are excipients in the antibiotic tablets. What is unusual and would need to be explored further is that they are the only excipients showing a high correlation when there are other known excipients in the model.

2.18.5 CWS Model 5: Raw Material Vs Ciprofloxacin

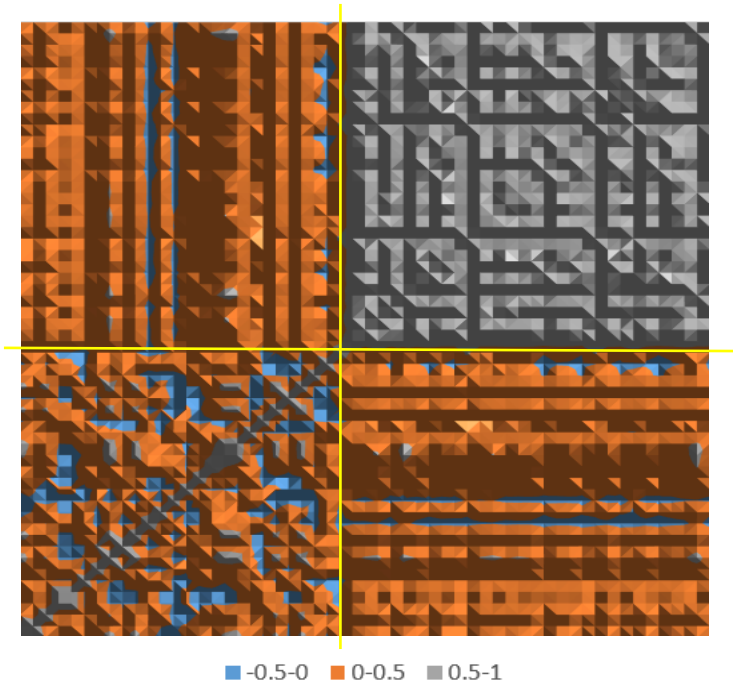


Figure 48: CWS -5 showing MSC-D1 pre-treated Raw Material FT- NIR data being compared against all of the ciprofloxacin batches with a max 'r' value of 0.99 and a min 'r' value of -0.47.

The overall 'r' value range for the raw materials compared to the ciprofloxacin batches ranged from 0.99 to -0.47.

Similar to CWS-4 the sections segregated in figure 48 illustrate the different comparisons, (1) & (4) the raw materials compared to the ciprofloxacin batches, (3) the raw materials compared to themselves and (2) the ciprofloxacin batches compared to themselves.

When inspecting the CWS-5 model as a whole the ciprofloxacin batches illustrate an extremely high correlation rate, even when they are a mix of authentic, generic and counterfeit samples.

In retrospect, because the raw materials are so diverse, they illustrate clearly the differences when they are compared.

However, when the raw materials are compared to the ciprofloxacin there are rare similarities shown and they cannot be distinguished easily in the visual model. Therefore, any similarity that causes an 'r' value of 0.5 or more becomes a grey

correlated square. Thus, any slight differences in the correlations would be hard if not impossible to distinguish.

To reduce this issue, the examination of separate classes of ciprofloxacin batches with comparisons to the raw materials would reduce the conformity issues of correlating such a large scale.

Those models that aid in distinguishing the conformity issues are illustrated in CWS 6-8.

CWS 6-8 also help to separate the correlative value of 0.99 max and -0.47 minimum. These values are from the overall model where high correlation occurs for the ciprofloxacin batches compared to the raw materials.

2.18.6 CWS Model 6: Raw Material Vs Authentic Ciprofloxacin

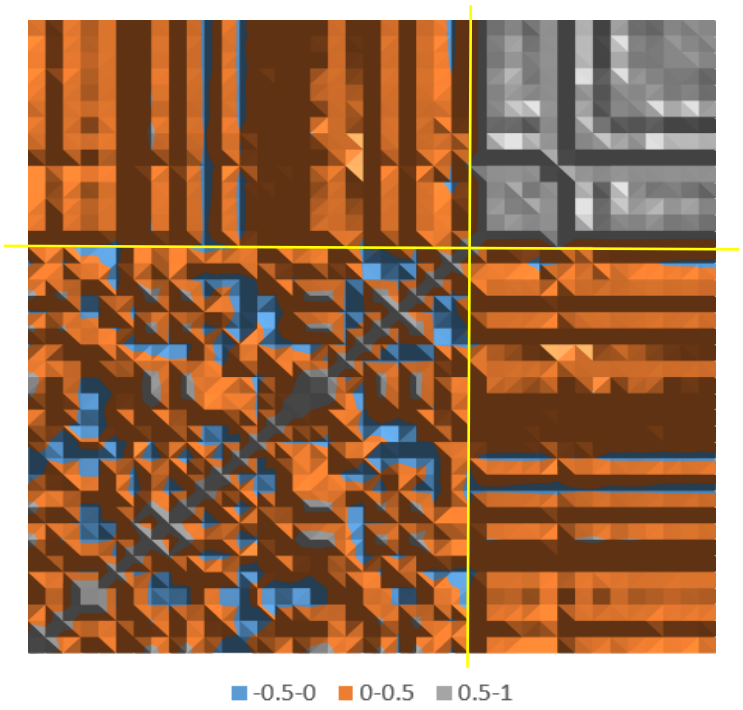


Figure 49: CWS -6 showing MSC-D1 pre-treated Raw Material FT- NIR data being compared against the authentic ciprofloxacin batches with a max 'r' value of 0.99 and a min 'r' value of -0.42.

CWS-6 illustrated in figure 49, illustrates the similarities found when comparing the authentic ciprofloxacin samples to the raw materials.

The overall 'r' value range for the raw materials compared to the authentic ciprofloxacin batches ranged from 0.99 to -0.42. The sections segregated in figure 49 illustrate the different comparisons, (1) & (4) the raw materials compared to the authentic ciprofloxacin batches, (3) the raw materials compared to themselves and (2) the authentic ciprofloxacin batches compared to themselves. Similar to the visual representation show by models CWS – 4 & 5.

It is hard to distinguish the rectangles that represent the comparisons between the authentic ciprofloxacin and the raw materials, again this is due to the wide range of similarities for the raw materials when they are compared to each other.

With the ciprofloxacin batches being highly correlated together with 'r' values of 0.5 to 1, the comparisons between the raw materials and ciprofloxacin batches thus correlate at a lower rate with 'r' values of 0.5 and lower.

However, there are a couple of hotspots of high correlation. These hotspots are representative of croscarmellose sodium, talc and lactose.

For the most part high correlation is not apparent, probably because of the differences in the chemical composition.

The lack of other high correlative peaks could be due to contamination of samples, with the wavelengths not being cleaned efficiently when comparisons were made.

2.18.7 CWS Model 7: Raw Material Vs Counterfeit Ciprofloxacin

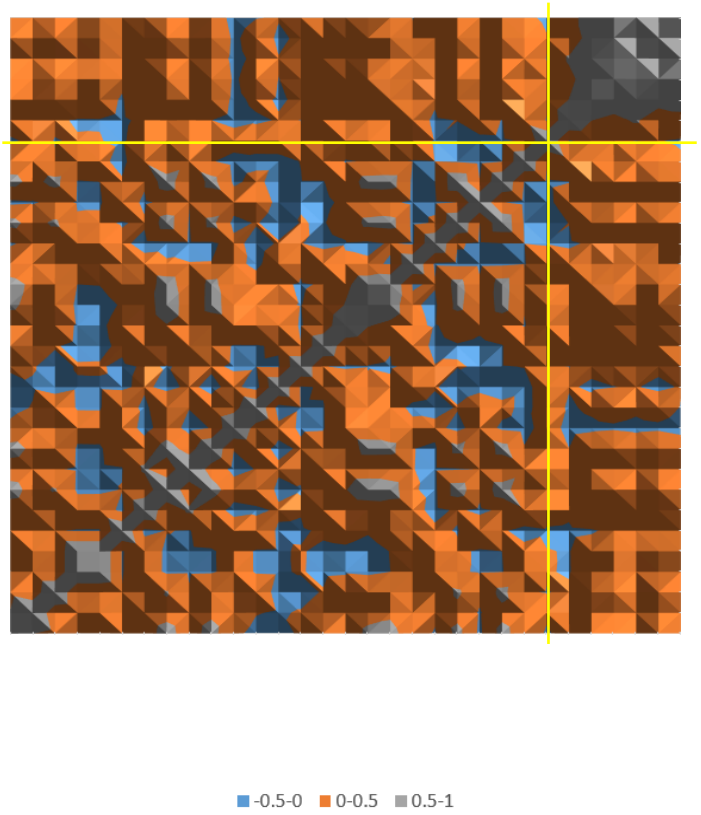


Figure 50: CWS -7 showing MSC-D1 pre-treated Raw Material FT- NIR data being compared against the counterfeit ciprofloxacin batches with a max 'r' value of 0.99 and a min 'r' value of -0.49.

CWS-7 illustrated in figure 50, illustrates the similarities found when comparing the counterfeit ciprofloxacin samples to the raw materials.

The overall 'r' value range for the raw materials compared to the counterfeit ciprofloxacin batches ranged from 0.99 to -0.49.

The sections segregated in figure 50 illustrate the different comparisons, (1) & (4) the raw materials compared to the counterfeit ciprofloxacin batches, (3) the raw materials compared to themselves and (2) the counterfeit ciprofloxacin batches compared to themselves.

Despite PCA being able to distinguish trends within the counterfeit medicines, CWS had an issue determining correlations between the raw materials and the counterfeit ciprofloxacin sample batches.

Even though some of the raw materials used in the comparison are known to be in the tablets due to being written on the tablet information label, there are no definitive correlative peak of 'r' values higher than 0.5.

This suggests that there is a high level of impurity in the samples of ciprofloxacin batches. The reason for this suggestion is that PCA was able to find differences with identification of the variables between samples, whereas CWS could not find significant similarities in the wavelengths.

One high correlative match found in some of the counterfeit batches was that of talc when the model was expanded. This is supportive of figure 17 where the counterfeit medicines are distinguished by the talc peak.

2.18.8 CWS Model 8: Raw Material Vs Generic Ciprofloxacin

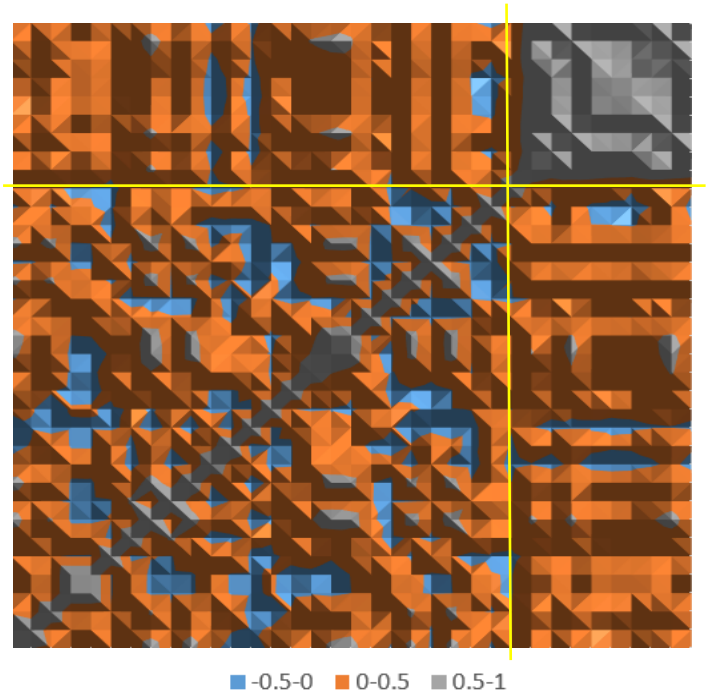


Figure 51: CWS -8 showing MSC-D1 pre-treated Raw Material FT- NIR data being compared against the generic ciprofloxacin batches with a max 'r' value of 0.99 and a min 'r' value of -0.45.

CWS-8 illustrated in figure 51, illustrates the similarities found when comparing the generic ciprofloxacin samples to the raw materials.

The overall 'r' value range for the raw materials compared to the generic ciprofloxacin batches ranged from 0.99 to -0.45.

The sections segregated in figure 51 illustrate the different comparisons, (1) & (4) the raw materials compared to the generic ciprofloxacin batches, (3) the raw materials compared to themselves and (2) the generic ciprofloxacin batches compared to themselves. Once again, the correlation shows between the samples and themselves has a 'r' value or 0.5 and above, illustrated via a grey line.

It is easier to see that there are a few correlative peaks between generic ciprofloxacin batch samples and the raw materials. There are only four peaks that can be seen using CWS, when comparing the generic batches against the raw materials illustrating 'r; values of 0.5 and above. These peaks correspond to titanium dioxide, croscarmellose sodium, lactose and stearic acid.

However, these peaks are only distinguishable because of the level of correlation (0.5 to 1), however it is not possible to determine how significant the correlation is and where the 'r' value lies within that range.

2.19 Medicine Identification Summary

The consensus of the experiments and tests conducted is that they are able to show a trend in the data that can be used to determine points of focus for the future with a far greater sample set.

FTNIR was able to distinguish the similarities of the binary mixture and also the volume ratio of each mixture, this validated the FTNIR being used for the analytical instrument of choice.

The binary mixtures that were used gave validity to the PCA being the primary illustration through being able to isolate the identity of chemical structures and how they are fundamental to the clusters being grouped.

When PCA was used to analyse the ciprofloxacin data it was able to identify small trends and anomalies that at first thought should not be there. Such example is PCA CC as the origin of the medicines should show more commonality between samples, whereas another batch from a different source was intermingled in the data.

This shows that even though PCA is a strong technique for large data set analysis it does still have flaws if not all parameters are met. The smaller the sample size the more variability there is in the components.

On the other hand, CWS, even though useful for visualising the comparisons of the antibiotics to the raw materials or when compared to themselves, it was not found to be as useful as PCA.

One reason being is that if failed to determine distinguishable features between the various classes of ciprofloxacin batches, either by comparison of the samples to themselves or the raw materials compared to the ciprofloxacin batches.

This difference would be so minute that their significance would be overshadowed by the similarities identified instead. When compared batch 1 to batch 1 it would show ~ 100% similarity whereas if you measured batch 1 to batch 2 there

could be a 99% match where only 1% of the chemical makeup of batch 1 differs from batch 2. Thus, CWS on its own is not strong enough to pick up that slight difference in a small data set.

However, it is found that the overall analysis of medicines was successful, as the properties of the ciprofloxacin batches were determined and categorised. There was in total 14 authentic, 9 generic and 5 counterfeits identified.

As close to 1:3 tablet batches were found to be counterfeit, with such a small sample set the number of counterfeits found is significant and a cause for concern. These medicines were screen by professionals and prescribed to the patients be it from a brick-and-mortar pharmacy or an online version.

This cause for concern stems from the basis that the medicines that we as a society consume even though thought to be tested, some may miss the mark of standards set.

As society grows and is ever evolving the standards of counterfeits in all walk of life have to adapt and become almost unrecognisable, only distinguishable under the microscope and tests.

Even though FTNIR has its advantages such as its quick, efficient and does not degrade a sample when tested, it also has its draw backs that it takes knowledge to decipher the spectra and needs treating before the analysis is complete.

Overall, this process would be time consuming and thus cost the industry a lot of money if it was to become standard practise for all batches to be tested before being released on market. However, spot checks, quality control of manufacturers and other measures are in place to help prevent and aid in counterfeit medicines from being pulled from the supply chain.

If counterfeit medicines were to enter the market the threat to public health would be greatly increased. One way for counterfeits to be countered is for the

regulations regarding them to be updated and amended. The new FMA Directive is the next stepping stone on the path to fighting counterfeits.

Chapter Three: Policies and Laws governing Online Pharmacies and Counterfeit Medicines.

3.1 The Falsified Medicine Directive (FMD)

Following on from the quantification of counterfeit medicines in Chapter Two, it is clear that the only way to verifiably detect if a sample was indeed a counterfeit was to look in depth at the chemical composition of the samples.

The medicines themselves are only one part of the problem, yet they cause the risk to the public's health and the individual who consumes them. The problem with counterfeit medicines - as will be explained throughout this study – is that they have very little traceability, and presence that stands out.

They are sophisticated enough to be hidden via normal means of detection such as the packaging or the continuity stamps for example the batch number or expiry date.

Thus, this causes a wide spread problem not just nationwide but worldwide, the impact of which is felt throughout all demographics and cultures as no country is primarily safe from some description of a counterfeit being present.

Apart from the counterfeits themselves another one of the issues in the supply chain that counterfeiters can take advantage of is the distribution and sites of the sellers if they sell through a third party.

The individuals that are most at risk from being supplied a counterfeit in particular are those that shop online or those who use pharmacies that are overworked and not managed sufficiently as explained below.

As ciprofloxacin – which is the focus of this research - is typically a prescription only medicine (POM), rather than a general sales list medicine such as ibuprofen, fall

under the scrutiny of the FMD. As is the directive that directly effects the security of counterfeit/ falsified POMs.

In this chapter the FMD will be analysed via how it worked, how is it tested/implemented and also how its structure passes onto pharmacies either local brick and mortar or online.

As stated previously in Chapter One, falsified medicines are fake/false medicines that are thought to be the genuine versions, with regard to the ingredients, the packaging or both among other things. Whereas counterfeits are "medicines that do not comply with intellectual property rights". These are the definitions that will be used throughout this chapter.

The European Union (EU) has developed legal frameworks for the licencing, distribution and manufacturing of medicines. The frameworks are centred around the directives on falsified medicines that are primarily for human use, so that only the authentic medicines are sold form licenced pharmacies and other approved retailers.

3.2 FMD Brief History

The FMD is EU Parliament legislation that has been passed with the aim of increasing the security of the manufacturing and delivery process of medicines across Europe, thus preventing falsified medicines from entering the supply chain.

The FMD was originally created with the 2001/83/EC Directive in 2001 by the European Commission (EC). The 2001/83 Directive was created for the sole purpose of bringing the various directives already in use into one manageable place of reference.

The directives placed in the 2001/83 Directive and the amendments that have been created over the years are as follows.

The following directives which were placed within the 2001/83 directives guidelines; Council Directive 65/65/EEC, the Council Directives 75/318/EEC and 75/319/EEC, The Council Directive 89/342/EEC, The Council Directive 89/343/EEC,

Council Directive 89/381/EEC, Council Directive 92/25/EEC, Council Directive 92/26/EEC, Council Directives 92/27/EEC and 92/28/EEC, Council Directive 92/73/EEC.

As stated in the 2001/83/EEC Directive 'In the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text' thus unifying the previous directives into one with the unified aim to 'govern the production, distribution and use of medicinal products to safeguard the public health'.

This unifying directive has subsequently been amended over the years with the following directives; Directive 2002/98/EC, Commission Directive 2003/63/EC, Directive 2004/24/EC and 2004/27/EC, Directive 2008/29/EC, Directive 2009/53/EC, Directives 2001/82/EC and 2001/83/EC, Commission Directive 2009/120/EC, Directive 2010/84/EU, Directive 2011/62/EU. Which brings us to the most recent amendment Commission Delegated Regulation (EU) 2016/161.

3.3 FMD Initiative

A problem, that has been gaining traction across Europe and the globe is falsified medicines for human use (Houston 2012). They first entered the market mostly for lifestyle medications; more recently however they have included other medicines such as antibiotics (Brady 2020). Consequently 2001/83 Directive was amended by the 2011/162/EU Directive by the recently published Delegated Act 2016/161.

The amendments that are imperative to this research are Commission Directive 2003/63/EC due to the code relating to the human use of medicinal products, which is a cause of concern when investigating counterfeits as explored in Chapter Three.

Furthermore Directive 2009/53/EC is an important amendment due to focusing on the terms of marketing authorisations for medicinal products, which relates to the importance of authentic pharmacies as discussed in Chapter Three.

The nature of Directive 2011/62/EU makes a great solution for it to be used for the recognition and risk of falsified medicines form entering the supply chain, when working with Commission Delegated Regulation (EU) 2016/161 which regards the

implantation of safety features on medicinal products for human use, the FMD 2019 was created.

Due to the unifying properties of the 2001/83 Directive, it is thought that the FMD will enable wholesalers, manufacturers, distributers and anyone else who supplies the medicines to patients to have the ability to verify the authenticity of the medicinal product, the individual packets and even check whether the outer packaging has been tampered with.

The FMD introduces and harmonizes safety and strengthens the various control measure across Europe to limit the risk to the public's health.

Essentially the FMD was created to provide safety measures against the entry of falsified medicinal products into the supply chain. This measurement is done by the 'mandatory' placement of the new safety features, including an anti-tampering device (ATD) and a unique identifier (UI) on the packaging of the medicinal products. Those products are for human use and the use of the safety features is to allow the authentication and identification of these medicinal products.

In conjunction with these safety features the FMD also provides an ability to aid security when purchasing medicinal products on the Internet. Falsified medicine as stated by the FMD "*poses a particular threat to human health and may lead to a lack of trust of the patient also in the legal supply chain*".

Thus, it is paramount that the scope of 2016/161 Directive, to protect patients from the health consequences of falsified medicines is understood.

Overall, it is estimated that the falsified medicinal products impact on the economics globally is €10.2 billion every year and increasing (EUIPO 2020). Unfortunately, the costly revenue produced from falsified medicines include all medicines, not just those that are covered by the FMD.

Despite, the cost of implementing the safety features on the packaging the pharmaceutical industry is progressing forward with the execution of 2016/161/EU

Directive. In addition to the cost and safety features, another relevance to the FMD is the staffing availability, a lack of which impacts the ability to handle large amounts of packages, as this is where one of the risks for entering the legal supply exists.

3.4 FMD Features

1. Safety Features of medicines

On and there after the 9th February 2019 the marketing authorised holders are obligated to place two safety features on the packaging of mostly prescribed medicines. However, some over-the-counter medicines in the EU are also obliged to have the safety features.

The safety features are as follows; an anti-tamper device (ATD) and a unique identifier (UI) in the form of a 2D matrix (Barcode) as shown below in figure 52 for examples. The features are in accordance with Commission Delegated Regulation (EU) 2016/161 with the annexes including which medicines are subjected to this regulation.

Figure 52: The two safety features now present on the packaging of medicines that is implemented due to the FMD.

The UI code must include the product code, the unique serialisation number, the expiry date and batch number. If the pack size permits, the UI code and the information will be printed side by side.

As mentioned previously, the manufacturer applies the ATD and the UI to the medicine containers and uploads the valid codes to the European Medicines Verification System (EMVS) via the European Medicines Verification Organisation

(EMVO). The EMVS will act as a hub that links all the national systems together allowing parallel trading of medicines to continue.

The development of such verification systems is being led through stakeholder models that involve five main sectors of the supply chain; (1) the research-based manufacturer, (2) the generic manufacturer, (3) parallel traders, (4) the wholesalers and lastly (5) the pharmacies. There are also five main areas which the new system identifies; (1) the manufacturer, (2) the pre-wholesaler, (3) the wholesaler, (4) the community pharmacy and finally (5) the hospital pharmacy.

At each stage the medicine is scanned, the National Medicine Verification System (NMVS) will identify the status of the product, either 'active' meaning it can continue down the supply chain or 'inactive' meaning it cannot be passed on. A product may be 'inactive' if it has been stolen, withdrawn.

It can also be 'inactive – dispensed' if the medicines have been dispensed already, this process prevents the same UI code from being authenticated and used by another dispensing entity.

If a product when scanned is found to be 'inactive' the NMVS will alert the MHRA as a potential falsified/ counterfeit medicine may have been discovered, thus it should be withdrawn from the supply chain for more investigation due to the guidelines set by the 10 – day rule.

Furthermore, when a medicine is found to be inactive it is decommissioned from the system. In regard to errors made and incorrect decommissioned UI codes the following can occur to reverse the status of the medicines in accordance to Article 22 of the FMD; the reversal is done not more than 10 days after the decommissioning (commonly known as the "10-day rule"), the product has not been supplied to the public, the product has not been marked by the NMVS as recalled, withdrawn, stolen or intended for destruction, the reversal takes place in the same location as the original decommissioning (ie, within the same dispensing entity) and finally the product has not expired.

2. Supply Chain and Good Distribution Practice

Wholesalers are tasked with new responsibilities introduced by the directive as well as a definition of brokering activities as well as new responsibilities for the brokers. The agency's good-distribution-practice (GDP) guidelines revised now included specific provisions for brokering activities. The EudraGMDP database now holds information on GDP.

3. Active Substances and Excipients

Commencing July 2013, all the active substances that are manufactured outside of the EU and those that are imported into the EU have had to be accompanied by a written confirmation from the current regulatory authority of exporting country.

The statements that are produced and issued per manufacturing site and per active substance ensure that the standards of the good manufacturing practice (GMP) or those that are the equivalent in the EU to be upheld. When a country is called 'equivalent' the regulatory framework of written statements will not be needed.

Several countries have already implemented the status of being 'equivalent' including Japan, Australia, Switzerland and the US. Other countries such as Brazil, Israel and Singapore have also requested to be an equivalent.

4. Internet Sales

The FMD has also introduced an obligatory logo that will appear on websites of legally authorised online pharmacies and approved retailers in the EU as discussed in Chapter Four. The Implementing regulation that established the new logo entered into force in July 2014

3.5 How effective is the UI Code?

In a recent study conducted by Dr Bernard D Naughton of Oxford University some concerns were raised with regard to the effectiveness of UI and ATD from the perspective of the patients. Firstly, the FMD is only responsible for prescription medicines, it does not cover over the counter (OTC) products (Naughton et al. 2016).

There have been some exceptions to the rule, one being omeprazole and paracetamol being covered by the FMD. As discussed in Chapters 1 and 2, falsified medicines can contain little to no amount of API, they can also contain toxic substances which can cause a public health risk.

Consequently, by description the FMD is primarily covering the interests of the pharmaceutical industry that produces the prescriptions drugs rather than the needs of consumers with the perspective of the patients (Naughton et al. 2016).

Secondly in the study conducted by Naughton (2016) the reliability of the 2D codes were tested. After performing an examination on over 4,192 packages, 180 falsified, expired or recalled boxes were found. Within those packages, despite 100% being detected with technical instruments, 64% of expired medicines, 58% of recalled drugs (product and batch) and only 31.8% of falsified medicines were excluded from dispensing.

Furthermore, a pilot study conducted by St James Hospital, Dublin contained a programme that simulated the flow of pharmaceutical products through a serialised, global supply chain.

The model proposed was supported by the delegated Act 2011/161/EC. Within this study known counterfeit products with barcodes copied from the originals in various forms were distributed alongside the authentic products.

The results from this study were that within the simulation 18 of the 50 falsified medicines were incorrectly verified and dispensed to patients. However, when multiple authentication points were added to the chain the number of counterfeits that were supplied to the patients reduced to 10 (Systech 2020).

Consequently, it can be assumed that if the producers of the falsified/counterfeit medicines obtained a list of random codes, it can be presumed that these producers could use the UI on falsified packages thus enabling them to enter the drugs into the market. As a result of this, whether the first code entered to be authenticated is on the authentic or falsified medicine, the code will be decommissioned and classed as authentic.

This makes the scenario of falsified medicines entering the supply chain still applicable, as the only hinderance to this situation is that the falsified medicines must enter the market before the authentic versions reach the pharmacies. Due to the complexity of the supply chain the falsified medicines will be dispensed as authentic and the public will be none the wiser to the risk.

As mentioned previously in Chapter One, the MHRA have alert policies where medicines can be recalled by the manufacturer when the public report adverse effects. Due to the falsified medicines progressing through the supply chain to the patients and the authentic medicines being classed as falsified, this causes manufacturers to recall at least the whole batch, even if only just one code was misused. Unfortunately, this may cause an unintended shortage of medicines.

Another issue that may arise from the serialisation of medicines and the use of the UI is technical error, including non-decommissioning of medicines when they are delivered to the pharmacies, malfunctioning of the scanners and staff misinformation of the codes.

As a conclusion, from the combination of Naughton and St James Hospital serialisation alone is not adequate to eliminate diversion and counterfeiting risks in the supply chain.

3.6 How effective is the ATD?

The ATD, otherwise known as a tamper-indicating device (TID), is designed to leave unambiguous, non-erasable evidence of unauthorized access or entry of the

packaging. The ATD that is used in conjunction with the FMD is referred to as a seal (Appel 2011).

A seal is used when recording of access is required, unlike a lock which is used to resist access. Thus, some seals are made of paper or plastic that can be easily removed. Seals must be inspected to determine whether an intrusion has occurred, and the device has been tampered with (Petersen & Johnston 1997).The ATD is a type of adhesive label seal. These types of seals are made with the consistency of tape (sticky labels) that become damaged if removed from what they are stuck to. Examples are shown in figure 53.

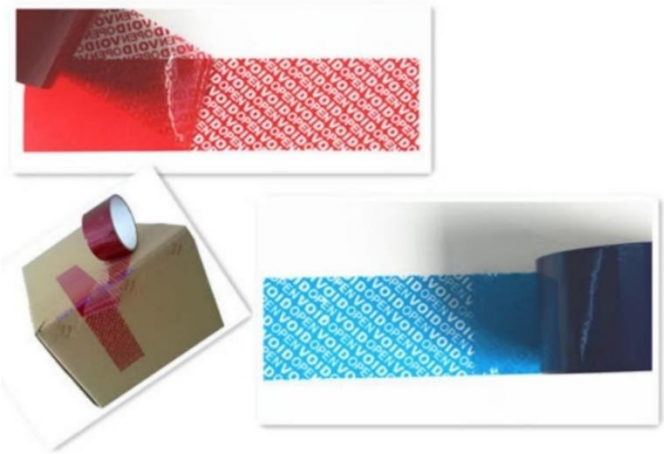


Figure 53: Examples of Adhesive seals

Adhesive seals are inexpensive, easy to use and able to mass produced. However, these types of seals do not offer or provide high levels of security, nor are they very robust. As discovered in a case study conducted by Andrew W. Appel from Princeton University when he was tasked with the testing, security and the use of seals on voting machines by the State of New Jersey (Appel 2011).

Appel found that when the seal is first removed or 'mostly pulled back' it is successful in recording tampering as shown in Figure 54 with 'open void' being present.

Figure 54:Pressure-sensitive adhesive tape. At left, as first installed; at right, when (mostly) peeled back and pressed down again.

To tamper with the seal Appel used a heat gun to remove the seal using the edge of a razor blade when the seal was softened enough by the heat. This method was successful in the fact that Appel could remove the seal completely without evidence showing tampering. All that it took was 80 seconds of heat to remove the seal and 2 seconds to replace a new one in its place (Appel 2011).

Therefore, it can be argued that the ATD alone is not enough to hamper falsified medicines from entering the supply chain and being detected. However, with the aid of the UI and the Frangible seals within the blister packs together, this should form the start of future attempts to stop falsified medicines from being supplied to the patients.

3.7 Supply Chain & Risk

As described in Chapter Four the use of online pharmacies poses a major risk to public health, due to the purchasing of falsified medicines. With comparison between Australia and the UK, Australia's Health Authority found that 95% of prescription drugs purchased via the Internet were falsified (Auf der sicheren Seite 2020).

On the other hand, within a 10-year period only 11 cases of falsified medicines were recorded to enter the supply chain, nine of which were due to parallel importing (Almuzaini et al. 2013). Whereas, according to overall global statistics, 30% of all purchases from the Internet are falsified as described in the introduction.

To counteract this rising issue, the FMD includes a regulation that implements the authentication logo for Internet pharmacies. This is the MHRA logo described in Chapter Four. This regulation is a step along the road to protect patients form falsified medicines.

Nevertheless, the successfulness of the regulation will be dependent on the patients being educated in how to distinguish fake pharmacies from real ones. Thus,

the relevance of the supply chain and the source of the medicines is important to be understood for patients and pharmacists, especially within hospitals.

3.8 Who will Benefit from the FMD?

Despite the issue of risk to public health, the FMD does not focus on the patients and offer them an opportunity to check the authenticity of the products they purchase, compared to the eTACT drug traceability system proposed by the European Directorate for the Quality of Medicines & Healthcare (EDQMH) (EDQM eTACT 2012).

This is a surprising concept as the purchasing of medicines on the Internet is increasingly popular, and a major source of falsified medicines (Auf der sicheren Seite 2020).

Creating patient/public awareness of the opportunity to seek out the authentication logo for Internet medicine purchasing may limit the risk to their health.

However, the effectiveness of this awareness has yet to be tested, compared to the discussion in Chapter Four which looked at online pharmacies that contained the various 'authentic' logos.

After the manufacturer applies the ATD and the UI to the medicine containers and uploads the valid codes to the European Medicines Verification System (EMVS), via the European Medicines Verification Organisation (EMVO), the EMVS will act as a hub that links all the national systems together allowing parallel trading of medicines to continue.

This data will be kept on the EMVO servers for several years, thus enabling recall of data if the need arises for inspection. It also allows for the respective authorities to keep track of reported incidents.

Consequently, the FMD does not restrict access to this data as other parties may be granted permission to access the data for pharmacovigilance reasons.

A negative of the FMD is that the system it is implemented on is dependent on a stable and good Internet connection. In most cases this should not influence services, however when considering rural and remote hospitals, major problems may occur, therefore requiring extra financial investment that has not been currently budgeted.

This is due to the technical prerequisites in hospital which is in accordance with the Association of Hospital Pharmacies. This means there is an insufficient amount of funding (Frontini et al. 2013).

Furthermore, hospital pharmacies mass purchase medicines either by direct contact with the manufactures or through qualified wholesalers. It is known that the scanning of individual packages is time consuming and the workforce will be removed from daily duties to repackage single packages.

In an ideal situation, with 2-3 second per scan using instruments such as the FT-NIR used in Chapter One, that can easily be used in a large pharmacy delivering 2.5million packages per year. The time taken to scan all the packages at the various hospitals would equate to at least one full time staff member.

Due to the implementation of the FMD across the EU the intention is that it would be cost neutral for pharmacies. On the contrary, making the operation realistic with focusing on the cost of additional workforce and technology has yet to be determined (EDQM eTACT 2012).

The FMD has not been assessed sufficiently in the case of its efficiency or its effectiveness. Furthermore, it has not been compared to other such initiatives e.g MEDICRIME Convention or the eTACT Healthcare (EDQM eTACT 2012) which justify the cost to be shared amongst the shareholders.

Additionally, it should be noted that by excluding all the OTCs – except those mentioned earlier – the FMD could be seen as ineffective from the patients/public perception.

3.9 Which Direction?

With regards to the time and work force resources required by the FMD and the Delegated Act 2016/161, a magnitude of pressure has been placed on the shoulders of the pharmacies. This is especially the case regarding hospital pharmacies, where an astronomical number of packages are supplied.

These packages are normally delivered to the wards directly rather than to the patients. As mentioned earlier the time taken to scan the individual packages would be time consuming and a challenge.

Ultimately it is important to ascertain if the FMD is beneficial and enhances the safety of patients. Concerning hospitals, this circumstance is highly questionable. As mentioned previously the hospital pharmacies usually purchase the medicines directly from the manufacturers or other reliable sources.

The purchase from the original manufacturer is placed at the same level as supply via the Internet. This suggests that the complexity of the supply chain has not been considered by the FMD, nor is the source of the medicine's purchase.

This is cause for concern as it shows that little effort has been placed in distinguishing the sources of purchase and into differentiating the risks.

Additionally, as proven many times over, no technical solution is without failures. Even if scanned packages emitted very low level false positive/negative output, the total number of incorrect scans would be considerable.

The efficiency of the distribution process in pharmacies would be hindered due to the time taken in identifying and clarifying the incidents into appropriate groups, both communally and in hospitals.

Despite purchasing from a reliable source, the safety of patients will not significantly increase. This is because purchasing from a reliable source does not mean that a falsified medicine cannot be purchased. To safeguard against this risk pharmacists are obliged to quality check the medicines they provide to patients.

Stronger controls and updates to the Good Procurement Practice (GPP) (WHO 2018) and Good Distribution Practices (WHO 2018) will further help to prevent counterfeit medicines from entering the market, especially when placed in every pharmacy, community and hospitals.

Fundamentally the FMD implements a bureaucratic system, which consumes a vast number of resources at every junction of the supply chain, especially in hospitals where there are staffing shortages.

Even though the probability of a falsified medicine is minimal the result could be fatal. With regard to hospitals and the FMD there are arguments for and against. On the one hand it may prevent further harm to the public, on the other it could be a hindrance to already tired and stretched staff members.

The FMD does not adequately protect patients who are purchasing from online sources where the risk of harm is greater. In addition, those patients are excluded from the verification process in spite of the technical possibilities that are available.

Some individuals believe that the FMD illustrates a bias towards the pharmaceutical industry with its massive influence, rather than considering the needs of the hospitals or the patients.

Unfortunately, hospitals must comply with the regulations that are set and are based on retail pharmacies. As explained earlier this notion is not feasible due to hospital pharmacies not supplying single packages like a community pharmacy does.

At both national and European levels, the consequences of the FMD need to be examined further, with regard to the distribution and ramifications of the regulation.

This is mainly for the hospital pharmacies as previously discussed in this chapter because some if not all of them have already secured and implemented an efficient supply chain by implementing GPP.

Codes that are specifically created for hospitals supplied directly from the manufacturer could be implemented to reduce the scanning process, and potentially the risk of codes being copied.

This is just one example of how the directive could be adapted for a more practical aspect, especially with regard to hospitals.

3.10 What's the EMA Role?

The European Medicine Agency (EMA) works with the EC and the EU Member States with regard to implementing the FMD. This cooperation includes the WHO International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT), the European Directorate for the Quality of Medicines and Healthcare (EDQMH).

The reason the EMA is important to this research is because the framework discussed further down is due to an incident being flagged by the safety features repository system. This is a requirement of Article 37 of Commission Delegated Regulation (EU) 2016/161, in which the medicine verification system is introduced.

If any (suspected) falsified medicines are believed to have been discovered, it is the duty of the marketing and/or the manufacturing authorisations holder to report to the EMA, due to the risk to public health these centrally authorised medicines pose.

In addition, the marketing authorisation holders of the centrally authorised medicines are to notify the country authorities where the falsified medicines are being distributed, whilst notifying the National Competent Authorities (NCA) of the Member States.

The EMA is responsible for the inter exchange of information relating to falsified medicines, this is in conjunction with the information being supplied to the NCA of the EU Member States. These Member States are often responsible in turn for investigating the supply chain and thus making decisions on the action taken within the markets.

The way the EMA can maintain control over the flow of information is through its reporting system, which consists of a falsified medicinal product template. This template is the framework that marketing, and manufacturing authorisation holders are required to use. This framework can notify the EMA of suspicious offer(s) that have been received and suspected/ confirmed falsified medicines.

Due to the success of the information exchange the EMA also cooperates closely with the international anti-counterfeiting trade agreements as well as other criminal-law instruments such as; Operation PANGEA, the Organisation for Economic Cooperation and development (OECD) and the Council of Europe's Medi-crime convention (OECD 2020).

During Operation PANGEA VII – that utilised the coordination of Interpol, customs and the health authorities in 2014, over 12,000 websites in the EU alone were disbanded and taken down. Over eight million counterfeit medicines were seized during this exploration.

It is thought that 97% of all websites that sell medicines online operate illegally, as stated by the European Alliance of Access to Safe Medicines (EAASM). despite the 12, 000 websites being shut down business is still going strong and increasing. Europe is thought to have over 30,000 'fake pharmacy websites' according to the EAASM. Alongside the discussion in Chapter Three it is proven that the online pharmacies need to be monitored closely and with strict regulations.

If a notified incident can cause serious risk to the public and/or animal health, the NCAs inform each other through a rapid alert system. The EMA in turn is responsible for the maintenance of the rapid alert list of contact points, which include the NCAs in EEA Member States, the international partner regulatory authorities, the European Commission and various other organisations.

3.11 Will Brexit Effect the FMD?

When the UK ultimately leaves the EU, there is a risk factor that the FMD will not be regulated to the best standard possible, due to the FMD being a European approach to deal with the rising global threat of falsified medicines.

This in turns paves the way for falsified medicines to be found in the supply chain due to the lack of enforcement and thus a risk to public health.

For the EU and the EEA Member States, the Delegated Regulation and the European Directive are binding. The future of the FMD in the UK will be dependent on the relationship that the UK maintains with the EU.

Even if the UK leaves the EU with less than amicable terms the UK is within its right to participate in the regulation of the FMD, as has been previously conducted by countries such as Norway, Iceland, Switzerland and Liechtenstein.

As the FMD is a globally occurring process, manufacturers and regulators alike are adopting pack serialisation as a way of countering falsified and counterfeit medicines.

Meaning that whilst the UK is still a major player in the supply chain of global medicines, and it retains a significant pharmaceutical manufacturing presence; the manufacturers and regulators may be reluctant to produce different packs for the UK medicines due to cost efficiency.

To remain a 'safe part of the medicine supply' it is believed that the UK would need to adopt the medicine pack serialisation, just as the rest of the EU complies. Currently this safety measure is the FMD.

At the present time, the MHRA and the National Competent Authorities for the UK have stated that they are 'continuing to implement the FMD in the UK'.

3.12 FMD Enforcement

The National Competent Authorities are responsible for the enforcement of the FMD in Member States. The MHRA and GPhC are responsible for the enforcement for manufacturers and wholesalers, and the enforcement for community pharmacies respectively, with the aid of the Pharmaceutical Society of Northern Ireland.

3.13 FMD Brief Summary

Overall, the FMD illustrates the progress we as a society have developed in the prevention of counterfeit/falsified medicines. It is a good basis for future adaptations of the directives that are used to regulate such discrepancies.

As demonstrated, there are both strength and limitations of the FMD that impede on its ability to be as efficient and thorough as it could be.

That being said the FMD and the other laws and regulations supporting the restriction place one medications and consumer good are only one part of an overall chain. The chain is only as strong as its weakest link.

The next step in the chain is the distributional hubs, the pharmacies. What are their defining features and how do they affect the supply of counterfeits to the greater public?

Chapter Four: Monitoring Online Pharmacies: Authentic?

Following on from the restrictions of medicine sales and use in Chapter Three, Chapter Four explores the differences between the sale of drugs online compared to physical shops.

An investigation into the products sold, the quantities sold and the regional differences across the UK, as well as the level of authentication and approval of the pharmacies.

4.1 Method

This chapter illustrates the combination of categorical and nominal data, which is the quantitative analysis of pharmacies that focus on the cataloguing of online, and physical pharmacies throughout the UK. The reason for analysing the pharmacies is because they are a crucial part in the distribution of medicines, not only in the UK, but worldwide.

This in turn causes a risk to public health through counterfeit medicines entering the supply chain. With the use of categorical and nominal data, regions can be clustered together, and a numerical value calculated as a result. This gives an added benefit from using a combined method (Bengtsson 2016).

All pharmacies in the UK, whether they are online distributions sites, or the physical brick and mortar counterparts needed to be catalogued for this research.

4.1.1 Pharmacy Data Collection

In regard to the physical pharmacies, the following stages occurred for the categorisation of each one; (1) each county was searched with the aid of the yellow pages and the phone book to identify pharmacies or medicine providers, (2) physical

pharmacies were name searched by county again with the use of the Internet – various search engines were used for example Google, Bing and Internet Explorer etc.

The search terms that were used included 'COUNTY (X) pharmacy' or 'pharmacies in COUNTY (X)'.

The counties that were categorised within the study of pharmacies included counties in England, Scotland, Wales and Northern Ireland. These counties are sub sectioned below and are illustrated further in figure 55.

Figure 55: Visual representation of the UK and the counties it comprises of. The counties are sperated in multiple different colours to aid the seperation between them.

ENGLISH COUNTIES

BEDFORDSHIRE, BERKSHIRE, BRISTOL, BUCKINGHAMSHIRE, CAMBRIDGESHIRE, CHESHIRE, CITY OF LONDON, CORNWALL, COUNTY DURHAM, CUMBRIA, DERBYSHIRE, DEVON, DORSET, EAST RIDING OF YORKSHIRE, EAST SUSSEX, ESSEX, GLOUCESTERSHIRE, GREATER LONDON, GREATER MANCHESTER, HAMPSHIRE, HEREFORDSHIRE, HERTFORDSHIRE, HUMBERSIDE, ISLE OF WIGHT, ISLES OF SCILLY, KENT,

LANCASHIRE, LEICESTERSHIRE, LINCOLNSHIRE, MERSEYSIDE, MIDDLESEX, NORFOLK, NORTH SOMERSET, NORTH YORKSHIRE, NORTHAMPTONSHIRE, NORTHUMBERLAND, NOTTINGHAMSHIRE, OXFORDSHIRE, RUTLAND, SHROPSHIRE, SOMERSET, SOUTH GLOUCESTERSHIRE, SOUTH YORKSHIRE, STAFFORDSHIRE, SUFFOLK, SURREY, TYNE & WEAR, WARWICKSHIRE, WEST MIDLANDS, WEST SUSSEX, WEST YORKSHIRE, WILTSHIRE, WORCESTERSHIRE

SCOTTISH COUNTIES

ABERDEENSHIRE, ANGUS, ARGYLL & BUTE, AYRSHIRE, BANFFSHIRE, BERWICKSHIRE, BORDERS, CAITHNESS, CLACKMANNANSHIRE, DUMFRIES & GALLOWAY, DUNBARTONSHIRE, EAST AYRSHIRE, EAST DUNBARTONSHIRE, EAST LOTHIAN, EAST RENFREWSHIRE, FIFE, HIGHLAND, INVERCLYDE, KINCARDINESHIRE, LANARKSHIRE, MIDLOTHIAN, MORAY, NORTH AYRSHIRE, NORTH LANARKSHIRE, ORKNEY, PERTH & KINROSS, RENFREWSHIRE, SHETLAND, SOUTH AYRSHIRE, SOUTH LANARKSHIRE, STIRLINGSHIRE, WEST DUNBARTONSHIRE, WEST LOTHIAN, WESTERN ISLES.

WELSH COUNTIES

BLAENAU GWENT, BRIDGEND, CAERPHILLY, CARDIFF, CARMARTHENSHIRE, CEREDIGION, CONWY, DENBIGHSHIRE, FLINTSHIRE, GWYNEDD, ISLE OF ANGLESEY, MERTHYR TYDFIL, MONMOUTHSHIRE, NEATH PORT TALBOT, NEWPORT, PEMBROKESHIRE, POWYS, RHONDDA CYNON TAFF, SWANSEA, TORFAEN, VALE OF GLAMORGAN, WREXHAM.

NORTHERN IRELAND COUNTIES

ANTRIM, ARMAGH, DOWN, FERMANAGH, LONDONDERRY, TYRONE.

The data that was collected from these searches was as follows: The Trading Name, The Owner Name, and the Address – Including the town, county and postcode. A total of 14,365 pharmacies were catalogued using the yellow pages and a further 200 from online searches for pharmacies in each county as seen in Figure 56 (Online Vs Brick).

For the online counterparts, multiple searches were conducted using various search engines on the Internet. The search terms that were used include 'online pharmacies', 'online distribution sites', 'distance selling pharmacies' and 'online

pharmacy'. All results were used if they followed the criteria of residing in the UK or making shipments to the UK.

The same data was collected for the online pharmacies/ distribution sites as was collected for the physical pharmacies. Alongside the data such as The Trading Name, The Owner Name, Address – Including the town, county and postcode, the URL was also included in the data. A total of 946 online pharmacies were identified and catalogued.

For both sets of searches online 200 pages of results were checked when the same results started to appear multiple times in quick succession it could be assumed that no more unique results would appear. The last 150 pages were also checked as they were the most likely to hold unauthorised sites, they were searched until repeats showed.

Once the data was found the information was input into an Excel document where further analysis could take place.

4.1.2 Pharmacy Data Collection: Authentication

Every pharmacy both online and brick alike have an authenticity to them that needs to be catalogued. To do that each pharmacy was checked against the MHRA and GPhC registry of authenticated and authorised dispatchers of medicine. This is explained further on in section 4.2. in Chapter Four as to how the pharmacies are authenticated.

4.1.3 Pharmacy Data Collection: Method & Characteristics

Due to the nature of this study the online pharmacies' multiple characteristics, along-side those mentioned above, were collected. The reason for so many variables being collected was that over the years there have been many classifications and authentication processes that are used with regard to online pharmacies.

The online pharmacy characteristics that were categorised and recorded were separated into several sections including:

1. The Pharmacies Brand
2. Are they physical on or the internet?
3. Geographical location
4. Do online pharmacies offer consultations
5. What are the medicines that are sold online?
6. Can you purchase prescription medicines online?
7. What reviews do the online pharmacies have?
8. Do they have a shipping cost and what range of prices are there for a product?
9. Do the online sites have a sales promotion advertised?
10. Are the websites maintained?
11. Is a privacy disclaimer available?
12. What contact details are asked for?
13. Are the pharmacies registered?

When an online pharmacy was found all of the previous points were searched for over a nine-month period.

The analysis of part seven and part nine recorded data was converted into averages for comparison. For example, if a pharmacy had a 3* review five out of 10 times checked and had a 6* for two visits and 1* for three then the overall rating for that pharmacy would be the average rating of 3*s.

For part nine if discounted items showed more often across the website compared to flash sales, then discounted items was used for primary analysis.

The other sections if they showed to be present even once then they were categorised for that pharmacy. Such as if the pharmacy shows a privacy disclaimer or if a consultant was available.

The website maintenance was looked into both the website as they sometimes have a time stamp of last update or identified in the website code itself as a time stamp. This time and date were recorded each visit and a correlation was able to be determined of how frequent the website was updated.

4.2 Authentication

With regard to online pharmacies, there are two main regulatory bodies in the UK that govern them; the MHRA and the GPhC. These organisations have the ability to authenticate pharmacies both online and physical.

Section 4.2.12 Quality Certificate highlights the mechanisms used for authorisation and provides evidence of how the public can verify authorised pharmacies.

Furthermore, the creation, role or governance of each organisation is important when understanding how each of the organisations approve or deny authentication of a Pharmacy.

4.3 Registry

Both the MHRA and the GPhC have a record of authentic certified pharmacies, these are kept in a directory that is open to the public, this is explained further on in the chapter under 'Quality certificate'. Online pharmacies and Brick & Mortar pharmacies are both required to register with either authority, the directory is updated every year, since the data was collected in March 2019, 35 online and brick & Mortar pharmacies have had their licences revoked and a further 20 licences have been suspended. This action took place on the 11th July 2019.

Alongside the directory of pharmacies, the MHRA also has a register of the manufacturers that are licenced to sell certain active substances. Each of the licences are due to the '*Written confirmation for active substances exported to the European Union (EU) for medicinal products for human use, in accordance with Article 46b(2)(b) of Directive 2001/83/EC'*.

The 2001/83/EC is explained further in Chapter Three. The register is updated on a monthly basis and the approval is held for three years before another inspection takes place.

4.3.1 What is the MHRA?

The Medicines Control Agency (MCA) gained control of the General Practice Research Database (GPRD) in 1999, this was then combined with the Medical Device Agency (MDA) in 2003 to create the MHRA.

In 2012 the Clinical Practice Research Datalink (CPRD) was and expansion of the GPRD. Later in 2013 the MHRA merged with the National Institute for Biological Standards (NIBSC), together they are the MHRA brand that is known today.

4.3.2 What is the MHRAs Role?

The MHRA takes on the role of supporting multiple governing committees, such as the British Pharmacopoeia Commission and the Commission on Human Medicine (CHM); previously referred to as the Committee on the Safety of Medicines (CSM).

Operating as part of the Europeans System of Approval, the MHRA along with other organisations process and verify pharmaceutical applications for industry members.

4.3.3 What is the GPhC?

The GPhC is responsible for the regulation of those on the pharmacy premises including the pharmacists and the pharmacy technicians, it is also the body responsible for the independent regulation of the pharmacy profession within the UK.

It was created in 2010 when the regulatory functions of the pharmacy profession could be separated (GPhC 2020).

4.3.4 What is the GPhC Role?

The GPhC aim to maintain the level of standard in the industry. Therefore, follow principal functions, which are set out in The Pharmacy Order 2010.

- To establish and maintain a register of pharmacists, pharmacy technicians and premises at which a retail pharmacy business is;

- To set and promote standards for the safe and effective practice of pharmacy at registered pharmacies;
- To set standards to which registrants must demonstrate that their fitness to practise is not impaired;
- To promote the safe and effective practice of pharmacy by registrants;
- To set standards and requirements in respect of the education, training, acquisition of experience and continuing professional development that it is necessary for pharmacists and pharmacy technicians to achieve to be entered in the register or to receive an annotation in the register and to maintain competence; and
- To ensure the continued fitness to practise of registrants.

The implementation of this order ensures that the GPhC are setting suitable measures, but also that members are operating to the guidelines set.

4.4 Pharmacy Analysis Results

4.4.1 Online Vs Brick & Mortar

A comparison of the numbers of online pharmacies and physical pharmacies (figure 56) demonstrates the considerable difference. There is a ratio of 15:1 of physical to online.

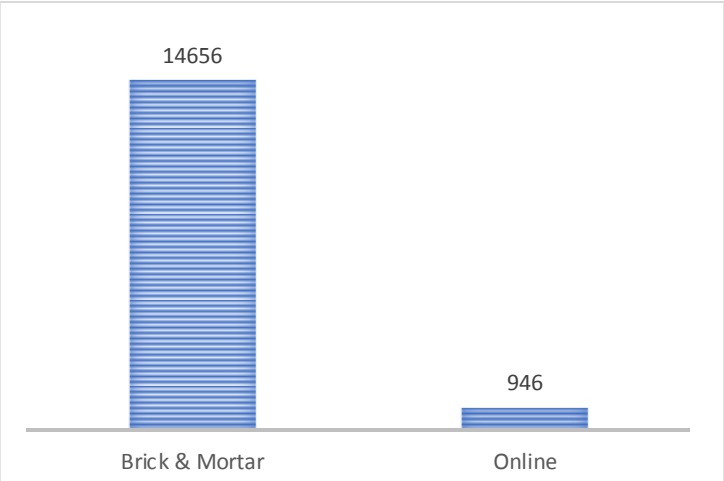


Figure 56: The visual comparison between online pharmacies and the brick and mortar versions.

Despite the volume of physical branches of particular companies (pharmacies), the impact of the online distribution is considerably more extensive.

For example to name the top three, Lloyds Pharmacy has 1598 branches across the UK and two online channels for distribution, Well (Best Way National Chemist Limited) has 760 branches and has only one online channel and Rowlands Pharmacy has 519 branches and two channels.

Now dispite having a limited number of online channels these companies can supply the whole country. This means that the number of distributional channels lessens for the counterfits to pass through, they only have to pass through tens rather than hundreds and thousands of branches.

This overall suggests that counterfeit medicines will become more of a health problem to the greater public as there will less checks, less correspondance with pharmacist and a far greater reach for sales.

It is known that counterfeit medicines can be bought from both types of pharmacies, however it is more difficult for counterfeits to be in the supply chain that are purchased from a brick and mortar pharmacy. This is one of the reasons that online pharmacies should be closely monitored and checked regularly as well as being one of the key points in this research.

As discussed in section 4.2.2, the location of the pharamcies may influence the number of branches, nevertheless online pharmacies have a distribution that spans the UK.

If the public influence what items are avaliable to purchase online then it stands to reason that they are also responsible for the safe purchase of such items.

4.4.2 Geographical Location

Figure 57: A visual representation of the regions across the UK that have be created - via collection of other counties - for this research.

Albeit online pharmacies have a presence on the Internet, for a company to be legally allowed to distribute any type of product it needs to be licenced under a physical address.

These addresses are recorded and are available to the public. These addresses were identified and documented, then categorised by region. The regions are depicted in figure 57.

The quantities of both online pharmacies and the brick-and-mortar versions were catalogued for each of the UK regions as seen in figure 58. It is important to note that for this figure the brick and mortar quantity is divided by 10, the reason being that a direct visual comparison can be made.

Alongside the various versions of the pharmacies the populace at each region was also calculated, the population was divided by 20,000. This is to illustrate that the

population does not account for how the pharmacies are spread out amongst the UK regions.

For instance, the West Midlands is in the top 5 for the population count, however it is in the bottom 5 for the quantity of pharmacies both physical and online versions.

The same can be said for the North West where the population is considerably more than the quantity of the pharmacies found with the region. Henceforth it can be assumed that even with a populace being of a sizeable quantity less pharmacies can operate and distribute to those customers.

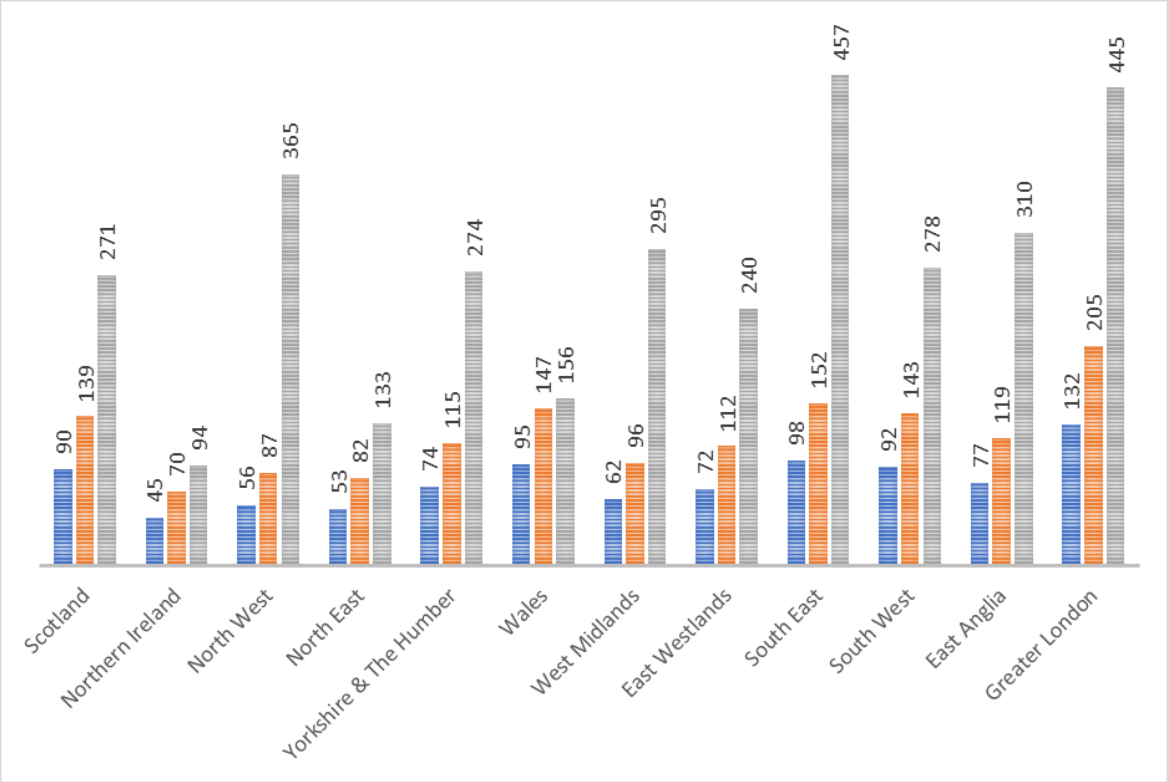


Figure 58: Online pharmacies (-) = 1:1 ratio, Brick and Mortar versions (-) = 1:10 ratio and the populace (-) = 1: 20000 ratio. The figures stated are in a calculated ratio for each reagion to aid in visual representation and so that all numerical data can be categorised on a clear compact scale. (Office for National Statistics (UK) 2019) at each region of the UK.

4.4.3 Consultation

When entering a physical brick and mortar pharmacy you can talk to a physician such as a doctor or at the very least talk to a pharmacist. When looking closely at the

online pharmacies it is noticeable that talking to a professional is not always an available option, as is the case in almost 50% of them.

26% of online pharmacies have a doctor/physician available to chat with and 24% of online pharmacies a patient has access to a pharmacist.

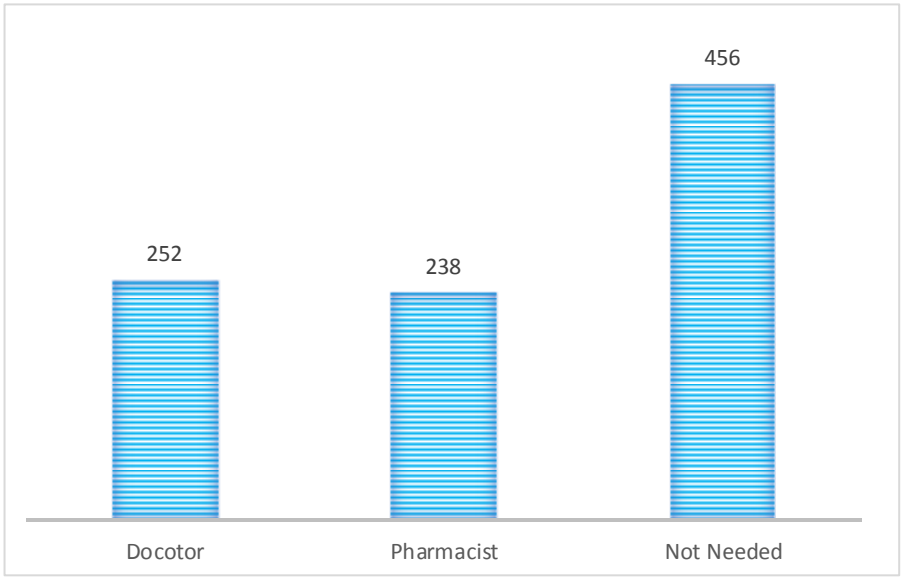


Figure 59: The availability of a professional consultatant in respect to the online pharmacy gthey are working with and which type of professional is on hand.

As shown in figure 59 there is a significant difference in the number of pharmacies online that allow for a consultation and those that deem it not a necessity. When comparing those numbers, it illustrates that the idea of consultation regarding medicines is a dwindling practise for the future.

If the online channels do not offer this basic curtesy, can they be trusted to monitor the medicines that are to be purchase and distributed. The public use the available consultation service if they are unsure and hesitant about using the medicines offered to aid their treatment, and to also talk through their concerns.

On the other hand if a patient can talk to a consultant before purchasing any type of medicine, is it then true that they can in turn trust that the consultant is authorised when speaking to them online rather than in a physical store.

A simple way to check the authenticity of a consultant or to find if they are licenced is to check against the General Medicine Council (GMC) register. The medical

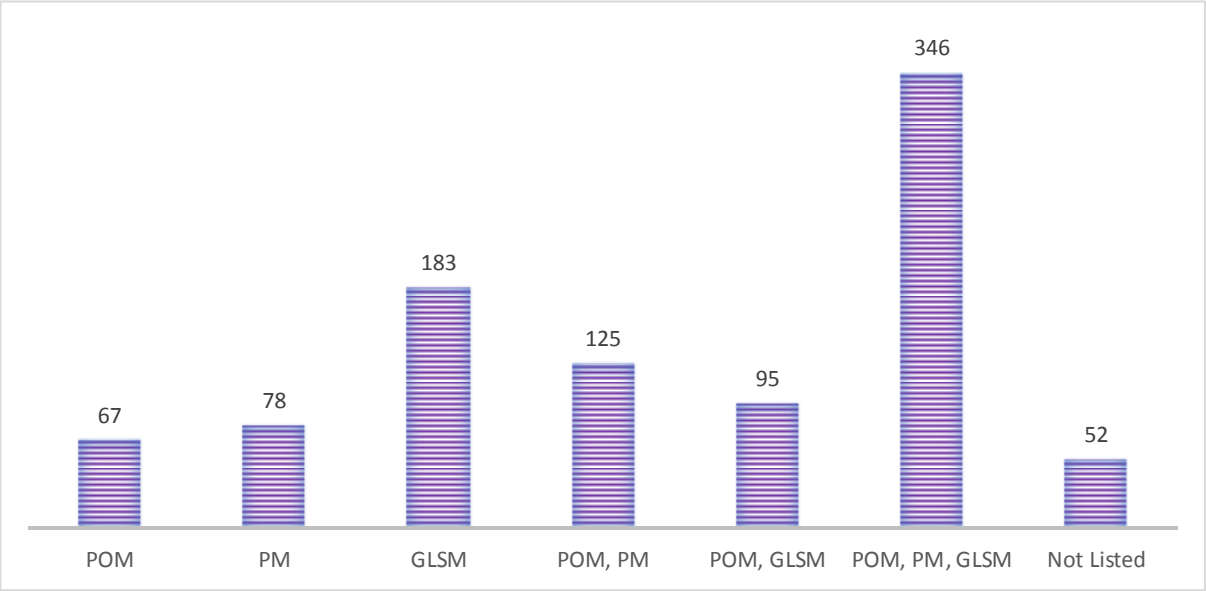
register is an online list of the doctors throughout the UK, it also shows the types of registration the doctor holds, what their individual training is and a variety of other information.

The medical register also offers details such as whether the consultant is a GP or a specialist consultant, the date they registered and whether they have a fitness to practise history since 20 October 2005 (GPhC 2019).

These registers along with the ability to talk to a professional aids the public's trust in online pharmacies and thus will enable counterfeits to easily reach the consumer if they are not monitored and maintained. By having a registered consultant, the pharmacies are more likely to be a trustworthy source but also the company may feel a responsibility to the patients they aid.

4.4.4 Medicines Sold

There are three main categories of medicines that can be purchased from the various pharmacies that were analysed. They are as follows; prescription only medicines (POM) such as ciprofloxacin, penicillin and Vicodin, general sales list medicines (GSLM) such as paracetamol and ibuprofen and lastly pharmacy medicines (PM) such as sleep



aids and domperidone (a high dosage of ibuprofen).

Figure 60: The comparison of medicines sold via online pharmacies. Prescription on Medicines (POM), pharmacy medicines (PM) and general sales list medicines (GSLM).

As can be seen in figure 60, the most likely combination of medicines to be found on an online pharmacy is that of POM, PM and GLSM. However, the most common medicine to be sold on any of the websites is GSLM, which was the hypothesis at the beginning of the research due to GLSM being sold nationwide in supermarkets.

It should also be noted that there were some websites that did not disclose what they were licenced to sell, see quality certificate later in this chapter for more information on licencing.

By having such a wide range of medicines available for purchase that can also be delivered to your door gives rise to a profitable market that is a cause for concern. With such a variety of medicines having the ability to be purchased online rather than in a physical store means that ages aren't checked for the purchaser if they were to be under the age of 16.

More than one of a type of medicine can be purchased in one transaction which is normally limited to two if purchased in a supermarket or physical store. This means that the public can easily get their hands on medicines that should be regulated and that could have dire consequences to those who need the counter measure in place.

4.4.5 Are there still restrictions on prescriptions?

Most if not, everyone has heard of a prescription, but what is a prescription? A prescription (Px) is an implementation tool of a health-care program used by a physician or other qualified health care practitioners, within the form of instructions that govern the plan of care for the individual patient (Jameson et al. 2016).

The term prescription often refers to a written authorisation of a health care provider for a patient to have the ability to purchase a prescription drug from a pharmacist.

A prescription must include:

- Name, address and telephone number of the prescriber,
- The date,
- The generic name of the drug, the strength,
- The dosage form, the total amount,
- The label, instructions and the warnings,
- Name, address and age of the patient,
- Signature or the initials of prescriber.

Within the UK the Medicines Act 1968 as well as the Prescription Only Medicines (Human Use) Order 1997 contain within them the regulations and guidelines that cover the supply of sales, the use, the prescribing, and production of the medicines. As stated previously there are three types of medicines, POM, PM and GLSM.

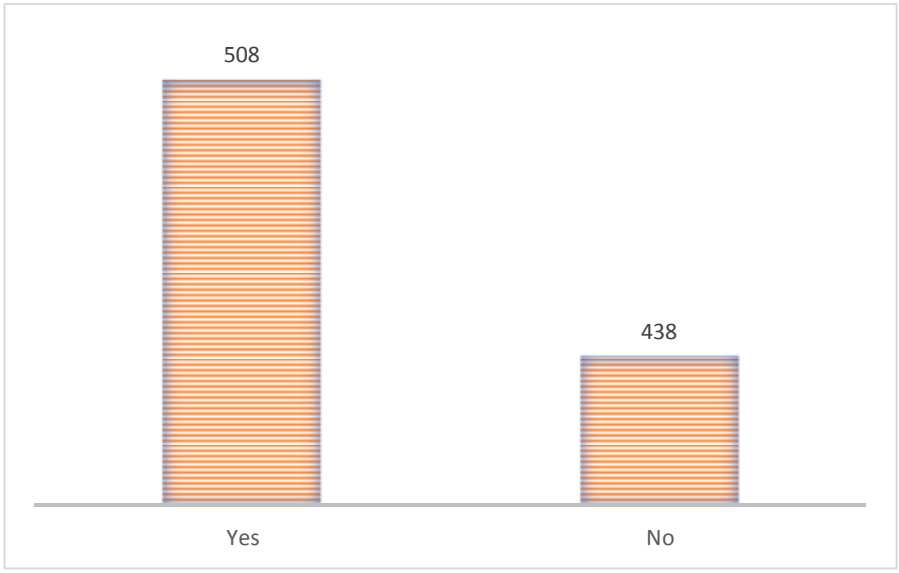


Figure 61: The comparison between the online pharmacies that require a prescription for purchasing a POM and those that do not. For every 1 pharmacy that does not require a prescription to sell a POM medcine 1.15 pharmacies that do.

54% of the sites that medicines can be purchased over the Internet need a prescription, whereas 46% does not require a prescription for the medicines to be purchased by the patient. However, as described by the Medicines Act 1968 the possession of a POM without a prescription is legal unless it is covered by the Misuse of Drugs Act 1971 (Mutsatsa 2016).

One of the reasons for having a restriction on POM – that it should only be sold in the presence of a signed prescription- maintains the public safety as it makes it more difficult to use if the patient is self-prescribing and may not need the medicine purchased.

The mindset that is apparent within society that purchasing for convenience rather than seeking out professional opinion, may lead to more dangerous outcomes. Not to say when purchasing GSLM that an individual would need a professional's opinion to purchase paracetamol or ibuprofen for their cold.

However, when the POM includes antibiotics or strong painkillers the risks far out way the benefits if used in treatment that the medicines are not intended to be used for.

To allow a POM to be purchased without a prescription endangers the consumer as there is not a safety check in place that would otherwise be. Limited if no instructions available, the dosage may be incorrect which could be fatal in some cases.

By not having a prescription needed those medicines maybe more likely to be counterfeit as the pharmacy themselves may not be strictly monitored and thus their safety check regarding the medicines may not be up to par. If that is the case, then these pharmacies are aiding in the reach and destruction caused by counterfeit medicines.

As of April 16th, 2019, the new guidelines set out by the GPhC and the MHRA state that patients will no longer be able to select a prescription only medicine without having an 'appropriate consultation' with the prescriber the online pharmacies state it is in collaboration with.

Online pharmacies will now need to take a stricter policy when they carry out identity checks on the patient obtaining the medicines and thus identify the inappropriate requests such as placing multiple orders to the same address of delivery.

Alongside this the pharmacy staff must be able to verify the patient's identity – following the Nation Health Service (NHS) digital identity verification and authentication standard – to obtain information to check that the supply of medicine is safe for use, the information can include; age, gender, other medications that may be taken.

On top of the ID checks, online pharmacies will also need reassurance that the prescriber they are in collaboration with 'will proactively share all relevant information about the prescription' with the various and relevant healthcare professionals – such as the patients GP – after the medicines are prescribed.

The online pharmacies that are found to not comply with the guidelines set out could face 'enforcement action'.

4.4.6 Public Influence

When monitoring online channels, it becomes clear that the public has a major influence on what can be sold and what will make profit. This suggests that certain criteria need to be met for an individual to be happy to hand over money and purchase the product.

These factors help determine if an individual is confident in the purchase and if that is the case, then more safety checks will need to implemented in the future to guard against counterfeit medicines from entering the supply chain.

When categorising the data that was collected for monitoring online pharmacies the groups that stood out for public influence include but not limited to; customer reviews, the price of shipping and delivery and if there was a sale.

4.4.7 Reviews

As with most purchase sites on the Internet, reviews can often be left for future customers to see and form an opinion. The reviews can consist of delivery standards, quality of shipping, price of the product, and other various comments.

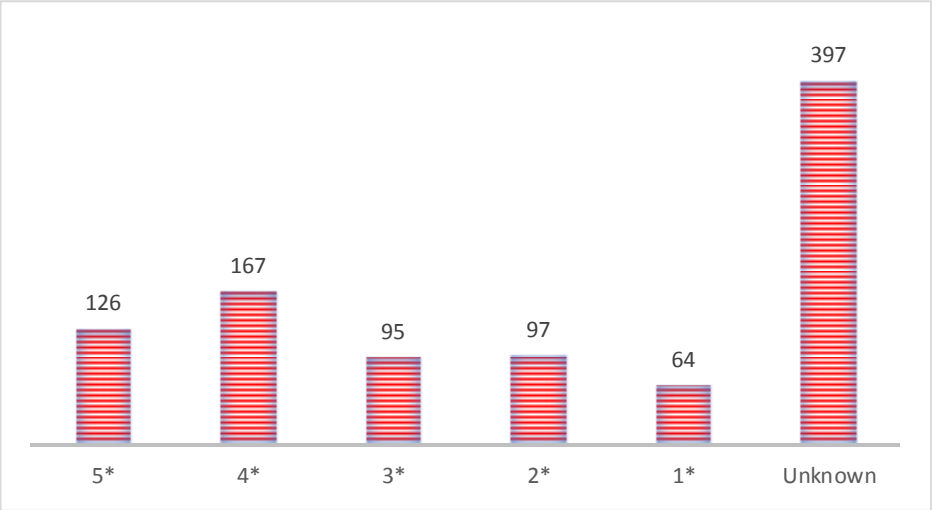


Figure 62: Customer ratings for particular online pharmacies that have been reviewed.

As seen in figure 62, the overall rating of a customer's review is almost even across the board, being evenly distributed due to the stars rating. As can be seen, more than 30% of the online pharmacies do not have access for customers to give a review.

Just as with any market site online the reviews have an impact on whether a person will trust them and purchase a product from them. Typically, the lower the review the lower sales made. These sites will normally try other tactics to gain support such as sales or reduced shipping and wait times. These factors are reviewed later in more detail.

However, what was interesting when looking at the sites was the percentage of online pharmacies that do not have the availability for review. Even those some sites have 1* reviews they still showed trustworthiness as they posted those reviews.

Whereas not giving the ability to rate a service or give and opinion for others to see illustrates distrust and could cause a problem in the future if more sites take this route.

If a site the way some reviews is based on difference experiences, did they find what they were looking for, could they purchase the medicine hassle free, could it be shipped to them and so forth.

4.4.8 Price & Shipping

When a customer is in the process of purchasing an item one of the staples of the site or item that seals the deal in the purchase is the price of the item and the shipping. The prices of the items that were searched for such as ciprofloxacin, ibuprofen and amoxicillin were relatively similar.

Therefore, the price could not be used as a deciding factor in this scenario, however the price ranged from £3.50 to £5 without shipping involved for the antibiotics the GSLMs such as ibuprofen ranged from £0.99 to £1.50 without shipping included. So, one of the only factors comparable to those prices available is the price of a prescription from the pharmacy which is close to £9.00 per ingredient.

Whether the online pharmacy has shipping, be it free or priced and collection was also documented.

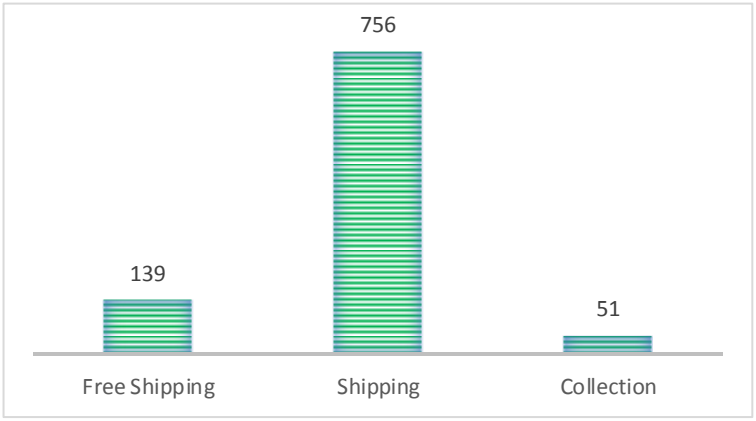


Figure 63: The types of delivery available to customers when purchasing medicines online.

95% of the online pharmacies have a type of shipping, 80% have a priced shipping and 5% ask for collection.

The pharmacies that offered free shipping were typically the big recognisable companies such as Lloyds Pharmacy, where as those who required a paid shipping fee were the less recognised pharmacies.

This suggests that the shipping fee is one of the ways that they claim back the loss in product costs. It should be noted that some of the pharmacies that has a shipping

cost attached would also promote free shipping as a sales tactic – illustrated in the next section.

By having a relatively low shipping cost or no cost at all promotes a sale for that pharmacy. The reason being that we as a society will typically purchase the most for the least amount of money.

So, if the shipping cost is saying £2 compared to £4 and the products were a similar price +/- £0.50 then the pharmacy with the £2 shipping cost would have their products purchased.

Also, another reason that shipping cost comes into effect is that the idea of shipping or delivery to your door is convenient and you don't have to remember to go to the store and pick up your medicines. This makes the process more comfortable and retainable in the future.

When an individual uses an online pharmacy the shipping cost is sometimes a deterrent for a purchase. So, for the pharmacy to make profit they may need to raise the cost of the product and reduce the shipping cost if the shipping cost is what is losing the customers. This is where the sales tactics come in to play.

4.4.9 Sales Promotions

For any business to be successful they need to be able to sell, this can be in the form of merchandise, time, assets even advice. For sales to continue the market needs to be investigated and the top tip for sales to continue is to have promotions that gain the interest of the buyer/client/customer.

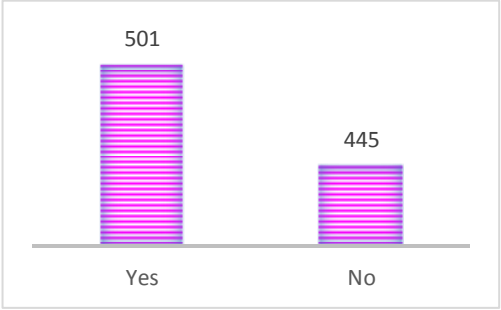


Figure 64: Comparison for if an Online Pharmacy use sales promotion techniques to promote custom.

53% of online pharmacies use some type of promotion. The 10 most popular types of sales are as follows: Discounted Products, Free Shipping/ Free Returns, Flash Sale – limited time offers, Buy More, Save More, Products Giveaways/ Branded Gifts, Loyalty Points, Coupon Giveaways, Competitions, Price Match Promises and Holiday Promotions.

The top four promotions that could be seen in the online pharmacies that used a method of sales when the data was collected are illustrated in figure 65.

62% of the pharmacies on average use discounted prices to gain custom, whereas 6% entice customers with free or discounted shipping, 8% with flash sale (hurry now the offer ends in 24hrs – for example) and 4% with a buy more, save more mind set, such as buy 3 for 2.

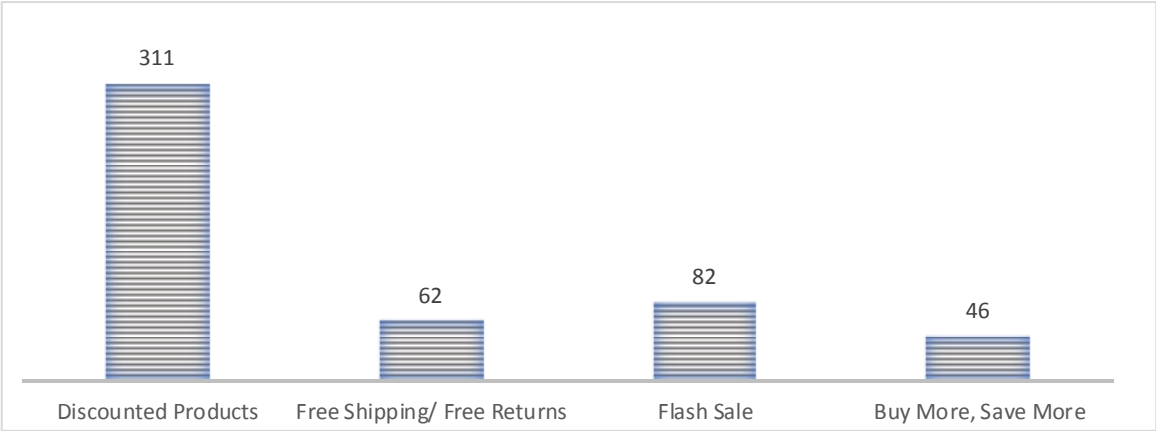


Figure 65: An illustration of which type of sales promotions are used by online pharmacies.

By having a sales tactic, the pharmacy can promote the sale of their merchandise which is the name of game at the end of the day. For society money is a very sensitive subject, which we as a whole typically hold close to our chest, but if we can save money for essentials then purchases are more likely to occur.

When offering discounts, the mark up price may never actually be the price that the medicine has sold for in the past. What this means is that the illustrated price for

say the 50% off at £3.50 and the RRP is a crossed out £7.00, the medicines price may never reach £7.00.

In certain studies, this is shown to have an effect on the consumer as they think they are having a bargain when in actual fact they would be spending a similar amount to somewhere else that didn't have the offer on.

It is this practise that sometimes leads to distrust in the markets as the majority of compares in any type industry around the world use this as a sales pitch to gain more customers, but they are clearly being dishonest.

When items are on offer and in the category of being in a flash sale the buyer feels panic that they may not get the best deal or they may lose out on purchasing the product they need.

This causes a rush of sales that may not be just. The way a seller can promote this type of sale is with phrases such as 'hurry now while stocks last' or 'offer ends in 13hours' sometimes 'last one left', these phrases reaffirm the point that buyer needs to purchase soon or lose out.

4.4.10 Pharmacy Integrity & Discretion

On the other side of public influence is the pharmacies duty of care, respect and integrity for the customers and the products they sell. The categories that illustrate these points are the website maintenance, privacy disclaimer for the public and how the contact details are held and processed.

These details demonstrate if a pharmacy has taken care with what is given to them and if it can maintain its transparency. All these factors impact whether a site or pharmacy is deemed to be trustworthy.

4.4.11 Website Maintenance

Whenever a website is created it leaves a digital fingerprint that when accessed you can see how often the site is maintained and updated. However, on some sites it is published in the print how often the site is maintained or updated. For the majority (27%) of sites it is not possible to determine the frequency of maintenance that the site undergoes

This shows that with regular maintenance, the online pharmacies take care in their reputation and how they respect their clients with continuous updates.

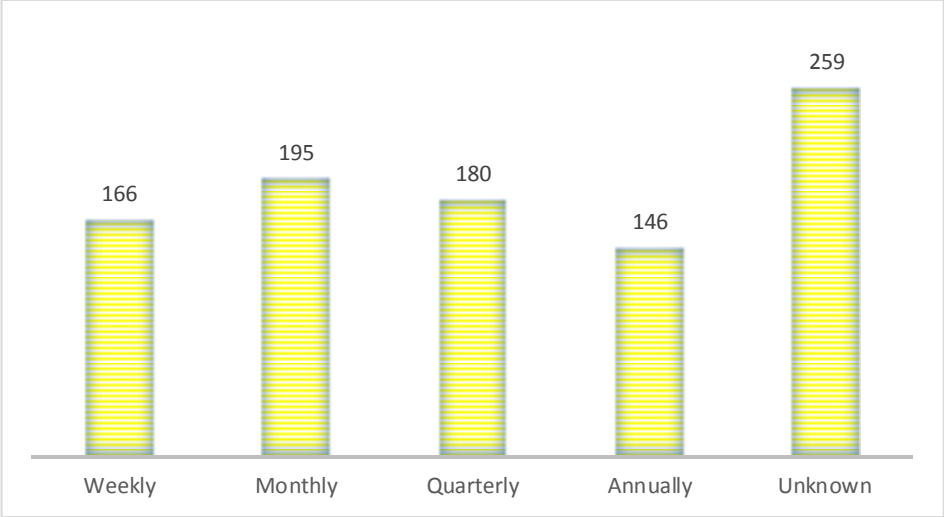


Figure 66: The frequency in which an online pharmacy site is maintained.

As shown in figure 66 the most common update partaken was monthly this was demonstrated in 21% of the online pharmacies checked. The others showed a normal distribution where an annual update (15%) occurred less often than a weekly update (18%) and quarterly updates which occurred 19% of the time.

When any website is updated regularly and monitored it can be assumed that it is more trustworthy as the facts, data and settings are constant. Having a trustworthy website is a dependable factor when purchasing products or gathering information on the internet.

For example, if you purchased a product on a 25% off offer but the price increased on receipt and you questioned it and the seller in return replied that the offer

ended last week and that product is not eligible for the deal so you need to pay full retail price, that annoyance and distrust grows.

Overall, it is not good for business, so up to date websites and product checks are important for a business to stay in touch with the public to gain influence and profit.

4.4.12 Privacy & Disclaimer

A privacy policy or disclaimer is a legal document (in privacy law) or a statement that discloses some if not all the ways a party gains, uses, discloses or manages a customer's/ client's data. Its duty is to fulfil a legal requirement that protects the client's or customer's privacy.

The personal information can be any means that can help to identify an individual, this includes but is not limited to (Donaldson 1994): Client / Customer Name, Address, Date of Birth, Marital Status, Contact Information, ID Issues, Expiry Date, Financial Records, Credit Information, Medicinal History, Travel Information and lastly the intentions to acquire goods and services.

With regard to a business a privacy disclaimer is often used as a statement that is a declaration of a party's policy on how it collects, stores, and releases the personal information that it collects.

The declaration informs the client or the customer what specific information is collected, and once it is collected whether it is shared amongst partners, sold to other firms or enterprises or whether it is kept confidential (Laurent & Levallois-Barth 2015).

Depending upon the requirements across geographical boundaries and legal jurisdictions, the contents of the privacy policy may change. Most countries have their own legislations and guidelines as to what information is collected, who is covered and what it can be used for. The data protection laws in Europe in general cover the private and public sector (Laurent & Levallois-Barth 2015).

Thus, the right to privacy is a highly developed area in European law, as all member states of the EU are also known to be the signatories of the European convention on human Rights (ECHR).

The Organisation for Economic Co-operation and Development (OECD) issued its 'Recommendations of the Council Concerning Guidelines Governing the Protection of Privacy and Trans-Border Flows of Personal Data' to create a comprehensive data protection system throughout Europe (OECD 2020) The OECD's seven principles that govern the protection of personal data are as follows (OECD 2020):

1. *Notice—data subjects should be given notice when their data is being collected;*

2. *Purpose—data should only be used for the purpose stated and not for any other purposes;*

3. *Consent—data should not be disclosed without the data subject's consent;*

4. *Security—collected data should be kept secure from any potential abuses;*

5. *Disclosure—data subjects should be informed as to who is collecting their data;*

6. *Access—data subjects should be allowed to access their data and make corrections to any inaccurate data; and*

7. *Accountability—data subjects should have a method available to them to hold data collectors accountable for not following the above principles.*

The Data Protection Directive (DPD) - more commonly known as directive 95/46/EC - that was created in 1995, was superseded by the General Data Protection Directive (GDPR) 2016/769/EC on the 25th May 2018 more commonly known as the Data Protection Act 2018, which harmonises the privacy rules across all the EU member states.

The GDPR not only imposes the seven principles but is the reason for the implementation of more stringent rules on the collection of the client's personal information.

The EU data is required for the purposes of privacy policies to be concise, clearly worded and the transparent disclosure of any collect, storage, processing or the transfer of the personal information that could lead to the identification of an individual.

The controllers of the data must also be able to erase the data under certain circumstances, and the data to be made portable in a common format follows.

Unfortunately, not every site follows the regulations set by the GDPR, 16% of sites do not have the disclaimer, however 84% of sites have a privacy disclaimer, and state what is being collected, how it will be used and so forth.

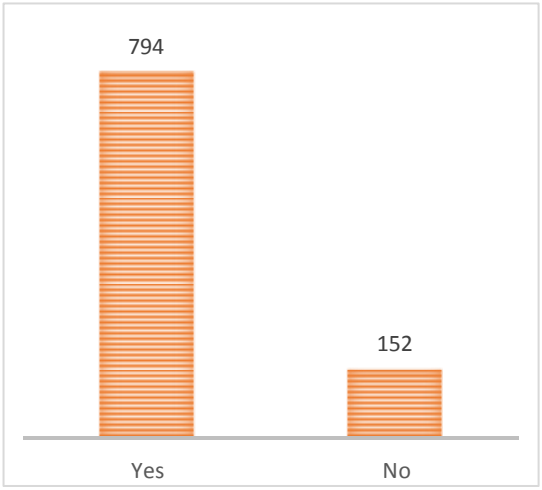


Figure 67: The representation of whether an online pharmacy has a privacy disclaimer 1in 6 pharmacies has a privacy disclaimer avalaible for the public to read..

Similar to having a website maintained, by having a privacy disclaimer for customers to read and question illustrates the transparency of the pharmacy's intent.

This gains the customers trust which in turn gains the pharmacies profit for the inevitable sales that will be conducted. Any customer has the right to know how their data is collected, how it is used, why it is being used and also where its being stored.

When a pharmacy refused to place a simple statement/disclaimer to acknowledge this basic right, then future issues will occur for those pharmacies as they are not cohering to the GDPR regulations set out and can be prosecuted. Not having a disclaimer is a definitely disadvantage for those pharmacies.

If those pharmacies aren't following the GDPR regulation, what other regulations aren't they following and could they be a threat to the public health?

All regulations, policies, guidelines are in place to prevent if not stop error and mistakes form occurring that can be a risk to society and have an impact on an individual.

One of those risks are counterfeit medicines, if the GDPR is not followed can we safely assume that the counterfeits are monitored and routinely checked to protect the public?

4.4.13 Contact Details

Whenever there is a purchase over the web, various details are taken to procure payment. These details often have an overall recurring theme, such as the following: Title, Forename, Surname, Email, Password – often used when registration takes place, Country, Phone Number (+44), Postcode, Address and the County.

However, what is often not recorded is whether privacy is maintained when payment details are taken. This includes if the customer can use PayPal or other payment methods that can give security to the customer with bank and card details.

Card details that are often required include, name of the customer, the card number, the expiry date on the card and lastly the card verification code (CVC).

More than 50% of online pharmacies recorded require the card details of the customer and do not offer payment security or protection.

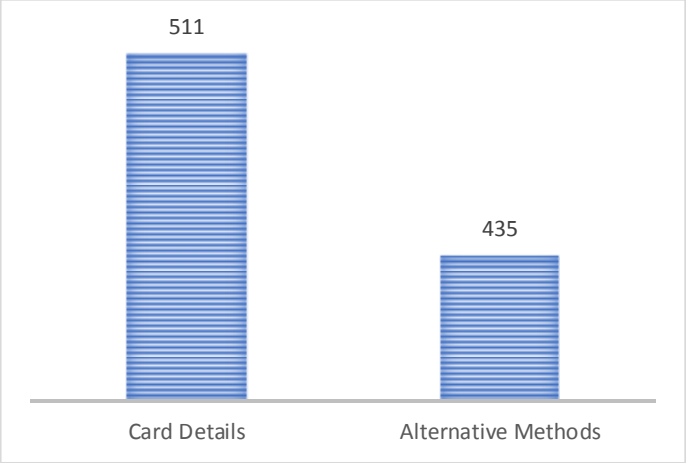


Figure 68: The comparison of payment methods available to the customers when purchasing medicines on the Internet. For every pharmacy that has alternative payment method card details can also be used.

A persons contact details need to be securely handled otherwise they can be used in cases of fraudulent activity. To not enable the user to pay with an alternative method is a risk to both the buyer and seller.

The buyer has a risk that their details could be used without their consent if the details were to be stored for a later date, also when the details are collected there is nothing stopping the company from using the details in an automatic purchase process if it's hidden in the fine print or programming.

The seller has a risk as some customers may be put off purchasing any products as the payment method, they use is not available, also they may be concerned for identity fraud.

4.4.14 Quality Certificate

As explained previously for an online pharmacy to be authentic it must be approved either by the GPhC or the MHRA. The MHRA initiated a compulsory EU common logo, also known as the 'Distance Selling Logo' in July 2015.

If there is intent to supply or sell any GSLM, POM or PMs on the Internet the MHRA logo - as shown in figure 69 must be applied and displayed on every page of the website. The Distance Selling Logo must also be shown on the websites of non-pharmacy retailers of GSLMs.

For the MHRA to accept a distance selling pharmacy or online pharmacy and place it on the register, the pharmacy needs to meet all the conditions set out in the law before it can be registered. Another option for a pharmacy is to have the voluntary GPhC logo - as shown in figure 68 on the website, this logo links directly to the GPhC registry.

Distance Selling Logo Voluntary GPhC Internet Logo

Figure 69: The MHRA Distance Selling Logo and the GPhC Voluntary Internet Logo

The pharmacy should only be given the GPhC Internet logo after it has applied and been given the MHRA Distance Selling Logo. However, that does not appear to be the case where 9% of online pharmacies only hold the GPhC voluntary logo.

The GPhC logo can only be used by pharmacies registered under that scheme. No third party is permitted to use that logo. However, 1% of the pharmacies are neither authorised by the GPhC nor the MHRA. Most sites (55%) are authorised by both the MHRA and the GPhC. General Pharmaceutical Council, 2020 & MHRA, 2020).

By following the MHRA and GPhC registry, pharmacies illustrate that they are licenced and regulated by the correct authorities. This means that they are trusted to uphold the strict guidelines set in place for the pharmacies, regarding what is sold, how they are sold and how they are tested and regulated.

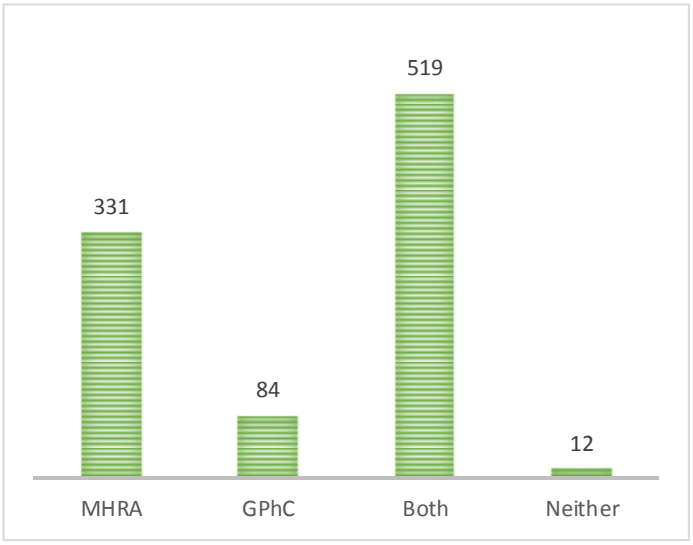


Figure 70: The comparison between what each of the online pharmacies has as a quality certificate, if they have one readlily avaliable to check and how many onnline pharmacies do not demonstrate that they are registered pharmacys and legally allowed to sell medcines.

By having this check in place helps the public to trust the pharmacies and thus be confident in the purchased products themselves. Those pharmacies that are not licenced or registered are essentially an endangerment to the public's health as they do not hold any regard for the laws and regulations set out for them.

This in turn enables the market for counterfeits to have a footing in the industry, which also causes concern as the more they are enabled to be used for profit the more likely they will be.

4.5 Online Pharmacy Summary

Society as a whole would be more likely to make purchases from a place that they have had a positive experience such as saving money, or a good review and had a show of authorisation.

Having a consultant available for advice and consultations improved the productivity of the pharmacy and in the opinion of the public. If a pharmacy is to sell POM or other medicines that should often be confirmed with via a professional then a consultant should be available. By having a consultant means that the safety and concerns of the public are met.

Furthermore, POM should only be available if a prescription is signed and checked by a medical professional, otherwise why would the medicine be so restricted for purchase. If POM do not have a prescription, then they either need to be revaluated to explore the health risks or all pharmacies need a prescription.

The Medicines Act 1968 needs to be validated for the flux of online distributional channels as when it was created only brick and mortar pharmacies were available and a prescription was needed.

As society increases its knowledge base the laws and regulation even the guidelines need to keep up with the change and evolve accordingly, otherwise it could be a potential to cause more harm than good.

These sales promotions and other influences that are affecting the consumers are having on the market is crucial in understanding how the online pharmacies will change and adapt in the future.

Will they need to be more closely monitored; can they only do certain sales in a strict period of the year and so forth.

By constantly updating and maintaining the website demonstrates respect for the clientele and for their business market. Thus, enabling the counterfeit industry to take root within online distribution channels.

Together all the sales promotions, the distribution and integrity of the pharmacies cultivate an environment for counterfeits to be present in.

Overall, it is believed that online pharmacies need to be more closely regulated as they have a far reach, they are convenient and, in the end, they seem to be the future of pharmacies.

This next stage in development is the subsequent step in securing the safety of the consumers and aiding in the fight against counterfeit medicines.

Chapter Five: Knowledge and Experience of Pharmaceuticals Regarding Online Pharmacies and Self-prescription.

5.1 Introduction

As explained previously in Chapter One, medicines are an essential part of today's society, curing ailments that decades ago would have been thought to have been impossible or a miracle.

As medicines became a crucial factor in society, counterfeit medicines arose to take advantage of the market for financial and personal gain. Counterfeit medicines are detrimental to a patient's health and thus cause a public health risk.

As it is the public that would be affected most of all by the presence of counterfeit medicines, it can be assumed that their view and perspective of them would be important.

For this to be interpreted, various questions would need to be asked to gain the appropriate perspective of the public. In view of this, the questionnaire that is the basis of this chapter was created, to analyse the purchasing of medicines from online distributers.

This included the trust placed in such distributers and the trust of the supply chain itself, alongside the types of medicines that are frequently purchased.

Understanding the public's view and perception of such matters is important in preventing further risk caused by counterfeit medicines. If the public's understanding can be analysed, then pre-emptive measures can be created to limit that risk.

5.2 Aim of the Questionnaire

The purpose of this study is to further explore the knowledge and experience of pharmaceuticals with regard to online pharmacies and self-prescription using a semi structured questionnaire.

The study will investigate the consumer perspective through their demography, the use of pharmacies, the reason behind using them and the public's opinions of counterfeit medicines and online pharmacies.

5.3 Objectives for the Questionnaire

Allow me to introduce the following focal points that are pivotal to this study:

1. Identifying the demographic factors of self-prescribing medicine users.
2. Identifying a correlation between gender or age and the reasons for purchasing medicines.
3. Exploring the motivation of the purchasing of medicines.
4. Assessing the public's opinion on counterfeit medicines.
5. Investigating the public's concern over the trustworthiness of online pharmacies.

5.4 Methods

Chapter 5, uses a semi structured questionnaire for extracting knowledge from a social environment. The use of semi structured interviews/questionnaires is a common methodological tool, used in cases where the goal is exploratory, discovery and interpretation of complex social events or trends such as the perception of counterfeit medicines and the use of online pharmacies (Morris 1984; Klandermans 2007).

5.4.1 Research Design

The reason for this study being conducted with a semi structured questionnaire, was to maximise the data received from the participants, with the primary focus being on those who purchase medicines.

A semi structured questionnaire is composed of two parts; the controlled questions and open-ended ones, compared to a fully structured questionnaire which is only comprised of ridged tick box answers (yes, no or categories).

With having a structured questionnaire, the participants are limited in what they can give as a response. Yes, it does make the data easier to correlate as there is only a selection of answers available.

However, a semi structured layout still incorporates some of the controlled tick box answer for easier correlation, but it also has open-ended questions such as 'what gender do you identify with?'.

By having these types of questions, it gives the participant freedom to come up with their own answers and comments, thus enabling their thoughts and feelings to be shown. The questions that had an open approach included the background and the opinions of the consumers, which are the primary interests of the study.

At the beginning of the questionnaire, it also focuses on the point that there is no right or wrong answers, meaning that we truly are interested in what the public think and feel with relation to medicines, pharmacies and counterfeits.

Participants were given the freedom to write a response to a question in their own word that would later be copied verbatim for analysis once the study had been collected.

One disadvantage for using a semi structured layout is that the answers need to be analysed in a different way. They need to be examined to see if there was a theme to the answers that could be grouped together for further analysis.

Overall, this results in a minimalistic intrusive approach to participant privacy and into their lives.

5.4.2 Data Collection

The questionnaire was distributed online for the furthest possible reach of participants. The criteria of the participants were for anyone above the age of 18, however it could reach to those that are 16.

The questionnaire was in circulation from February to May 2019. Any participants that did not answer the questions appropriately or did not fit the criteria set out for the participants, would be excluded from the data pool.

5.4.3 Definitions

For the purpose of the questionnaire, self-prescribing can be defined as prescribing medicines yourself. E.g., buying cough medicine when you have a sore throat. The rationale for using the WHO's definitions of both a counterfeit and substandard drug/medicine is because WHO is an internationally known organisation and the definitions are recognised worldwide (WHO 2020).

The reason that this is important is so that the knowledge and perhaps the perception of the definition is far-reaching and understood by more than solely the participants in the UK.

Another motive for using the WHO's definitions, is that numerous researchers over the years, of multiple specialities, have already been successful in informing others of such dangers, by having these definitions as a framework.

(Zhou 2005) uses the WHO's definitions to further the point that one definition can be used across multiple disciplines and be successful.

In this survey the medicines that are being described are medicines such as Antibiotics, Antimalarial and such.

Furthermore, as stated by the WHO, a counterfeit is (WHOa 1999):

> *"A product that is deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting occurs with both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredient or with insufficient active ingredients".*

Whereas (WHOb 1999)....

> *"Substandard drugs are manufactured with the intent of making a genuine pharmaceutical product, but the manufacturer saves costs by not following GMP (Good Manufacturing Practice) or using poor quality raw materials. Another potential problem relates to inadequate storage or transport conditions, leading to deterioration of the product. The performance of such medicines is questionable".*

5.4.4 Data Analysis

This pilot's study consists of 76 questionnaires that were collected between February and May 2019. The studies were collected online and copied to excel verbatim. After numerical analysis and the coding of the data within excel, the data was then imported on RStudio for statistical descriptive analysis.

The questionnaire consisted of four parts; (1) the demography characteristics of the consumers, (2) the use of pharmacies and medicines, (3) the reasons for using them and (4) public opinion of online pharmacies and counterfeits.

Further investigation into the data created Comparison Models for the variables most relevant to the research question of counterfeit medicines and the use of online pharmacies.

Age groupings were created to be four/five years apart over a 60-year range. The reason for this is due to the belief that a change can become more apparent with the aid of a four/five-year range (Teater 2015).

5.4.5 Data Validation

Once the data was collected it was imported into RStudio and Excel, which was then used to analyse descriptive and numerical statistics. The data was interpreted with an unbiased and non-judgemental view, and an open mind and attitude was also used during the research to keep the results fair and accurate.

Bias is when you illustrate prejudice, favouritism or preference for someone or something, where being judgemental or showing judgement suggests that you allow your own values and tastes to guide your discissions (Sitthi-amorn & Poshyachinda 1993).

A non-judgmental and unbiased view means that you disassociate yourself with what you think you know and what your own beliefs are about a topic when you are looking at someone else's answers to a question that has been asked (Sitthi-amorn 7 Poshyachinda 1993).

By allowing the questions to be answered in a non-judgemental and unbiased environment you are more likely to get an accurate honest answer than someone trying to tell you what they think you want to hear.

A good way to show non-judgmental and unbiased feelings or ask questions is for it to be conducted anonymously, for how can you be judged if you are not known.

For example - this is in theory only!

Two people are standing next to each other. Person A is against anything new, different and expressive such as (Race, Gender, Sexuality for scenario purposes). Person B identifies with one or more of those differences and expressive changes in life (Race, Gender, Sexuality for example).

Both individuals are asked by Person C to tell them what colour the sky is. Person A looks up and say its green. Person B looks up and says Blue.

Person C shares the same belief as Person A and shows a biased view so they ignore the reason for Person Bs answer and sides with Person A and takes that as truth. Person B changes their answers to be more alike Person A.

However, person D has an unbiased view and askes the same question, Person A and B answer again. Person D ignores their own beliefs and listens to both and questions are either of you colour-blind. Person A answers well yes, I am and Person B answers no, not that I'm aware of.

There is always a reason for someone's answer.

The reason that the data would be examined with an unbiased view is because multiple answers were needed for correlation to occur, this means that various opinions were needed for analysis and some of those would oppose the thoughts I had originally when conducting the study. Nevertheless, the bias and judgement needed to be removed for an accurate and just assessment to take place.

With a variety of answers, no one answer or expected answer would be looked at more highly than others, thus an unbiased view. Also, to further avoid the problem of a biased viewpoint skewing the data, only the answers needed for analysis were examined together. So, the whole data was not interpreted at once, thus the answers were kept anonymous throughout.

5.4.6 Ethical Considerations

Before the questionnaire was distributed online, ethical approval was sought from Bournemouth University Internal Ethics Committee (Ref 24172).

To protect those who completed the questionnaire, no data that would be able to be used to identify the participants were used or stored, such as full names.

Also, the data that was collected in this study was not shared outside of the scope of the study.

5.5 Results

5.5.1 Demography

Due to the semi structure of the questionnaire the groupings for the demography are manually created. Also, for the purpose of this study the percentages have been rounded to whole integers.

It should be noted that the data in this study is interpreted from a modernism and post modernism view. The reason being that the understanding on modernism and postmodernism is important for this study.

The motive behind the use of a modernism view versus a post-modern view is because of the concept of each.

Modernism can often class as the living in a qualified, new and different world which no longer belongs to the past (Kahraman 2015).

Sarıbay (2001 cited by Gürkan 2012) states that modernism is;

> *"A situation in which a differentiation of progressing, economic and administrative rationalization and social world opposite to traditional order in parallel with modern capitalist –industrial government and which has been started to be used in West with the Enlightenment in the eighth century"*

Meaning that modernism is the collection of individuals who are embracing various relationships that are the base for a world which is regularly formed due to an individual's intellect and enlightened individuals and the organisations formed of such individuals (Kahraman 2015).

Whereas the postmodernism period, seen as a historical period which is the cause of a serious paradox. In addition to various individuals adapting to the countless changes and developments in every area of society, there is an increase in the status of societies lifestyles such as economic and social developments.

Even though most accept postmodernism to be classed as an extension of modernism with the thought of a living situation, some believe postmodernism exists to be a reaction against the modernism global view in the context of mind and values, development of humanist ideological values and knowledge gained by the individual.

As stated by Adak (2010) postmodernism can be classed and categorised in three branches. The first being the different styles in arts and architecture. The second branch being the historical period starting from 1900's.

Finally, the third branch is the ethical and philosophical view, due to the knowledge of an individual being tested as radical epistemological.

With these views being considered, the understanding of a person's perception can be focused on, and the identification of reasoning behind a view may become clear. Since no matter what changes society faces, creates or are presumed, we overcome them and adapt.

This becomes crucial when focusing on the public perceptions of counterfeit medicines and medicine purchasing. As seen below the focus and ideals of each generation, alongside the modernism versus postmodernism view is expanded further.

The ideals of each generation are as follows (Kahraman 2015):

Baby Boomers (age 52-70)

- Live to work
- Self-worth = work ethic
- Loyal to employer
- Competitive
- Goal-centric
- Process oriented

- Focused
- Disciplined
- Enjoy working in teams and proving themselves to the team
- Need to know that they are valued
- Want to make a difference

Generation X (age 51-37)

- Work to live
- Crave independence
- Scepticism
- Focused on results
- Think Globally
- Adapt to change
- Eager to learn
- Thrive on flexibility
- Education is a necessary means to succeed

Generation Y / Millennials (age 22 – 36),

- Fully transparent, shares everything
- Do well with detailed instructions
- Desire to make an impact
- Commerce & conscience together
- Value Diversity
- Love technology
- Education is a highly expensive necessity
- Do not perform at their best in a traditional work environment
- Find solutions using technology

Gen Z (age 21 -7)

- Tech-innate (first generation to grow up with modern technology)

- Accepting of others
- Make things
- Realists
- Individualistic
- Competitive
- Transparent
- Entrepreneurial and inventive spirit
- Concerned about the cost of education

Whilst the view of modernism and post modernism is essential, another view will also be a part of the framework for this study. That view is the generational view.

"A generation can be considered a segment of the population who have shared experiences and have a sense of history that influences their thinking and behaviour today. In Western countries like the United States (US) and Canada in North America, most countries in Western Europe, Australia and New Zealand can be considered to have three distinct generations that influence society today, the baby boomers, generation X and generation Y. The baby boomer generation came in a mass population bubble after World War Two until around 1964." (Norway Global 2020)

The Baby Boomers were the children of the silent generation who in turn were the children of the Greatest Generation. Baby boomers' children born between 1965 and 1979 are Generation X. Generation X children born between 1980 and 1999 are Generation Y.

Generation Z are the children born after the millennium. Whereas Generation Alpha is the new generation being born today. The focus of this study is from Baby boomers to Generation Z, as they are the generations of the participants who answered the questionnaire.

It is known that what we ourselves think and how we view life is often different from the generations created before and after us. Furthermore, it is often reflected upon that the ideals that we grow up with influence later decisions in life.

This includes, but is not limited to, the flux of individuals losing their jobs, the ever-expanding influence of the Internet, the constant creation of new technology, of the updated variations of versions past, the changes in the normal values of society – e.g., the LGBT community for one, and lastly the various forms communication – the Internet, TV, email, social media, letters, texts etc.

The reason that understanding how the ideals of different generations change and adapt depending upon what they need to or have endured is important due to how they perceive different scenarios such as online pharmacies, counterfeits and the harm to the public's health. On that basis the demography is split into four main categories; age, gender, ethnicity and level of education.

As shown in table 11 the demography is laid out to demonstrate the groupings the participants answer where clustered in and the percentage of the participants that link to the corresponding groups.

Table 11: Demographic characteristics reported from the participants in the survey

Parameter	N	(%)
Gender		
Male	24	32
Female	51	67
Other	1	1
Age Range (Years)		
20 - 25	38	50
26 - 30	4	5
31 -35	2	3
36 - 40	6	8
41 - 45	2	3
45 - 50	4	5
51 - 55	9	12
56 - 60	5	7
61- 65	4	5
66 - 70	0	0
71 - 75	1	1
76 - 80	1	1
Occupation		
Unemployed	4	5
Self - employed	1	1
Student	15	20
Graduate & Postgraduate	7	9
Education	12	16
Director / CEO	2	3
Medical	5	7
Science / Engineering	6	8
Admin	5	7
Sales	1	1
Hospitality	5	7
Public Services	2	3
Retired	3	4
Other	8	11

Parameter	N	(%)
Ethnicity		
Arab	1	1
Asian	1	1
British	11	14
English	3	4
European	1	1
Indian Other	1	1
Mixed	4	5
White	18	24
White British	33	43
White Other	3	4
Country of Birth		
Australia	1	1
Canada	1	1
France	1	1
Germany	1	1
Ireland	1	1
Malaysia	1	1
Peru	1	1
Portugal	1	1
Saudi	1	1
UK	0	0
Education Level		
A Level	8	11
Bachelors	30	39
Doctorate	8	11
GCSE & BTEC	3	4
Masters	11	14
O Level	2	3
Other	14	18

A total of 12 groups were reported in this study which included 20 – 25 years (n=38, 50%), 26 – 30 years (n=4, 5%), 31 – 35 years (n=2, 3%), 36 – 40 years (n=6, 8%), 41 – 45 years (n=2, 3%), 45 – 50 years (n=4, 5%), 51 – 55 years (n=9, 12%), 56 – 60 years (n=5, 7%), 61 – 65 years (n=4, 5%), 66 – 70 years (n=0, 0%), 71 – 75 years (n=1, 1%) and 76 – 80 years (n=1, 1%).

It's should be noted that there is a clear underrepresentation in some of the age groups e.g., 66-70 years has no participants claiming to be in that age range, whereas others may only have one or two participants. This causes the study overall to have limitations in the date analysis.

The data collected would not show an accurate depiction of clinical knowledge gained as the data correlations would be skewed.

As one of the main focuses on the study is the ages of the participant and cross factors, the results themselves from this analysis need to reflected on and adapted for the main study to be conducted in the future.

However, as there is a wide range of ages from the limited number of participants the ages will still be used to gain a general idea of trends and motives for self-prescribing throughout this study.

For gender three groups were reported male, female and non-binary with most participants identifying as female (n= 51, 67%), males following behind with (n=24, 32%) and non-binary (n=1, 1%).

10 ethnic groups were identified with the participants which included Arab (n=1, 1%), Asian (n=1, 1%), British (n = 11,14%), English (n=3, 4%), European (n=1, 1%), Indian Other (n=1, 1 %), Mixed (n=4, 5%), White (n=18, 24%), White British (n=33, 43%) and finally White Other (n=3, 4%).

The reason that some of the groups are typical ethnic groups that are found in other surveys, such as White British or Mixed, and some are more uncommon, such as English, is because the participants had the ability to write their answers.

It is believed that some got confused on what ethnicity means and confused it with nationality, for example one participant stated '*sorry, I don't really understand ethnicity – non-native speaker*'.

Following ethnicity, the participants created 10 groups regarding the country of their birth; Australia (n=1, 1%), Canada (n=1, 1%), France (n=1, 1%), Germany (n=1, 1%), Ireland (n=1, 1%), Malaysia (n=1, 1%), Peru (n=1, 1%), Portugal (n=1, 1%), Saudi (n=1, 1%) and the UK (n=67, 88%).

Lastly the highest level of education of the participants was reordered, A Level (n=8, 11%), Bachelor's Degree (n=30, 39%), Doctorate (n=8, 11%), GCSE + BTEC (n=3,

4%), Masters (n=11, 14%), O Level (n=2, 3%) and other qualifications such as NVQ's or Aircraft Licence (n=14, 18%).

The ethnicity and place of birth was originally placed in the study due to a hypothesis that people who are from different cultures would purchase different types of medicine and comparisons could be made about the birthplace purchases against ethnicity.

However, this was not the case as there was insufficient variety in the results and not enough participants for this to be included in the study.

5.5.2 Use of Pharmacies

Pharmacies are often used by many people. This part of the study identifies the frequency of use and purchase of medicines, and it also introduces the types of medicines that are used/purchased.

One of the penultimate questions of the study was asked in this part of the questionnaire, 'Have you ever used an online pharmacy?' Due to the way the questionnaire is structured some of the questions have multiple answers available for selection, therefore some of the percentages will be more than 100% when tallied together.

As shown in table 12 when pharmacies are used and why is shown to demonstrate the groupings the participants answer.

Table 12: Parameters for questions asked within the questionnaire 'the use of pharmacies' section of the study.

Parameter	N	(%)
Frequency		
Daily	3	4
Weekly	1	1
Monthly	3	4
Quarterly	34	45
Biannually	21	28
Annually	6	8
Biennially	7	9
Never	1	1
Reason for Self-prescription		
Convenience	4	5
Cost Efficient	46	61
Lack of Trust in Health Care Professionals	25	33
Other	16	21
N/A	4	5

Parameter	N	(%)
Type of Medicine		
Analgesics	62	82
Antibiotics	8	11
Anticancer	1	1
Anti-emetics	6	8
Antihistamine	43	57
Antipyretics	2	3
Antiseptics	30	39
Hormone	0	0
Mood Stabilisers	3	4
Oral contraceptives	8	11
Statins	0	0
Stimulants	2	3
Tranquilisers	2	3
Other	8	11
Used an Online Pharmacy		
Yes	16	21
No	59	77
Maybe	1	1

When identifying the frequency in which medicines are purchased the most common answer for participants (n=34, 45%) is quarterly – every three months. Close behind for the frequency of purchase with 28% is biannually – every six months. The least likely for medicine purchase is weekly with 1%. The same goes for a participant who stated they have never purchased medicine.

As expected, the primary reason for self -prescribing is due to the cost (n=46, 61%), with lack in health care professionals coming in second (n=25, 33%). Other reasons that were stated by participants included 'don't want to waste NHS time or money' and 'delivery options.

At the beginning of the study, it was hypothesised that the top three types of medicines that would be purchased would be analgesics as pain relief such as ibuprofen and paracetamol are the most common medicines on the market.

Antihistamine was considered due to it being the hay fever season when the questionnaire was distributed, and allergies emerging more commonly. And lastly antiseptics as they are often found in first aid kits and so forth to help clean wounds.

As predicted the analgesics where the most popular medicines purchased by participants (n=62, 82%), followed by antihistamine (n=43, 57%) and antiseptics (n=30,

39%). When the participants were asked, have they ever used an online pharmacy, 77% of participants said no, 21% said yes and 1% said maybe.

The reason for the maybe when asked the participant stated, 'I use boots and Lloyd's pharmacies – not sure if they count?' which leads to the belief that not everyone knows what classes as an online pharmacy.

For this study an online pharmacy is both an original pharmacy and the extension of a physical version such as Boots, Lloyds, Tesco and such.

5.5.3 Motivation for Using Them?

When people take medicines there are often multiple different reasons for different people. This section follows what the typical reason is and why they purchase the medicines. Also, what brings about the public view that a certain type of medicine is better than another.

This is closely followed by how the public really view online pharmacies and the trust freely given to them. Whenever a person falls ill to an ailment, they often show symptoms. When these symptoms are then categorised, certain medicines are used to counteract the effects and aid in curing the persons affliction.

As shown in table 13 the reason for using medicines and pharmacies is shown to demonstrate the groupings the participants answer.

Table 13: Parameters for questions asked within the questionnaire for' motivations for using medicines' section of the

Parameter	N	(%)
Symptoms		
Aches & Pains	60	79
Cough	25	33
Diarrhoea	9	12
Fever	16	21
Nasal Congestion	32	42
Runny Nose	40	53
Skin Wounds	23	30
Sore Throat	28	37
Vomiting	11	14
Other	19	25
Medicine Selection		
My Own Experience	57	75
Opinion of Family Members	28	37
Previous Doctor's Prescription	27	36
Recommendation of online Forums	5	7
Recommendation by Community Pharmacist	13	17
The Advertisement	3	4
Opinion of Friends	8	11
Other	5	7

Parameter	N	(%)
Medicine Factors		
The Brand	15	20
The Price	36	47
The Type	46	61
Possible Adverse Reaction	6	8
Desired Reaction	26	34
Indication for Use	6	8
Other	7	9
Trust		
1	11	14
2	2	3
3	9	12
4	8	11
5	18	24
6	9	12
7	10	13
8	5	7
9	1	1
10	2	3

study.

As was hypothesised before the study was conducted the most common symptoms that present themselves are aches and pains, such as a headache and sore muscles, with 79% of participants having these as a complaint.

Nasal congestion and runny nose coming in close second with between 42% and 53% of participants suffering with an affliction in the nose. And lastly a sore throat that has been known to plague many people, which produced lozenges such as Lockets and Strepsils to name but a few.

When a person selects a medicine there are various methods for choice. Most of the participants go with their gut instinct and have their own experience (n=57, 75%), mostly trial and error as some say, *'if a medicine did not work, try a new one next time'*.

After a person's own experience with the medicine they have taken, the opinions of the families (n=28, 37%) and GPs (n=27, 36%) are similar in how the participants viewed those options. Meaning they valued opinions of those they trust, be it a family member or a healthcare professional.

The least common view on the deciding factor of purchasing medicine is the advertisement (n=3, 4%) and recommendations from the Internet (n=5, 7%).

After self-experience or other opinions taking effect on the purchase of medicines the appearance and other factors come into play, the most common aspect of a medicine being purchased was the type of medicine and its purpose (n=46, 61%).

The second most common reason was the price of the medicine (n=36, 47%), as would be expected. Finally, the third view of the public was the desired reaction (n=26, 34%) the medicine is known from having, this would coincide with the trial-and-error experience.

When purchasing any item there has to be a certain amount of trust between the buyer and the distributer. When the participants were asked to rate the trust, they have for online pharmacies the most common answer was 5 (n=18, 24%), with 1 being not

trusted and 10 being trustful, this suggests that if people are not used to online pharmacies, they would choose neither for or against them in regard to trust.

This is backed up by the suggestions either side of 5 showing similar results to each other ranging from 11% - 13%. Despite this the second most common view was a trust score of 1 (n=11, 14%), the view that online pharmacies are not to be trusted.

5.5.4. Opinions

After investigating the use of pharmacies and the motivations for using them, the next section in the questionnaire identified the opinions of counterfeit medicines.

Could someone from the public identify a counterfeit, how would they identify one, and the knowledge the public has on counterfeits with regard to the harm they cause.

As shown in table 14 the participants opinions on counterfeit medicines are illustrated to demonstrate the groupings the participants answer.

Table 14: Parameters for questions asked within the questionnaire for the 'opinions of counterfeit medicines' section of the study.

Parameter	N	(%)
Authenticity		
Barcode	11	14
Medicine Tag	18	24
Ask a Doctor	17	22
Ask a Pharmacist	42	55
Other	15	20
Concerned with Taking a Counterfeit		
Yes	2	3
No	65	85
Maybe	9	12
Counterfeit Encountered		
Yes	3	4
No	73	96

Parameter	N	(%)
Identify Counterfeit		
Appearance	4	5
Label	2	3
Never Encountered One	68	89
Packaging	2	3
Lower Cost	1	1
Production Stamp	1	1
Other	1	1
Analysis	1	1
Extent of Harm		
1 - Mild	0	0
2	2	3
3	1	1
4	2	3
5	4	5
6	2	3
7	17	22
8	19	25
9	7	9
10 - Lethal	22	29

After being asked to rate their belief on 'what is the extent of harm caused from counterfeit medicines' most participants selected 10 (n=22, 29%) lethal. There was close clustering around 7 and 8 for the harm scale with 17% and 19% respectively, this suggests that the public have some degree of knowledge with regard to health issues caused by counterfeit medicines.

When asked about counterfeit medicines and the concern that the participants may have taken some, the consensus was that no they were not concerned (n=65, 85%).

However, 12% of the participants were on the fence with concern as they were not sure if they had taken some. The thinking behind the majority of these participants' thoughts was through the lack of medicines working.

On the other hand, when asked if they have ever encountered a counterfeit medicine the majority of 96% said no once again. This proved to be an interesting statistic when compared to how one would identify a counterfeit and checking the authenticity of the medicine.

For one to identify a counterfeit, various parameters were available to be selected including but not limited to; appearance, label, cost and even production stamp. The participants were able to select that they have never encountered one. The reason that this was an option was for a double blind in the study.

By having this available it tested what the public really thought of counterfeit medicines and if they could identify them on sight. 89% of participants selected this option, suggesting that those who selected other answers may have thought they had encountered counterfeits before even if not educated about them at the very least.

However, when asked how to check authenticity of a medicine, the majority selected;' ask a pharmacist' (n=42, 55%), with the other options such as barcode, medicine tag and ask a doctor being similar in amount of response 11% - 18%.

Even though asking a health care professional would be a logical step and understandable in reason, the only real way – as explained in Chapter One – is for an

investigation of the medicine itself. Other studies have shown that packaging can give reason to doubt the authenticity of a medicine. However, the real test is if the medicine itself holds up to scrutiny.

5.6 Discussion

Due to nature of the questions asked within this study and the results given, it can be understood that the results are inconclusive due to the flux in the data. As a side note, some of the percentages will overlap and thus not equal 100% when grouped together, this is due to the structure of the questionnaire where multiple answers were available.

Modernism and postmodernism are a subtle yet a crucial part of today's society, as they are the cause of the creation of different lifestyles and thought processes (Kahraman 2015). Some would say they are the basis of many people's ideals, and the way a person's perception may be influenced.

Be it the control of one's self and the development of tomorrow, or the relevancy of the environment in which one is placed (Adak, 2010). These views are critical in understanding why a person would purchase a medicine from an online source or stay close to home and purchase from a local pharmacy.

Alongside the perception gained from a modern and post modernism view, examining the generational ideals also gives a perspective that individuals of different ages will hold. As explained previously, most ideals come from experience. With these ideals gained from either the generational outlook or from a modern and post modernism view, a person's age would be a key factor in determining reasons behind purchasing medicines.

Also, another key factor in the determination of a person's reason to purchase medicines is the prerequisite need that an individual will have for the use of them. With the modern and post modernism view of society, alongside the generational ideals the perception of the public is crucial for understanding how various scenarios affect the populace, such as the purchasing of medicines.

One obvious known reason for purchasing medicines is to alleviate any aliments present. The symptoms that generate a need to purchase medicines and the reason for purchasing particular medicines were compared to one another.

As can be expected, aches and pains were the top symptom to cause the purchase of medicines (50%), next came runny nose and nasal congestion (29% and 28% respectively) then a sore throat (25%). The reason for choosing a particular method of purchasing medicines illustrated that the main factor was convenience, with cost efficiency come in close second.

Table 15: Symptons Vs Reason for purchase. A comparison between the symptoms felt by the participants and reason an individual would purchase medcines.. The most common grouping is highlighted in red, the next most common groups are highlighted in yellow and the green coloum and rows are the cross points that focus on the most prominent answer.

Symptoms Exhibited	Reasons for Purchasing Medicines: Lack of trust in health care professionals	Convenience	Cost Efficient	Other	N/A
Aches & Pains	2	38	9	11	
Cough	2	17	4	2	
Diarrhoea		5	2	2	
Fever		10	4	2	
Nasal Congestion	2	22	1	7	
Runny Nose	1	13	3	23	
Skin Wounds	2	14	4	3	
Sore Throat	1	19	5	3	
Vomiting	1	6	2	2	
Other		10	2	7	

Other reasons were given such as the medicine 'was not covered by the NHS' or that a participant wanted to 'save the NHS money' as they purchased items such as ibuprofen and paracetamol. Other participants have also stated that they have a lack of trust in health care professionals. Which gives cause to be examined further in a different study where more questions can be asked regarding an individual's view on the NHS and other services.

Trust, as expected comes from age and some would say wisdom from experience. When growing up and having different circumstances or even the fact that the older a person becomes the less trusting they are due to being hardened by conditions of life

experienced (Breiner et al. 2016). This is the case when a person's age was compared to the trust shown in an online pharmacy.

The younger the participant was the more trust they were willing to show for online pharmacies. As illustrated in 'Age Vs Trustworthiness' 12% of participants are between the age ranges of 20 – 25 years old and have valued an online pharmacy to rate a 5 on the trustworthy scale, with 1 being un-trustworthy and 10 being very trustworthy.

Table 16: Age Vs Trustworthiness. A comparison between the age of the participant and what they rated the trustworthyness of online pharmacies. The most common grouping is highlighted in red, the next most common groups are highlighted in yellow and the green coloum and rows are the cross points that focus on the most prominent answer.

		Trustworthy									
		1	2	3	4	5	6	7	8	9	10
Age	20 - 25	4		5	2	9	6	6	5		1
	26 - 30			2		1	1				
	31 -35		1		1						
	36 - 40	1		1	1		1	1			1
	41 - 45	1						1			
	45 - 50	1		1		2					
	51 - 55	1	1		2	3				1	
	56 - 60	3			1			1			
	61- 65					2	1	1			
	66 - 70										
	71 - 75					1					
	76 - 80				1						

Throughout this age bracket (20-25) a wide range of ratings occurred, the individuals in that age range, trend towards trusting an online pharmacy with the highest rating of 8 being formed by 7% of participants and 1% saying they are very trustworthy and granting a rate of 10.

As you progress through the age brackets it can be seen to have a negative proportional review, meaning that as the ages of the participants increased the less likely they are to trust an online pharmacy.

Even though there is negative proportional relationship between age and trust, the majority of participants (24%) valued the trust of an online pharmacy to be a 5, this

value can neither be for or against an online pharmacy, which shows there is hesitation, no matter what age an individual may be.

Despite the differences in ages most participants (61%) give the reason for purchasing medicines online to be of convenience. The other reason for purchasing a medicine from an online source is of cost efficiency (33%). So, it can be assumed it does not matter the circumstances it is in our human nature to be comfortable and look for convenience (Dick, 1835).

Table 17: Age Vs Reason for Purchasing Medcines. A comparison between the age of the participant the reason why they purchase medcines. The most common grouping is highlighted in red, the next most common groups are highlighted in yellow and the green coloum and rows are the cross points that focus on the most prominent answer.

Age	Reasons for Purchasing Medicines				
	Lack of trust in health care professionals	Convenience	Cost Efficient	Other	N/A
20 - 25	2	24	15	7	2
26 - 30		4	1		
31 -35	1	1	1		
36 - 40		4	1	1	
41 - 45			1	1	
45 - 50		1		2	1
51 - 55		5	5	2	
56 - 60		4			1
61- 65		2	1	3	
66 - 70					
71 - 75		1			
76 - 80	1				

When a reaction occurs that is unexpected and unwanted the first thing to do is to stop whatever is making us uncomfortable in the first place, be it placing a hand on a hot surface or to stop looking at the sun when it shines in your eyes.

This thought process can be assumed to come from instinct as well as coming from knowledge passed on from past generations (Dick 1835).

As shown the most common answer no matter the age, was to stop taking the medicines (55% of 76 participants) or consult a doctor (47% of 76 participants) when faced with an adverse reaction.

Table 18: Age Vs Adverse Reaction.. A comparison between the age of the and what the participants do following on from an adverse effect occuring after taing medcines.. The most common grouping is highlighted in red, the next most common groups are highlighted in yellow and the green coloum and rows are the cross points that focus on the most prominent answer

	Adverse Reaction							
Age	Stop taking the medicine	Consult a GP	Consult a Pharmacist	Switch to another medicine	Consult friends or family members	Use the internet	Other	N/A
20 - 25	20	20	9	3	4	1	1	2
26 - 30	3	2	3					
31 -35	1							1
36 - 40	5	3	1	1	2			1
41 - 45	1			1	1			1
45 - 50	2	2	2	1	1			
51 - 55	6	2	3	3	2			2
56 - 60	2	4	3	1				
61- 65	1	2		1				1
66 - 70								
71 - 75		1	1					
76 - 80	1							

As hypothesised, the top three medicines to be purchased are analgesics (82% of 76 participants), antihistamines (57% of 76 participants) and antiseptics (40% of 76 participants).

This was hypothesised as explained earlier due to the circumstances that happens in everyday life. Cuts and grazes, a simple headache and pesky hay fever all play a part.

Despite the clusters in each type of medicine, age did not play a part in the decision making for these purchases, which may mean in theory that modernism and post modernism cannot overcome true human nature in need to alleviate any illness or wounds that need to be healed.

When the types of medicines are once again compared, this time to the frequency of purchase of a medicine, the top three medicines from the previous statement, remain the leaders with analgesics (80% of 76 participants), antihistamines (54% of 76 participants) and antiseptics (39% of 76 participants).

Table 19: Age Vs Type of Medcines Purchased.. A comparison between the age of the and what type of medcines the participants purchase.

Age	Type of Medicine Purchased													
	Analgesics	Antibiotics	Anticancer	Anti-emetics	Antihistamine	Antipyretics	Antiseptics	Hormone Replacements	Mood Stabilisers	Oral Contraceptives	Statins	Stimulants	Tranquillisers	Other
20 - 25	32	3		3	20		12		1	7		1	1	2
26 - 30	4	3		1	1		2		1					
31 -35	2				1	1								
36 - 40	5	2		1	6		2			1		1	1	
41 - 45	2				2		2							
45 - 50	3				2	1			1					1
51 - 55	7			1	6		7							
56 - 60	3				3		2							1
61- 65	2				2		1							3
66 - 70														
71 - 75	1						1							1
76 - 80	1		1				1							

After the main medicines that are purchased are identified the most come purchase is monthly – as it was available as a multichoice question with multiple answers available for selection, a statistical analysis could not be conducted for this comparison for overall frequency purchases.

Table 20: Frequency of Purchase Vs Type of Medcines Purchased.. A comparison between the frequency an individual purcahses medcines and what type of medcines the participants purchase.

Frequency of Purchase	Analgesics	Antibiotics	Anticancer	Anti-emetics	Antihistamine	Antipyretics	Antiseptics	Hormone Replacements	Mood Stabilisers	Oral Contraceptives	Statins	Stimulants	Tranquillisers	Other
	Type of Medicine Purchased													
Never	1													2
Daily					1		1							
Weekly	3			1	3		1			1				
Monthly	29	3	1	4	21	1	19		2	3		1	1	3
Quarterly	16	2		3	13	1	5			3		1	1	1
Biannually	6	2			1									
Annually	5	1			1		3		1	1				1
Biennially	1				1		1							

However, it is shown that purchasing medicines monthly, is the most common amongst participants, this is closely followed by a medicine's purchase occurring quarterly during the year. The last close comparison is the purchase of medicines biannually.

When the questionnaire was first distributed it was hypothesised that the more frequent a medicine is purchased, the more likely an individual is to trust a pharmacy due to experience and good faith. However, on closer inspection that appears to have been a null hypothesis.

Table 21: Frequency of Purchase Vs Trustworthy.. A comparison between the frequency an individual purcahses medcines and how the medcines purchases are rated for trustwothiness..

Frequency of Purchase	1	2	3	4	5	6	7	8	9	10
	Trustworthy									
Never	1			1		1				
Daily	1									
Weekly					2		1			
Monthly	5	1	4	5	7	5	5	1		
Quarterly	2	1	4	1	5	2	3		1	2
Biannually			1		3	1		1		
Annually	1				2		1	3		
Biennially								1		

The reason being that on closer inspection the opposite held true. The least amount of trust came from those who purchased medicines the most frequently, daily and sometimes weekly – if any – throughout the year from an online pharmacy. 9% (n=7) of participants stated that when they purchased medicines monthly, they valued the trust of an online pharmacy as a five.

Whereas those who purchased medicines once a year, twice a year or even every two years rated the value of trust to be six and above. The most varied range of trust however came from those who purchased medicines quarterly. This could be due to reason that the option of quarterly – when never purchasing a medicine is excluded from the options available – is the middle option.

It is neither frequent nor non- frequent when compared to the other available options, thus it could be hypothesised that the reason for this option having the most range available in trust is due to having multiple different age groups within it.

This could mean that various generational ideals and viewpoints are clustered together in one area/ option. For a further conclusive answer to this question, the comparison between age, trustworthiness and the frequency of purchase would need to be conducted.

Even though the frequency of purchase was compared to the level of education an individual experienced, the frequency at which an individual will purchase medicines stayed constant with monthly and quarterly being the most common.

Table 22: Frequency of Purchase Vs Education. A comparison between the frequency an individual purcahses medcines and the educational level an indiviual has acquired.

		Frequency of Purchase							
		Never	Daily	Weekly	Monthly	Quarterly	Biannually	Annually	Biennially
Education Level	A Level			1	4	2		1	
	Bachelors	1			13	10	2	4	
	Doctorate				5	3			
	GCSE & BTEC	1			2	1	1	1	
	Masters			2	2	2	1	1	1
	O Level				1	1			
	Other	1	1		7	2	2		

The commonest level of education of a participant is a bachelor's degree (38%) with a master's degree (12%) and a doctorate degree (11%) coming in as the second and third most common degree held by the participants.

On the comparison between the education and the reason for purchasing medicines on the Internet, the results support those explained earlier with convenience and cost efficiency being the determined reasoning for the purchases.

Table 23: Reasons for Purchasing Medicines Vs Education Level. A comparison between the reason an individual purcahses medcines and the educational level an indiviual has acquired.

Education Level	Lack of trust in health care professionals	Convenience	Cost Efficient	Other	N/A
	Reasons for Purchasing Medicines				
A Level	1	3	2	2	
Bachelors	1	20	11	6	
Doctorate		4	1	3	
GCSE & BTEC		4	2	1	
Masters		6	3	4	
O Level		1		1	
Other	1	8	5	4	

The hypothesis however was that the more educated an individual was, the less likely they would use convenience as a staple for purchasing medicines online as they may know the dangers that presents. However, that was found to be incorrect and a failed hypothesis.

On a further examination of an individual's education, when questioned if the participants would be able to identify a counterfeit, most participants (89%) stated that they did not know how to.

Table 24: Identifying a Counterfeit Vs Identification of a Counterfeit. A comparison between if an individual believe they have come into contact with an counterfeit and how they would identify the presence of a counterfeit medicine.

Identification of a Counterfeit	Appearance	Analysis	N/A	Packaging	Lower Cost	Label	Production Stamp	Other
	Identifying a Counterfeit							
Yes		1		2	1			1
No	3		73			2	1	
Maybe								

The category itself of N/A was a combination of written answers that gave the participants the freedom to write what they believed was how to identify a counterfeit.

It is shown that they did not deviate from their thoughts and answer a question with an already suggested answer. In an opinion this can be classed as a modernism view of an enlightened individual, as they have a freedom of thought, but in a controlled environment.

Table 25: Identifying a Counterfeit Vs Education Level. A comparison between the educational level an indiviual has acquired and how they would identify the presence of a counterfeit medicine.

		Identifying a Counterfeit							
		Appearance	Analysis	N/A	Packaging	Lower Cost	Label	Production Stamp	Other
Education Level	A Level			7					
	Bachelors	1		32	1		1		1
	Doctorate			7	1	1			
	GCSE & BTEC			3					
	Masters	2		5			1	1	
	O Level			2					
	Other	1	1	12					

When the individuals were then presented with the question of asking if they could tell if a counterfeit had come into their possession, the results were in parallel to whether they could identify a counterfeit.

The majority of those who believed they did not come into contact with a counterfeit stated that they could not tell if medicine was in fact a counterfeit.

Whereas those who stated they could detect a counterfeit selected the options of scientific analysis, the packaging and the cost.

Some of the individuals however believed they had not had contact with a counterfeit in their possession, even though they gave answers for how to detect a counterfeit, these included the appearance of the medicine, the label on the packaging and brand, and the production stamp on the packet.

As mentioned previously the trust in online pharmacies can be seen to accommodate the full spectrum of answers. Some participants stated they do not trust them and believe they are untrustworthy; others believe they are very trustworthy.

Even though the value of trust varies amongst the participants, when questioned how they can identify a counterfeit most participants state once again they are not sure, or that it is not applicable as they have never encountered one.

Table 26: Trustworthiness of an online pharmacy Vs Indentifying a Counterfeit. The comparison between how the participants believe can identify counterfeit medcines and how trustworthy a participant rates online pharmacies overall.

Identifying a Counterfeit	Trustworthy 1	2	3	4	5	6	7	8	9	10
Appearance			2				1			1
Analysis	1									
N/A	10	2	7	8	18	8	9	4	1	1
Packaging						1		1		
Lower Cost						1				
Label					1					1
Production Stamp										1
Other								1		

This becomes interesting when the trust of an online pharmacy is used in comparison to the question as to whether they have ever used an online pharmacy. The results showed a similarity between those who have used an online pharmacy against those who have not.

The trust did not deviate as there was still a wide range of answers given. The difference being that most participants have claimed to have never used an online pharmacy.

Table 27: Trustworthiness of an online pharmacy Vs the Use of Online Pharmacies. The comparison between how many participants use online pharmacies and how trustworthy a participant rates online pharmacies overall.

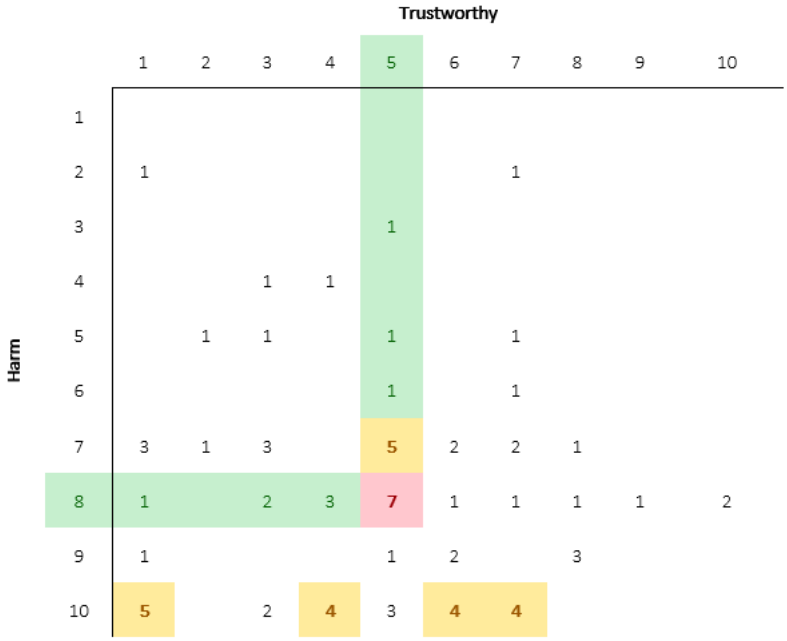
Use of Online Pharmacies	Trustworthy 1	2	3	4	5	6	7	8	9	10
Yes	1	1	3	1	2	1	3	3	1	
No	10	1	6	7	16	8	6	2		2
Maybe							1			

When looking at the trustworthiness of the online pharmacies from the viewpoint of the participants, compared to the view of how harmful counterfeits are, the trend is indirectly proportionally to the estimate.

It was hypothesised at the beginning of the distribution that no matter the trustworthiness of an online pharmacy the harm caused by a counterfeit would be reflected just so.

The reason for this hypothesis is that no matter the source of purchase and the trust built up in that environment, the harm caused by a counterfeit entering an individual's systems has no correlation.

Table 28: Trustworthiness of an online pharmacy Vs the Harm a Counterfeit. The comparison between how trustworthy a participant rates online pharmacies overall against how harmful they believe a countefeit medicine can be. The scale for trustworthiness is 1 - untrustowrthy – 10 – trustworthy, the scale of how harmful a counterfeit is viewed to be 1 - less likely to cause harm and 10 - lethal.



The participants mostly believed that counterfeits could cause severe health risk or even fatalities, so they ranked them high on the harmful scale. The trustworthiness of the online pharmacies as perceived by the participants as concluded before has a full range of answers.

In conclusion, despite differences in age and the education an individual has achieved, they are still likely to purchase medicines. It can also be determined that regardless of the education a person may have received the participants were not able to determine if they had received a counterfeit medicine or how to identify one.

The consensus of trust towards an online pharmacy has a variety of outcomes, depending on the subject it has been compared to.

Overall, this shows that no matter a person's age and education, an individual is still likely to purchase medicines, so it can be concluded that despite the education a person may have received the participants were not able to determine if they have received a counterfeit medicine or how to identify one.

This proves that the public need to be cautioned on identifying a counterfeit medicine and what to do in case they encounter one.

5.7 Critical Analysis

5.7.1 Research Question and Study Design

The purpose of this study was to explore the knowledge and experience of individuals regarding self-prescription and online pharmacies.

The study investigated the consumer perspective by examining different parts of the participants responses relating to their demography, the use of pharmacies, the reason behind using them and the public's opinions of counterfeit medicines and online pharmacies.

The objectives were for the majority successful as trends and reasoning became apparent. As a recap these were the objectives set out in this study:

1. Identifying the demographic factors of self-prescribing medicine users.
2. Identifying a correlation between gender or age and the reasons for purchasing medicines.
3. Exploring the motivation of the purchasing of medicines.
4. Assessing the public's opinion on counterfeit medicines.
5. Investigating the public's concern over the trustworthiness of online pharmacies.

For this type of research, the questionnaire as a basis was the correct method for data collection as it was constructed as semi structured.

Thus, the participants could freely answer what their thoughts and feelings were without influence, and ultimately it gave the truest representation of the publics opinion from the sample data collected.

This is paired with the structured multiple-choice questions which gave the study some structure but also sectioned that could be statistically analysed without much data handling.

For this type of research there have been previous questionnaires in supply for the public to answer regarding counterfeits and medications in general.

The reason a new questionnaire was created and adopted for this study is to create an amalgamation of previous successful study questions into one combined resource.

The reason for this new questionnaire is so that questions that enable the aims to be answers were used, were some of the questions used in the previous studies were not relevant.

One fallback of the questionnaire was that the publics/participants opinion of design, distribution, and administration of the questionnaire were not sought after in great detail.

If the feedback had been apparent then the modifications of the questionnaire for the future would be more suited to the public and perhaps the data set would be more significant.

5.7.2 Validity and Reliability

The accuracy of the study can be rated as medium to high due to the questions asked measuring what needed to be measured from the goals of the objectives.

The reliability of this study is considered to be high as with most questionnaires the more closed questions used the more reliable the research in general. However, this study could potentially be put into question what is reliability?

As this is the pilot study for future work meaning that it has yet to have all the problems have not been resolved if any were to crop up. One way this can be solved in the future is to ask a set number of questions and ask them again a set amount of time apart to the same participants. Following that identify if the participants have changed their answers of kept consistency.

5.7.3 Format

It is believed that the title of the questionnaire 'Knowledge and Experience of Pharmaceuticals Regarding Online Pharmacies and Self-prescription' was sufficient for the main goals of study.

However, it may have caused limitations to what could be asked of the public. Furthermore, the questions themselves may have not been as in depth as they could have been asked and thus not all the answers were a good representation of subconscious decisions.

As said previously the questionnaire was forced of open and closed questions, illustrating that the questions themselves were not restrictive. The use of both types of questions for this study was the correct method of approach.

During this study the questions that were asked may have seem to be threatening – not in a violent or rude way but they may have come across as aggressive.

The aggression comes from the way the question was asked, for example:

- How frequently do you buy medicine(s)?
- What type of medicine(s) did you use when self-prescribing?
- Have you ever used an online pharmacy?
- Do you change the dosage of your medicine during a course of treatment?

By forming the question in such a way, the participants may have subconsciously defended themselves, rather than neutral open-ended questions that would have more open results.

For example, a question for the future would be 'tell me more about your experience when purchasing medicines'. This type of question leaves the participants in control of how much they answer.

Overall, the questionnaire was kept as brief as it could be considering how many questions were asked and what types of questions were involved. Also, the language for the questionnaire was kept simple and not overly complicated.

The majority of the public would understand it as shown by the participants who answered the questionnaire. However, the definitions even though direct from source may be shortened in the future.

5.7.4 Instructions

The participants did not need much instruction on how to complete the and return the questionnaire as it was done automatically when the participants selected the finish button at the end of the questionnaire.

If certain questions needed a response and none was given it would highlight the question that needed the answer for the participant to add something in the criteria box even if it was as simple as a N/A.

When a ticked or written response was needed it was indicated at the beginning of the question, for example – please tick all that apply.

At the beginning of the questionnaire there was an introduction stating the research that was being conducted and why the information was important. A thank you message was presented both at the beginning and the end of the questionnaire to show appreciation for the participants answering the questions.

5.7.5 Sampling

The data set collected from the participants was not a significant and sufficient amount. The reason being is that not all groups were represented well enough for them to have an accurate data response.

For example, with age being one of the main focuses it is an important part of the basis of this study, but some of the groups of specific ages did not have a high response rate. Meaning that they could not be accurately represented for data trends.

The same limitation occurred with ethnicity and what country of origins and individual came from. These questions help to understand what culture an individual grew up with and if that upbringing could influence how an individual perceives different scenarios such as counterfeit medicines.

5.7.6 Distribution, Administration and Response

The questionnaire was created for an online form database – this online questionnaire was then distributed on various social media platforms to gain a worldwide presence.

The questionnaire was left open for a certain amount of time as explained previously and the results were then collected once the questionnaire had closed for new entries.

Those results were then administrated to determine if the answers were something that was workable or if a different approach to the distribution of the questions ask needed to be adapted.

Not all the information pertaining to the individuals who opened the questionnaire were acknowledged due to some of the participants closing the survey before they had answered all questions, thus eliminating them from the study as the data was not saved.

Out of all the results gathered only one set of data was removed due to not being a serious answer to any of the questions, however those answers were still recorded and mentioned earlier such as the individual whose gender was a shark.

Most if not all biased was removed when this study was conducted to show that the results were more accurately defined and could be used for determining trend such as cause and effects.

5.7.7 Coding and Analysis

The data that was collected from the questionnaire, was subjected to multiple types of statistical analysis; descriptive, inferential, casual and exploratory. The reason being that the data itself fell into different categories. The data itself is both quantitative and qualitative in nature.

The data could be illustrated via graphs and models, whilst it could be combined to create relationship and trends to help in making predictions of what could occur for the whole population.

Even though some of the data was based on hypothesis in how it was correlated and compared for analysis, there was however some data dredging due to not all of the data being analysed was due to a hypothesis being created.

5.7.8 Results

The majority of the data reported was relevant for the study except from a few answers that had a shark stated as a gender and Tatooine as an answer to where an individual lived. These answers were not added into the main data analysis however it was still recorded.

The qualitative results were unbiasedly categorised and analysed, where appropriate quotes were used to determine the thoughts of the participants and lastly the data collected was justified as the answers led to trends and characteristics of how the public perceives online pharmacies and counterfeit medicines.

5.7.9 Conclusions and Discussion

The data collected even though it was a small sample size, it has illustrated that there could be a potential link between the age of an individual and how they purchase their medicines.

Along with the relationship between the age/education and the level at which the individual identifies the harm that a counterfeit can cause and if they are able to distinguish if they have seen a counterfeit medicine before.

This can aid in understanding the principles that lead to counterfeit medicines from being prevented from entering the supply chain to end with the consumer.

This study can help to breach the gap left in today's societal knowledge of the consumers opinion of online pharmacies and counterfeit medicines.

5.8 Questionnaire

Part I:

1. With what gender do you identify with, if any?
2. In what year were you born?
3. With which ethnic group do you identify yourself?
4. What country were you born in?
5. What is your occupation?
6. What is the highest level of education you have completed?

Part II:

Self-prescribing can be defined as prescribing medicines yourself. E.g., buying cough medicine when you have a sore throat. In this survey the medicines that are being described are medicines such as antibiotics, antimalarials and such.

1. How frequently do you buy medicine(s)? (Please select all that are applicable)
    a. Never
    b. Daily
    c. Weekly
    d. Monthly
    e. Quarterly
    f. Biannually (twice a year)
    g. Annually
    h. Biennially (once every 2 years)

2. Can you identify the country of origin with regards to the medicines you buy?
    a. Yes (please specify)
    b. No

3. To the best of your knowledge can you tell you are buying from an authentic source.
    a. Yes (please specify)
    b. No

4. What was the reason behind self-prescribing?
    a. Convenience
    b. Cost efficient
    c. Lack of trust in health care professionals
    d. Any other reasons, please specify

5. What type of medicine(s) did you use when self-prescribing? (Please select all that are applicable)
    a. Analgesics (pain relief)
    b. Antibiotics
    c. Anticancer
    d. Antiemetics (anti sickness)
    e. Antihistamine (allergy)
    f. Antimalarial (treat malaria)

g. Antipyretics (fever relief)
h. Antiseptics (cuts and wound treatment)
i. Hormone replacements
j. Mood stabilisers (lithium and valpromide etc.)
k. Oral contraceptives (the pill)
l. Statins (simvastatin etc.)
m. Stimulants (amphetamine etc.)
n. Tranquilisers (diazepam and anti-psychotics)
o. Any other please specify

6. Have you ever used an online pharmacy?
a. Yes
b. No

Part III:

1. For which of the following symptoms (adverse effects) did you use the medicine(s) purchased for? (Please select all that are applicable)
a. Aches and pains
b. Cough
c. Diarrhoea
d. Fever
e. Nasal congestion
f. Runny nose
g. Skin wounds
h. Sore throat
i. Vomiting
j. Any others please specify

2. When you selected the medicine(s) what was your solution based on? (Please select all that are applicable)
a. My own experience
b. Opinion of family members
c. Previous doctor's prescription
d. Recommendation on online forums
e. Recommendation by community pharmacists
f. The advertisement
g. Opinion of friends
h. If any other reasons, please specify

3. When you purchased medicine(s) what were the deciding factor(s)? (Please select all that are applicable)
a. The brand
b. The price
c. The type (e.g., penicillin, ciprofloxacin or erythromycin etc.)
d. Possible adverse reactions
e. Desired reaction
f. Indications for use
g. Any others please specify

4. How did you know what correct dosage of medicine(s) to use were? (Please select all that are applicable)

a. From the Internet
b. From my previous experience
c. By consulting a doctor/GP
d. By consulting a pharmacist
e. By checking the package insert
f. By guessing the dosage
g. By consulting friends or/and family members
h. Any other reason please specify

5. On a scale of 1 - 10 how much do you trust online pharmacies? (1- untrustworthy, 10 – trustworthy)

6. Do you change the dosage of your medicine during a course of treatment?

a. Yes
b. Sometimes
c. No

If yes, how often did you change and what were the reasons?

7. Would you switch your medicine during a course of treatment?

a. Yes
b. Sometimes
c. No

If you do, please state how often and whether it is like for like (e.g., antibiotic for antibiotic) or different (antibiotic for anti-inflammatory)?

8. Have you ever found out that you have taken the same antibiotics/antimalarial just under a different name at the same time? (For example, Paracetamol maybe called Panadol).

a. Yes (please specify)
b. No

9. What do you do when you encounter an adverse reaction? (Please select all that are applicable)

a. Switch to another medicine
b. Consult a GP
c. Consult a pharmacist
d. Nothing
e. Stop taking the medicine
f. Consult family members/ friends
g. If any other, please specify

Part IV:

As Stated by the World health Organisation a counterfeit is: "A product that is deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting occurs with both branded and generic products and counterfeit medicines may include

products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredient or with insufficient active ingredients".

Whereas "Substandard drugs are manufactured with the intent of making a genuine pharmaceutical product, but the manufacturer saves costs by not following GMP (Good Manufacturing Practice) or using poor quality raw materials. Another potential problem relates to inadequate storage or transport conditions, leading to deterioration of the product. The performance of such medicines is questionable".

7. Are you concerned that you may have taken counterfeit and/or substandard medicine(s)?
   a. Yes (please explain your concerns)
   b. Somewhat
   c. No

8. How did you decide to use a certain online pharmacy? (Please select all that are applicable)
   a. Friends' recommendation
   b. Family recommendation
   c. Own experience
   d. The advertisement
   e. If any other, please specify
   f. For any other reason please specify

9. How would you check the authenticity of your medicine? (Please select all that are applicable)
   a. Barcode
   b. Medicine tag
   c. Ask a doctor
   d. Ask a pharmacist
   e. If other, please specify

10. Have you ever encountered a counterfeit medicine?
    a. Yes
    b. No

If yes, how did you identify it?
   a. Appearance
   b. Label
   c. Never encountered one
   d. Packaging
   e. Side Effects
   f. Any other reason, please specify

11. On scale of 1 to 10, what do you believe is the extent of harm resulting from counterfeit medicines? (1 - Very mild, 10 - Lethal):

Any Further Comments - (please state any online pharmacies that you may use of that you know about below):

Chapter Six. Conclusion & Summary

This project has investigated the issues surrounding counterfeit/falsified medicines. The main topic areas of discussion and review were as follows; the increasing issue caused by counterfeit/falsified medicines, the public perception of such drugs, the overall use of medicines and the distribution of medicines, the analysis of the online pharmacies and the distribution of medicines, the quantification of counterfeits and the law that regulates the supply chain.

As discussed in the introduction, the issue of counterfeit medicines is a very serious threat to the public's health that has shown traction in recent years and is continuously growing, especially in the case of counterfeit medicines.

Other studies have surmised that the threat of counterfeits is non-discriminatory in respect of which countries are affected. Everyone is at risk. On record 50% of products sold are counterfeits and 30% are counterfeit medicines.

For a future safe from counterfeits certain measures need to be taken to protect the public from harm. One such measure would be to first fully understand the reasons influencing the purchase of medicines even if it seems like a common notion.

The finding of Chapter Five suggests that medicines are purchased primarily for relief and healing, with the exception of a few cases where individuals buy medicines for bodily control (e.g contraceptive or hormone control).

These results are found to be independent of the age groups, education levels and genders. Thus, illustrating that despite the ideals of generations growing up and the modern and postmodernism view as a framework there is not a conclusive rule or trend to follow. The same can be assumed about the frequency of purchase and the reasons for purchasing medicines, experience is the key to everything.

However, if an individual purchased medicine more frequently, they would be more inclined to trust the source of purchase, even if the purchasing occurred from an online source.

Some individuals did not realise that a pharmacy who had an online delivery service was classed as an online pharmacy, which suggests that the public need to be made aware of the distribution and risk of buying form online sources.

Despite the purchases from physical pharmacies being known to be a trustworthy source of pain relief, the route of distribution using the Internet has not been inspected regularly or uniformly in one place.

Chapter 4 analysed the route of distribution for medicines including online pharmacies. Not only do online pharmacies offer deals and sales promotions of some description, they can offer prescription medicines without a consultation from a medical practitioner.

This alone can entice a clientele or consumer base. The study also confirmed the known fact that offering deals encourages individuals to purchase more than they need; especially if it is a prescription medicine such as antibiotics, which could cause serious harm in the future.

The individual may consume more than the recommended dose for the ailment it is trying to control, or at the other end of the spectrum they may not have enough to combat the issue.

As shown in Chapter Four the online pharmacies are outnumbered by the physical brick and mortar pharmacies. However, the distribution range when compared illustrates those online pharmacies outreach the range of the brick and mortar.

This alone demonstrates that if the online pharmacies gain traction, then the brick-and-mortar pharmacies would eventually become redundant as is the way with small vendors competing with large chains.

The next logical step as illustrated in this research is the isolation and detection of counterfeits within the supply chain. This follows on from the previously discussed perception of counterfeits and the distribution of medicines.

To do this they must first be identified, and as it has been tested in previous studies, the only true way of discovering a counterfeit is to analyse the medicines chemical compositions and phases. One such way of this identification process is to use spectroscopic techniques such as FT-NIR that was used in Chapter Two.

The identification of counterfeit ciprofloxacin tablets was successful in Chapter Two, where five counterfeit batches were detected, 14 authentic and nine generic batches were identified as well. The regions of origin of the medicines were also ascertained and grouped with the aid of PCA.

Even if the manufacturer was not the same, the medicines from the same region clustered together, which could potentially show that the regulations within the regions have an impact on the manufacturing process. More research would need to be conducted to confirm this hypothesis as discussed in recommendations further on.

PCA was useful in determining counterfeit medicines, it was also helpful with determining the composition of the binary mixtures. It catalogued the change of ratio within the mixture from 100% difference between the components, 100:0 ratio, to a 50:50 ratio mix.

The differences enabled clusters to be formed, which in itself suggested the strength of the FT-NIR and the PCA combination. By using a various ratio mix, it could be ascertained that even the smallest number of components could be detected, and a counterfeit match could be found.

The use of CWS on the other hand proved an efficient protocol to correlate various classes of antibiotics and the chemical components themselves. It justly illustrated that the same component /medicine when compared to itself shows a very high match.

On the other hand, various classes of antibiotics had some similar components and some that were completely unique/rare to the antibiotic class. Also, as illustrated with the binary mixtures of PCA, the components that have a similar chemical structure

tend to cluster together, when CWS is applied the correlation becomes more significant.

Due to similar mixtures in both PCA and CWS showing almost parallel results, it demonstrates that stronger instruments or techniques would be needed to completely isolate the chemical present in a mixture, one such method would be to use GCMS.

All of the findings illustrated in Chapter Four & Five showed the significance of the threat of counterfeit medicines and the possibility for inflicting a health risk on the public as they can come from any source and throughout the supply chain.

Counterfeit/falsified medicines are becoming a health risk with the dangers of the medicines themselves being harmful to a patient's progress, and the public maybe not being aware fully of the hazards of counterfeits or the process of purchasing medicines online.

A path for discouraging falsified medicines from entering the supply chain is to make it as difficult as possible for those who wish to make profit from these falsified products.

Therefore, with the understanding of how to identify a counterfeit being the primary function of this study along with the inclusion of public perception, the law is the secondary. Countless changes have been made to the laws over the years to reduce the risk of counterfeit/ falsified medicines from entering the supply chain.

To combat the risk of counterfeit/ falsified medicines entering the supply chain and ultimately reaching the patients, the Falsified Medicines Directive (Directive 2011/62/EC) was created in 2011 and published on the 2nd January 2013. This EU directive was created with the aim of preventing the entrances of counterfeit/falsified medicines into the legal supply chain.

Eventually it was amended with the Commission Delegated Regulation (EU) 2016/161 that was published on the 9th February 2016 and implemented February 2019. This amendment as discussed in Chapter Three, was created to set out detailed

rules for the new safety features that would be used on the medicinal packages that are for human use.

As demonstrated in Chapter Three the FMD contains new safety features on the medicine's packaging, which incorporate barcodes and anti-tampering strips. With these safety features, the number of counterfeits should be reduced.

However, the implementation of such features may cause some disruptions within the supply chain system for the consumers and pharmacies, such as hospital pharmacies. The reason being that there are some flaws within the system as discussed in Chapter Three. Some of these flaws are:

1. The UI barcodes may not be scanned in the system
2. There could be duplicates of the UI Code
3. The counterfeit could pass through the supply chain and the authentic medicine stopped.
4. The ATD can be tampered with, without much hassle.
5. Added pressure would be on the staff to check the packages thoroughly, which would mean a few more jobs just for this purpose.

Overall, the identification of the public perceptions leads to the identification of the distribution methods such as online pharmacies. Those distributional areas lead to the identification of the counterfeits entering the supply chain and the supply chain must adhere to the laws and regulations set. Separately the chapters tell a picture, together they explain how the future will proceed. For counterfeits to be truly eradicated the public need to be much more informed.

Thus, by understanding the public perception and motivation for purchasing online, and who is more likely to, more advertisement in awareness can be aimed at a

target audience. Therefore, the public become knowledgeable and the threat to the collective health diminishes.

6.1 Outlook - Strengths and Limitations

6.1.1 Quantification of Counterfeit Medicines

The identification of counterfeit ciprofloxacin tablets was successful in Chapter Two, where five counterfeit batches were detected, 14 authentic and nine generic batches were identified as well.

The regions of origin of the medicines were also ascertained and grouped with the aid of PCA. Even if the manufacturer was not the same, the medicines from the same region clustered together, which could potentially show that the regulations within the regions have an impact on the manufacturing process.

Even though the identification methods used (CWS & PCA) were able to identify counterfeit medicines, the methods themselves could not easily distinguish between batches of the various groups.

When placed together the counterfeits stood out against the generic and the authentic, but when clustered together the counterfeit batches posed a difficulty for analysis.

PCA was useful in determining counterfeit medicines, it was also helpful with determining the composition of the binary mixtures. It catalogued the change of ratio within the mixture from 100% difference between the components, 100:0 ratio, to a 50:50 ratio mix.

The differences enabled clusters to be formed, which in itself suggested the strength of the FT-NIR and the PCA combination. By using a various ratio mix, it could be ascertained that even the smallest number of components could be detected, and a counterfeit match could be found.

The use of CWS on the other hand proved an efficient protocol to correlate various classes of antibiotics and the chemical components themselves. It justly

illustrated that the same component /medicine when compared to itself shows a very high match.

On the other hand, various classes of antibiotics had some similar components and some that were completely unique/rare to the antibiotic class. Also, as illustrated with the binary mixtures of PCA, the components that have a similar chemical structure tend to cluster together, when CWS is applied the correlation becomes more significant.

The binary mixtures themselves were beneficial to be used as they could help show the accuracy in which the FTNIR functioned. However, for the future more mixture at a greater level would need to be analysed such as tertiary mixtures as explained previously.

If it was found that there was not sufficient tablet data in the future, but there was an authentic batch available, tablet/powder models may be used. These powder models may be created by; mixing a dilution of crushed tablets or API excipients, standard addition of crush tablets to the API or sequential addition of various excipients to the crush tablets.

These models can be used in conjunction with the other powder mixtures such as the binary and tertiary ones. The one drawback with these methods is that only powdered tablets can be analysed using the data gathered where as new models would be needed if capsules and liquid solvents were used.

Due to similar mixtures in both PCA and CWS showing almost parallel results, it demonstrates that stronger instruments or techniques would be needed to completely isolate the chemical present in a mixture, one such method would be to use GCMS.

One limitation that was identified during the experimental process was that there were not enough batches of medicines available to set a sufficient sample size. By not having a large data set with samples collected from multiple regions but also from multiple manufacturers, a true trend in the data could not be successfully determined.

For example, one question to be answered in the future would be 'which manufacturer or region of supply is more heavily affected by counterfeit medications?'

All of the findings illustrated in Chapter Five showed the significance of the threat of counterfeit medicines and the possibility for inflicting a health risk on the public as they can come from any source and throughout the supply chain.

6.1.2 Effectiveness of the FMD

Even though the FMD takes into consideration each stage of the supply chain, and that will subsequently limit the risks of a counterfeit being procured, it fails to realise that there are still holes in the directive that can be abused.

One such example being that the blister packs themselves could be taken out of the packets and the counterfeit version could be reinserted in their place, the blister packs would need a stamp of production (manufacturer), the expiry date and batch number.

The authentic versions of the counterfeit could then be used at a later date, some could be crushed and mixed in with the other batch materials. The anti-tampering strips are the same, there is insufficient deterrent to prevent someone from removing the strip and placing a new one in its place when the pack is due for shipping further along the supply chain. It has been proven that it can be tampered with without damaging it or leaving any evidence that it has been tampered with.

The blister packs themselves or the packaging in which they are contained do not have a guarantee that the medicines within them are what they say they are. For this to be overcome the blister packs themselves could be scanned at random stages in the supply chain by instruments that can examine the tablets contents through the blister pack, thus limiting further the risk of counterfeits being supplied to the public.

As illustrated in Chapter Five, the only way to thoroughly examine medicines and properly identify a counterfeit is with various scientific instruments, this has had proven success for many years.

A disadvantage with this process is that it would be time consuming and cause waste of the ATDs when they need to be replaced at the stage that they are opened to scan. There is no guarantee that the seal would break successfully recording opening of the package which would skew results later on in the supply chain if that package was tampered with.

One thought would be for the ATD to have a design that only those that produced them and scanned them would know, a hidden identification that would not be possible to replicate without a certain type of machine. It would also be beneficial for the seals to be heat resistant so that they cannot be removed as stated in Chapter Six.

As an extra precaution the QI codes could be printed on both the blister packs and a feature of the anti-tampering strip. This unfortunately does not limit the risk of the codes being reproduced with a falsified version being passed into the supply chain; it does however limit the risk with regards to replacement of the blister packs.

Overall, I accept as true that with any regulation there will be growing pains for individuals and organisations to comply with, agree to and implement such regulations.

My belief is that by analysing the FMD and various aspects of the problem resulting from counterfeit/falsified medicines, the public, health care professionals and policy regulators have a better understanding in creating new systems to target the problem.

The FMD is one step of many that have been introduced. However, more of an effort needs to be made towards the public and patients to make them aware of the risks inherent in purchasing medicines online. By killing the demand, the supply will reduce, thus limiting the risk of health issues and falsified medicines entering the supply chain.

In my opinion the FMD needs to be re-evaluated to become second nature for everyone and not a tedious task that is faulty. Meaning that if there are purchases

directly from the manufacturer, just as hospitals do, then only various scans of batches need to be conducted for quality control. Only time will tell its effectiveness, until then more analysis needs to be conducted.

6.1.3 Online Pharmacy Data

The data collected for research regarding the online pharmacies' aids in the future knowledge of how to further prevent counterfeits; from entering the supply chain, from giving the producers profit and gain, and to reduce the risk posed to the public's health.

The online pharmacies have an influence on an individual enabling them to confidently self-prescribe medication, be it from simple cold and flu treatment to antibiotics for infection.

These influences also demonstrate how the public is targeted with regards to certain sales and profit margins for the pharmacies.

Some of the strengths of the online pharmacy data collection is that multiple sources were found and categorised. The whole country was able to be configured in a way that the online pharmacies could be mapped.

The data that was able to be analysed whether the pharmacy is geographically situated or what types of medicines can be sold. Even the privacy disclaimers and contact details that are obtained could be categorised through extensive research.

One of the limitations is only the information that can be seen at face value is gathered such as prices or reviews, rather than the information that is used solely by the website creators, such as online traffic.

By viewing how much the website is seen and the rough the IP address (location) of the consumer. By tracking how many people visit a website the true value of an online pharmacies influence can be ascertained to a greater degree of accuracy.

Another limitation of the research is that it took a considerable amount of time to gain the data but to also categorise it in a way that would be analytically beneficial. For the information to be sufficient in both gathering and analysing the data itself needs to be collated in a way that would thorough and not time consuming.

6.1.4 Questionnaire Study

Every part of research has both strength and weaknesses. By understanding those it makes it easier to succeed in the future and overcome the obstacles that are faced. On that note one limitation that was discovered in this study was that when the participants can answer questions in their own way rather than a closed question and tick box answers.

This enabled inappropriate answers in the study, one example being 'which gender do you identify with' and the answer coming back as 'shark'. This makes the study subject to vulnerability.

A response to counter this is to have three boxes, one for male, female and other, the other box will then have a further response of 'please specify'. That way it will make the data closed and outliers such as imputes like shark can be discarded from the results.

On the other hand, one strength of this study is how it was distributed on social media such as LinkedIn and Facebook, as well as via email distribution. The reason this factor is a strength is because the study had a wide reach and participants from all over the world had an opportunity to answer.

As can been seen in the demography there were participants from Australia, France, Malaysia and Portugal to name but a few.

Another limitation of this study is that the ethnicity and birthplace/nationality could not be used further. The reason being that the number of participants could not represent the various ethnic backgrounds and the nationalities around the world well enough for the data to be used in a conclusive study.

Future researchers could use different means of distribution - such as emails to universities around the world or collection booths in different countries/ overpopulated cities e.g., London – to overcome this problem.

However, another strength of this study is that the participants are of a wide range of ages, from 22 years to 79 years of age. The reason that this is so important is that it shows that society adapts and changes, and with that the use of the Internet becomes ingrained into society. The use of the Internet is important in this study as a primary topic relates to online pharmacies and how the public perceives them.

References:

Abraham, D. and Burger, A., 2003. *Burger's medicinal chemistry and drug discovery.* 6th ed. Hoboken, N.J.: John Wiley & Sons, Inc.

Abrantes, C., Duarte, D. and Reis, C., 2016. An Overview of Pharmaceutical Excipients: Safe or Not Safe? *Journal of Pharmaceutical Sciences*, 105 (7), 2019-2026.

Adak, N., 2010. Past to today sociological approach to environment. *Ege Akademik Bakış Dergisi* [online], 10(1), pp. 371 -382.

Alumuzaini, T., Choonara, I., Sammons, H., 2013. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open* [online], 3(8), pp. 1-7.

Andalo, D., 2004. Counterfeit drugs set alarm bells ringing. *The Pharmaceutical Journal*. [online], Volume 273, No 7316, pp. 341.

Appel, A., 2011. *Security Seals on Voting Machines. ACM Transactions on Information and System Security*, 14(2), pp.1-29.

Appelbaum, P. and Hunter, P., 2000. *The fluoroquinolone antibacterial: past, present and future perspectives.*

Assi, S., 2016. *Evaluating handheld spectroscopic techniques for identifying counterfeit medicines* [online], UK: Bournemouth University

Assi, S., Watt, RA., Moffat, AC., 2011. On the qualification of ciprofloxacin in proprietary tablets using handheld Raman spectroscopy. *Journal of Raman Spectroscopy* [online], 43(2012), pp. 1049-1057.

Atkins, P., De Paula, J. and Atkins, P., 2002. *Atkins' Physical Chemistry.* Oxford: Oxford University Press.

Auf der sicheren Seite., 2020. *Zahlen Und Fakten - Auf Der Sicheren Seite* [online]. Available at: <http://www.auf-der-sicheren-seite.at/das- milliardengeschaeft/> [Accessed 20 March 2019].

Badr, A., 2011. *Near Infra-Red Spectroscopy. Wide Spectra of Quality Control.* London: IchtechOpen.

Barnes, R., Dhanoa, M. And Lister, S., 1989. Standard Normal Variate Transformation and De-Trending of Near-Infrared Diffuse Reflectance Spectra. *Applied Spectroscopy* [online], 43 (5), pp. 772-777.

Bengtsson, M., 2016. How to plan and perform a qualitative study using content analysis. *NursingPlus Open* [online], 2, pp. 8-14.

Bewick, V., Cheek, L. and Ball, J., 2003. Statistics Review 7: Correlation and Regression. *Critical Care* [online], 7(6), pp. 451 - 459.

BioSpcae 2021. *Top 20 Pharma Companies by Market Cap in Q1 2019* | BioSpace [online]. BioSpace. Available from: https://www.biospace.com/article/top-20-pharma-companies-by- market-cap-in-q1-2019/ [Accessed 29 Jan 2021].

Blackstone, Erwin A., Fuhr Joseph P., Pociask, Steve., 2014. The Health and Economic Effects of Counterfeit Drugs. *The American Health and Drug Benefits Journal* [online], 7(4), pp. 216 – 224.

Blandeau, J., 1999. Expanded activity and utility of the new fluoroquinolones: A review. *Clinical Therapeutics*, [online] 21 (1), pp 3-40.

Boy, D., Well, M., Kinzig-Schippers, M., Sörgel, F., Ankel-Fuchs, D. and Naber, K., 2004. Urinary bactericidal activity, urinary excretion and plasma concentrations of gatifloxacin (400 mg) versus ciprofloxacin (500 mg) in healthy volunteers after a single oral dose. *International Journal of Antimicrobial Agents*, 23, 6-16.

Brady, D., 2020. *Comparing "Bricks and Mortar" Store Sales with Online Retail Sales - Office for National Statistics* [online]. Ons.gov.uk. Available at: <https://www.ons.gov.uk/businessindustryandtrade/retailindustry/articles/comparingbricksandmortarstoresalestoonlineretailsales/august2018 > [Accessed 14 Feb 2019].

Brereton, R., 2007. *Applied chemometrics for scientists* [online]. Hoboken, N.J.: Wiley.

Brereton, R., 2009. *Chemometrics for Pattern Recognition* [online]. New York: Wiley.

Brunner, M., Langer, O., Dobrozemsky, G., Müller, U., Zeitlinger, M., Mitterhauser, M., Wadsak, W., Dudczak, R., Kletter, K. and Müller, M., 2004. Ciprofloxacin, a New Positron Emission Tomography Tracer for Noninvasive Assessment of the Tissue Distribution and Pharmacokinetics of Ciprofloxacin in Humans. *Antimicrobial Agents and Chemotherapy*, 48 (10), 3850-3857.

Buckley, G. and Gostin, L., 2014. *Countering The Problem Of Falsified And Substandard Drugs.* Washington: National Academies Press.

Chatwal, G.R., 2009. *Spectroscopy* [online]. Mumbai: Himalaya Pub. House

Christensen, S., 2020. *Tens Of Thousands Die In Africa Each Year Due To Fake Drugs*. [online] U.K. Available at: <https://uk.reuters.com/article/us- westafrica-drugs-fake/tens-of-thousands-die-in-africa-each-year- due-to-fake-drugs-idUKKCN1NK23I> [Accessed 30 March 2019].

Clark, D., 2019. *Population of regions in England in 2018* [online]. Statista. Available from https://www.statista.com/statistics/294681/population- england-united-kingdom-uk-regional/ [Accessed 5 Sep 2019].

Cozzarelli, N., 1980. *DNA gyrase and the supercoiling of DNA*. Science, 207 (4434), 953-960.

Davies, J., 2007. *The pharmacological basis of therapeutics. Occupational and Environmental Medicine*, 64 (8), e2-e2.

Dax, S., 1997. *Antibacterial chemotherapeutic agents*. London: Blackie Academic & Professional.

de Almeida, M., Saraiva, M., de Souza, M., da Costa, C., Vicente, F. and Lourenço, M., 2007. Synthesis and antitubercular activity of lipophilic moxifloxacin and gatifloxacin derivatives. *Bioorganic & Medicinal Chemistry Letters*, 17 (20), 5661-5664.

Dégardin, K., Guillemain A., Guerreiro, NV., Roggo, Y., 2016. Near infrared spectroscopy for counterfeit detection using large database of pharmaceutical tablets. *Journal of Pharmaceutical and Biomedical Analysis* [online], 128, pp. 89-97.

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

Dégardin, K., Roggo, Y., Margot, P., 2013. Understanding and fighting the medicine counterfeit market. *Journal of Pharmaceutical and Biomedical Analysis* [online], 87(2014), pp 167-175.

Dégardin, K., Roggo, Y., Margot, P., 2014. Forensic intelligence for medicine anti-counterfeiting. *Forensic Science International*/[online] [Accessed], 248(2015), pp. 15-32.

DeGroot, L., Lazaurus, J., Amino, N., 2016. *Chronic (Hashimoto's) Thyroiditis in: Jameson, JL. Endocrinology: Adult and Paediatric* [online]. 7th Edition. Amsterdam, Netherlands: Elsevier, pp. 1515-1527.

Delepierre, A., Gaypot, A., Carpentier, A., 2012. Update on counterfeit antibiotics worldwide; Public health risks. *Médecine et maladies infectieuses* [online] [Accessed], 42(6), pp. 247-255.

Di Giulio, A. and Bonamore, A., 2008. *Globin Interactions with Lipids and Membranes. Methods in Enzymology*, pp.239-253.

Dick, T,. 1835. *The Philosophy of Religion. In; The Christian Library. A weekly publication of religious works*. [online]. Volume 2. New York: Thomas George. Pages 737 – 798.

Dollery, C., 1999. *Therapeutic drugs*. Edinburgh: Churchill Livingstone.

Donaldson, M., 1994. *Health Data In The Information Age: Use, Disclosure, And Privacy.* Washington: National Academy Press.

Duffin, J,. 2016. *History of Medicine, Second Edition: A Scandalously Short Introduction*. University of Toronto Press.

Dunteman, G., 2016. *Principal components analysis*. Newbury Park [etc.]: Sage Publications.

EDQM, eTACT, 2020. *EDQM, eTACT,.* [online] Edqm.eu. Available at: <https://www.edqm.eu/medias/fichiers/etact_progression.pdf> [Accessed 29 March 2020].

Efthymiopoulos, C., Bramer, S., Maroli, A. and Blum, B., 1997. Theophylline and Warfarin Interaction Studies with Grepafloxacin. *Clinical Pharmacokinetics*, 33 (Supplement 1), 39-46.

Einax, J., 1995. *Chemometrics in Environmental Chemistry - Statistical Methods*. Berlin, Heidelberg: Springer Berlin Heidelberg.

EMA, 2020. *Falsified Medicines: Overview - European Medicines Agency.* [online] European Medicines Agency. Available at: <https://www.ema.europa.eu/en/human-regulatory/overview/public- health-threats/falsified-medicines-overview> [Accessed 29 March 2020].

Eser, Z., Kurtulmusoglu, B., Bicaksiz, A. and Sumer, S., 2015. Counterfeit Supply Chains. *Procedia Economics and Finance*, 23, pp.412-421.

EUIPO., 2020. *€10.2 billion lost every year across the EU due to fake medicines.* [online]. Alicante, Spain: European Union Intellectual Property Office. E-03008. Available at: https://euipo.europa.eu/tunnel eb/secure/webdav/guest/document_library/observatory/resources/research-and-studies/ip_infringement/study9/Press_release-pharmaceutical_sector_en.pdf

Fan, P., Gao, Y., Zheng, M., Xu, T., Schoenhagen, P. and Jin, Z., 2018. Recent progress and market analysis of anticoagulant drugs. *Journal of Thoracic Disease*, 10(3), pp.2011-2025.

Farhi, D., Hotz, C., Poupet, H., Gerhardt, P., Morand, P., Poyart, C., Sednaoui, P., Avril, M. and Dupin, N., 2009. Neisseria gonorrhoeae Antibiotic Resistance in Paris, 2005 to 2007: Implications for Treatment Guidelines. *Acta Dermato Venereologica*, 89 (5), 484-487.

Farrukh, M., Tariq, M., Malik, O. and Khan, T., 2019. Valsartan recall: global regulatory overview and future challenges. *Therapeutic Advances in Drug Safety*, 10, pp.204,209,861,882,345.

Feliciano, J., Teper, E., Ferrandino, M., Macchia, R., Blank, W., Grunberger, I. and Colon, I., 2008. The Incidence of Fluoroquinolone Resistant Infections After Prostate

Biopsy—Are Fluoroquinolones Still Effective Prophylaxis? *Journal of Urology*, 179 (3), 952-955

Frontini, R., Miharija-Gala, T. and Sykora, J., 2013. EAHP survey 2010 on hospital pharmacy in Europe: parts 4 and 5. Clinical services and patient safety. *European Journal of Hospital Pharmacy*, 20(2), pp.69-73.

Gaudiana, MC., Antoniella, E., Bertocchi, P., Valvo, L., 2010. Development and validation of a reversed-phase LC method for analysing potentially counterfeit antimalarial medicines. *Journal of Pharmaceutical and Biomedical Analysis* [online] 53, 158-164.

General Pharmaceutical Council, 2019. *General Pharmaceutical Council* [online]. Pharmacyregulation.org. Available from: https://www.pharmacyregulation.org/ [Accessed 20 Sep 2019].

General Pharmaceutical Council. 2020. *Our Governing Council | GeneralPharmaceutical Council* [online]. <https://www.pharmacyregulation.org/about-us/who-we-are/gphc- council> [Accessed 20 Sep 2019].

gov.UK, 2020. *Alerts and Recalls for Drugs and Medical Devices*. [online] GOV.UK. Available at: <https://www.gov.uk/drug-device-alerts> [Accessed 29 March 2020].

Green MD. 2006. Antimalarial drug resistance and the importance of drug quality monitoring. *Journal of Postgraduate Medicine* [online] [Accessed], 52, Pages 288 –290.

Green, MD., Hostetler, DM., Nettey, H., Swamidoss, Ranieri, N., and Newton, PN., 2015. Integration of Novel Low-Cost Colorimetric, Laser Photometric, and Visual Fluorescent Techniques for Rapid Identification of Falsified Medicines in Resource-Poor Areas: Application to Artemether– Lumefantrine. *American Journal of Tropical Medicine and Hygiene* [online], 92(6), Pages 8-16.

Green, MD., Nettey, H., Wirtz, RA., 2008. Determination of oseltamivir quality by colorimetric and liquid chromatographic methods. *Emerging Infectious Diseases* [online] [Accessed], 14, Pages 552–556.

Guo, Q., Wu, W. and Massart, D., 1999. The robust normal variate transforms for pattern recognition with near-infrared data. *Analytica Chimica Acta*, 382 (1-2), 87-103.

Guo, Q., Wu, W. And Massart, D., 1999. The robust normal variate transforms for pattern recognition with near-infrared data. *Analytica Chimica Acta*, 382 (1-2), 87-103.

Gupta, R,. 2017. *Reproductive and Developmental Toxicology*. Saint Louis: Elsevier Science.

Gürkan, H., 2012. Postmodernism and Cinema: Postmodernism Discourse in themovie of David Lychs "Blue Velvet". *Akdeniz Üniversitesi İletişim Fakültesi Dergisi* [online], Issue 17, pages 102 – 110.

Hariharan, P. and Hariharan, P., 2007. *Basics of Interferometry* [online]. Amsterdam, Netherlands: Elsevier

Herold, C., Ocker, M., Ganslmayer, M., Gerauer, H., Hahn, E. and Schuppan, D., 2002. Ciprofloxacin induces apoptosis and inhibits proliferation of human colorectal carcinoma cells. *British Journal of Cancer*, 86 (3),443-448.

Hirai, K., Aoyama, H., Irikura, T., Iyobe, S. and Mitsuhashi, S., 1986. Differences in susceptibility to quinolones of outer membrane mutants of Salmonella typhimurium and Escherichia coli. *Antimicrobial Agents and Chemotherapy*, 29 (3), 535-538.

Ho, P., Que, T., Tsang, D., Ng, T., Chow, K. and Seto, W., 1999. Emergence of Fluoroquinolone Resistance among Multiply Resistant Strains of Streptococcus pneumoniae in Hong Kong. *Antimicrobial Agents and Chemotherapy*, 43 (5), 1310-1313.

Hogerzeil, HV., De Goeje, MJ., Abu-Reid, IO., 1991. Stability of essential drugs in Sudan. *The Lancet* [online], 338(8769), pp. 754-755.

Houston, P., 2012. *Chemical Kinetics and Reaction Dynamics*. Dover Publications.

Howarth, O., 1973. *Theory of Spectroscopy*. London: Thomas Nelsons and Sons Ltd

Islam, M., Yoshida, N., Kimura, K., Uwatoko, C., Rahman, M., Kumada, S., Endo, J., Ito, K., Tanimoto, T., Zin, T. and Tsuboi, H., 2018. An *Investigation into the Quality of Medicines in Yangon, Myanmar. Pharmacy*, 6(3), p.96.

Jee, R.D., 2016. Infrared Spectroscopy. In: Moffat, A.C., Osselton, M.D. and Widdop, B. *Clarke's Analysis of Drugs and Poisons* [online]. London: Pharmaceutical Press,

Jolliffe, I., 2010. *Principal component analysis*. New York: Springer.

Kahraman, A., 2015. Relationship of Modernism, Postmodernism and Reflections of it on Education. *Procedia - Social and Behavioural Sciences* [online],174, pp. 3991-3996.

Kayumba, PC., Risha, PG., Shewiyo, D., Msami, A., Masuki, G., Ameye, D., Vergote, G., Ntawukuliryayo, JD., Remon, JP., Vervaet, C., 2004. The quality of essential antimicrobial and antimalarial drugs marketed in Rwanda and Tanzania: influence of tropical storage conditions on in vitro dissolution. *Journal Clinical Pharmacology & Therapeutics* [online], 29, pp. 331–338.

Kelesidis, T., Falagas, ME., 2015. Substandard/Counterfeit Antimicrobial Drugs. *Clinical Microbiology Reviews* [online], 28(2), pp. 443-464.

Kelesidis, T., Kelesidis, I., Rafailidis, PI., Falagas, ME., 2007. Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence. *Journal of Antimicrobial Chemotherapy* [online], 60, pp. 214-236.

Kepa, L., Oczko-Grzesik, B., Stolarz, W. and Sobala-Szczygiel, B., 2005. Drug-induced aseptic meningitis in suspected central nervous system infections. *Journal of Clinical Neuroscience*, 12 (5), 562-564.

Khan, M., Akazawa, M., Dararath, E., Kiet, H., Sovannarith, T., Nivanna, N., Yoshida,

N. and Kimura, K., 2011. Perceptions and practices of pharmaceutical wholesalers surrounding counterfeit medicines in a developing country: a baseline survey. *BMC Health Services Research*, 11(1).

Klandermans, B., 2007. *Methods Of Social Movement Research*. Minneapolis, Minn: University of Minnesota Press.

Komsta, L., Vander Heyden, Y. And Sherma, J., 2018. *Chemometrics in chromatography*. America:CRC Press

Krakowska, B., Custers, D., Deconinck, E., Daszykowski, M., 2016. Chemometrics and the identification of counterfeit medicines – A review. *Journal of Pharmaceutical and Biomedical Analysis* [online], 127, Pages 112-122

Krekora, M,. 2008. *Contract manufacturing of medicines*. Austin, Tex.: Biggleswade.

Kubin, R., 1993. Safety and efficacy of ciprofloxacin in paediatric patients —Review. *Infection*, 21 (6), 413-421.

Laurent, M. and Levallois-Barth, C., 2015. Privacy Management and Protection of Personal Data. *Digital Identity Management* [online], pp.137-205.

Lee, C. and Ronald, A., 1987. Norfloxacin: Its potential in clinical practice. *The American Journal of Medicine*, 82 (6), 27-34.

Lennard, M., 2004. Clarke's Analysis of Drugs and Poisons. *British Journal of Clinical Pharmacology*, 58(1), pp. 99.

Leone, M., 2002. Brain tissue penetration of ciprofloxacin following a single intravenous dose. *Journal of Antimicrobial Chemotherapy*, 50 (4), 607- 609.

Lietava, J., 1992. Medicinal plants in a Middle Paleolithic grave Shanidar IV? *Journal of Ethnopharmacology*, 35(3), pp.263-266.

Lipman, J., Allworth, A. and Wallis, S., 2000. Cerebrospinal Fluid Penetration of High Doses of Intravenous Ciprofloxacin in Meningitis. *Clinical Infectious Diseases*, 31 (5), 1131-1133.

Liu, L., Guo, K., Lu, J., Venkatraman, S., Luo, D., Ng, K., Ling, E., Moochhala, S. and Yang, Y., 2008. Biologically active core/shell nanoparticles self- assembled from cholesterol-terminated PEG–TAT for drug delivery across the blood–brain barrier. *Biomaterials*, 29 (10), 1509-1517.

Lon, CT., Tsuyuoka, R., Phanouvong, S., Nivanna, N., Socheat, D., Sokhan, C., Blum, N., Christophel, EM., Smine, A., 2006. Counterfeit and substandard antimalarial drugs in Cambodia. *Transactions of the Royal Society of Tropical Medicines and Hygiene* [online],100, Pp 1019-1024.

Lubasch, A., Keller, I., Borner, K., Koeppe, P. and Lode, H., 2000. *Comparative Pharmacokinetics of Ciprofloxacin, Gatifloxacin, Grepafloxacin, Levofloxacin, Trovafloxacin, and Moxifloxacin after Single Oral Administration in Healthy Volunteers. ,* 44 (10), 2600-2603.

Manley, M., 2014. Near-infrared spectroscopy and hyperspectral imaging: non-destructive analysis of biological materials. *Chemical Society Reviews*[online], 43 (24), pp. 8200-8214.

Mao, Z., Ma, L., Gao, C. and Shen, J., 2005. Preformed microcapsules for loading and sustained release of ciprofloxacin hydrochloride. *Journal of Controlled Release*, 104 (1), 193-202.

MHRA, 2020. *Services and Information - Medicines and Healthcare Products Regulatory* Agency - GOV.UK. [online] Gov.uk. Available at: <https://www.gov.uk/government/organisations/medicines-and- healthcare-products-regulatory-agency/services-information> [Accessed 28 Jan 2020].

Moffat, AC., Assi, S., Watt, RA., 2010. Identifying counterfeit medicines using near infrared spectroscopy. *Journal of near Infrared spectroscopy* [online], 18(1), pp. 1-15.

Moffat, AC., Assi, S., Watt, RA., 2011. Identification of counterfeit medicines from the Internet and the World market using near-infrared spectroscopy. *Analytical Methods* [online],3, pp. 2231-2236.

Moken, MC., 2003. Fake pharmaceuticals: how they and relevant legislation or lack thereof contribute to consistently high and increasing drug prices. *American Journal of Law Medicine* [online], 29, pp. 525-542.

Morgan, J., 1997. Principles of Pharmacology: Basic Concepts and Clinical Applications. JAMA: *The Journal of the American Medical Association*, 277 (19), 1563.

Mutsatsa, S., 2016. *Medicines Management in Mental Health Nursing. Los Angeles: Learning Matters*. National Academies of Sciences, Engineering, and Medicine., 2016. Parenting Matters: Supporting Parents of Children Ages 0-8. Washington, DC: TheNational Academies Press.

Naughton, B., Roberts, L., Dopson, S., Chapman, S. and Brindley, D., 2016. Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study. *BMJ Open* [online], 6(12), p.e013837.

Nazerali, H., Hogerzeil, HV., 1998. The quality and stability of essential drugs in rural Zimbabwe: controlled longitudinal study. *BMJ Open* [online], 317, Pages 512-513.

née Lybecker, K., 2020. *Pharmaceutical Counterfeiting: Endangering Public Health, Society and The Economy* [online]. Fraserinstitute.org. Available at: <https://www.fraserinstitute.org/sites/default/files/pharmaceutical-counterfeiting-endangering-public-health-society-and-the- economy.pdf> [Accessed 03 March 2020].

Newton, P., Proux, S., Green, M., Smithuis, F., Rozendaal, J., Prakongpan, S., Chotivanich, K., Mayxay, M., Looareesuwan, S., Farrar, J., Nosten, F., White, NJ., 2001. Fake artesunate in southeast Asia. *The Lancet* [online], 357, pp. 1948 – 1950.

Newton, PN., Amin, AA., Bird, C., Passmore, P., Dukes, G., Tomson, G., Bate, R., Guerin, PJ., White, NJ., 2011. The primary of public health considerations in defining poor quality medicines. *PLOSmedicine* [online, 8(12), pp. e10011139.

Newton, PN., Green, MD., Fernández, FM., 2010. Impact of poor-quality medicines in the 'developing' world. *Trends in Pharmaceutical Sciences* [online], 31(3), pp.99-101.

Newton, PN., Green, MD., Fernández, FM., Day, NPJ., White, NJ., 2006. Counterfeit anti-infective drugs. *The Lancet* [online], 6, pp. 602-613.

Newton, PN., McGready, R., Fernandez, F., Green, MD., Sunjio, M., Bruneton, C., Phanouvong, S., Millet, P., Whitty, CJ., Talisuna, AO., Proux, S., Christophel, EM., Malenga, G., Singhasivanon, P., Bojang, K., Kaur, H., Palmer, K., Day, NP., Greenwood, BM., Nosten, F., White, NJ., 2006. Manslaughter by fake artesunate in Asia—will Africa be next? *PLOSmedicine* [online], 3, pp. e197.

Norway Global, 2020. *Generational Attitudes and Behaviour - The Nordic Page* [online]. Oslo: The Nordic Page. Available at: <https://www.tnp.no/norway/global/2859-generational-attitudes-and-behaviour> [Accessed 04 Jan 2020].

OECD., 2020. OECD *Guidelines On The Protection Of Privacy And Transborder Flows Of Personal Data* [online]. Paris: OECD. Available at: <https://www.oecd.org/Internet/ieconomy/oecdguidelinesontheprotectionofprivacyandtransborderflowsofpersonaldata.htm> [Accessed 20 April 2019].

O'Shaughnessy, K., 2015. *BMA new guide to medicine & drugs.*. London: DK.

Pandeya, S., 2006. *Text book of medicinal chemistry*. Varanasi: SG Publisher.

Pandit, JK., Tripathi, MK., Babu, RJ., 1997. Effect of tablet disintegrants on the dissolution stability of nalidixic acid tablets. *Pharmazie* [online], 52, pp.538-540.

Parsaie, A. And Haghiabi, A,. 2015. Principle Component Analysis of Longitudinal Dispersion Coefficient Parameters. *International Journal of Waste Resources,* 05(04).

Patrick, G., 2017. *An introduction to medicinal chemistry*. 6th ed. Oxford: Oxford University Press.

Petersen, D. and Johnston, R., 1997. Effective Vulnerability Assessment of Tamper-Indicating Seals. *Journal of Testing and Evaluation*, 25(4), p.451.

Polachek, H., Holcberg, G., Sapir, G., Tsadkin-Tamir, M., Polachek, J., Katz, M. and Ben-Zvi, Z., 2005. Transfer of ciprofloxacin, ofloxacin and levofloxacin across the perfused human placenta in vitro. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 122 (1), 61-65.

Reidenberg, MM., Conner, BA., 2001. Counterfeit and substandard drugs. *Clinical Pharmacology & Therapeutics* [online], 69, pp. 189-193

.Renschler, J., Walters, K., Newton, P. and Laxminarayan, R., 2015. Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub- Saharan Africa. The *American Journal of Tropical Medicine and Hygiene*, 92(6_Suppl), pp.119-126.

Riedel, S., 2005. Edward Jenner and the History of Smallpox and Vaccination. *Baylor University Medical Center Proceedings*, 18(1), pp. 21- 25.

Rimoy, GH., Moshi, Mj., Massele, AY., 2002. Comparative bioavailability of oral sugar-coated and plain formulation of chloroquine phosphate marketed in Tanzania. *Tropical Doctor* [online], 32, pp. 15-17.

Rinnan, A., Van de Berg, F., Engelsen, SB., 2009. Review of the most common pre-processing techniques for near-infrared spectra. *Trends in Analytical Chemistry* [online], 28(10), pp. 1201-1222.

Risha, PG., Msuya, Z., Clark, M., Johnson, K., Ndomondo-Sigonda, M., Layloff, T., 2008. The use of Minilabs to improve the testing capacity of regulatory authorities in resource limited settings: *Tanzanian experience. Health Policy* [online], 87, pp. 217–222.

Risha, PG., Shewiyo, D., Msami, A., Masuki, G., Vergote, G., Vervaet, C., Remon, JP., 2002. In vitro evaluation of the quality of essential drugs on the Tanzanian market. *Tropical Medicine and International Health* [online],7, pp. 701–707.

Rowe, R., Sheskey, P. and Weller, P., 2003. *Handbook of pharmaceutical excipients.* London: Pharmaceutical P.

Rozendaal, J., 2001. Fake antimalaria drugs in Cambodia. *The Lancet* [online], 357, pp. 890.

Ruizdiaz, J., Torriero, A., Salinas, E., Marchevsky, E., SANZ, M. & RABA, J., 2006. *Enzymatic rotating biosensor for cysteine and glutathione determination in a FIA system*. Talanta, 68 (4), 1343-1352.

Singh, S., Prasad, B.,. Savaliya, A. A., Shah, R. P., Gohil V. M. and Kaur, A., 2009 *Trends in Analytical Chemistry* 28, pp. 13-28

Sacré, PY., Deconinck, E., Daszykowski, M., Courselle, P., Vancauwenberghe, R., Chiap, P., Crommen, J., De Beer, JO., 2011. Impurity fingerprints for the identification of counterfeit medicines-A feasibility study. *Analytica Chimica Acta* [online], 701, pp. 224-231.

Sacré, PY., Deconinck, E., De Beer, T., Courselle, P., Vancauwenberghe, R., Chiap, P., Crommen, J., De Beer, JO., 2010. Comparison and combination of spectroscopic techniques for the detection of counterfeit medicines. *Journal of Pharmaceutical and Biomedical Analysis* [online], 53, pp. 445-453.

Salganicoff, L., 1998. Near-infrared spectrophotometry. *Biofactors*, 7 (3), pp. 239- 242.

Sárközy, G., 2001. Quinolones: a class of antimicrobial agents. *Veterinární Medicína*, 46 (No. 9–10), 257-274.

Savitzky, A. And Golay, M., 1964. Smoothing and Differentiation of Data by Simplified Least Squares Procedures. *Analytical Chemistry*, 36 (8), pp.1627-1639.

Schmitz, F., 1998. Relationship Between Ciprofloxacin, Ofloxacin, Levofloxacin, Sparfloxacin and Moxifloxacin (BAY 12-8039) MICs and mutations in grlA, grlB, gyrA and gyrB in 116 unrelated clinical isolates of Staphylococcus aureus. *Journal of Antimicrobial Chemotherapy*, 41 (4), 481-484.

Sesay, MM., 1988. *Fake drugs – a new threat of health care delivery*. Africa Health [online] , June/July, pp. 13-15.

Settanni, E., Harrington, T. and Srai, J., 2017. Pharmaceutical supply chain models: A synthesis from a systems view of operations research. *Operations Research Perspectives*, 4, pp.74-95.

Singh, S., Prasad, B., Savaliya, A., Shah, R., Gohil, V. And Kaur, A., 2009. *Strategies for characterizing sildenafil, vardenafil, tadalafil and their analogues in herbal dietary supplements, and detecting counterfeit products containing these drugs.* TrAC Trends in Analytical Chemistry, 28(1), pp.13-28.

Sitthi-amorn, C. and Poshyachinda, V., 1993. Bias. *The Lancet*, 342 (8866), 286-288.

Smalley, i., 1970. Cohesion of soil particles and the intrinsic resistance of simple soil systems to wind erosion. *Journal of soil science*, 21(1), pp.154-161.

Stancliffe, R., 1991. Dinoflagellate cysts from the Oxfordian (Upper Jurassic) of Skye, Scotland and Southern Dorset, England. *Journal of Micropalaeontology*, 10 (2), pp. 185-202.

Stationary Office., 2017. *British pharmacopeia* 2017. [S.l.]: The Stationary Office TSO.

Stuart, B.H., 2004. *Analytical Techniques in the Sciences (ants) Ser.: Infrared Spectroscopy: Fundamentals and Applications* [online]. John Wiley and Sons inc

Sun, D., 2009. *Infrared Spectroscopy For Food Quality Analysis And Control*. Amsterdam, [etc.]: Elsevier.

Sun, L., Hsiung, C., Pederson, CG., Zou, P., Smith, V., Gunten MV., O'Brien, NA., 2016.

Pharmaceutical Raw Material Identification Using Miniature Near- Infrared (micronir) Spectroscopy and Supervised Pattern Recognition Using Support Vector Machine. *Applied Spectroscopy* [online], 70(5), Pages 816-825.

Systech., 2020. *Unisecure Case Study* [online]. Systech International. Available at:

<https://cdn2.hubspot.net/hubfs/3844090/2018%20UniSecure/Assets/Uni Secure-Case-Study-Sharp-St-James ystech.pdf?fbclid=IwAR0StyU_s4wRKoHOrsIp8qFgQHfx5iDbWzTajI8xQc -iSpy-Kyu0coEpD9c> [Accessed 01 Feb 2020].

Teater, B., 2015. *Social Work Theory*. International Encyclopedia of the Social & Behavioral Sciences, pp.813-820.

Ten Ham, M., 1992. Counterfeit drugs: implications for health. *Adverse drug reactions and toxicological reviews* (Toxicol Rev) [online],11, Pages 59-65.

Terrell, M., 2019. *FT-NIR Frequently Asked Questions - Advancing Materials* [online]. Advancing Materials. Available from: https://www.thermofisher.com/blog/materials/ft-nir-frequently-asked- questions/ [Accessed 26 Nov 2019].

Van Bambeke, F., Mingeot-Leclercq, M., Glupczynski, Y. And Tulkens, P., 2017. Mechanisms of Action. *Infectious Diseases*, 1162-1180.e1.

Varanda, F., Pratas de Melo, M., Caço, A., Dohrn, R., Makrydaki, F., Voutsas, E., Tassios, D. and Marrucho, I., 2006. Solubility of Antibiotics in Different Solvents. 1. Hydrochloride Forms of Tetracycline, Moxifloxacin, and Ciprofloxacin. *Industrial & Engineering Chemistry Research*, 45 (18), 6368-6374.

Vargesson, N,. 2015. Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Research Part C: Embryo Today: Reviews*, 105(2), pp.140-156.

Walters, J., Zhang, F. and Nakkula, R., 1999. Mechanisms of Fluoroquinolone Transport by Human Neutrophils. *Antimicrobial Agents and Chemotherapy*, 43 (11), 2710-2715.

Weathermon, R., Crabb, D. W. (1999). Alcohol and medication interactions. Alcohol research & health. *The journal of the National Institute on Alcohol Abuse and Alcoholism*, 23(1), pages 40–54.

Wertheimer, A., Chaney, N. and Santella, T., 2003. Counterfeit Pharmaceuticals: Current Status and Future Projections. *Journal of the American Pharmacists Association*, 43 (6), 710-718.

Wertheimer, A. and Santella, T., 2005. Drug Counterfeiting. International *Journal of Pharmaceutical Medicine*, 19 (5-6), 301-308.

Westad, F., 2005. *Data handling in science and technology* (Volume 20B). B. M. G. Vandeginste, D. L. Massart, L. M. C. Buydens, S. de Jong, P. J. Lewi and J. Smeyers-Verbeke (eds), Elsevier, Amsterdam, 1998, pp. xiv +713, ISBN 0-444-82853-2. Journal of Chemometrics, 19 (5-7), 404-404.

Whiffen, D.H., 1966. *Spectroscopy*. London: Longmans and Green and Co Ltd.

Williams, P., 1996. Book Review Excipients and delivery systems for pharmaceutical formulations. *Journal of Chemical Technology & Biotechnology*, 66 (2), 213-213.

Wold, S., Geladi, P., Esbensen, K. And Öhman, J., 1987. Multi-way principal components-and PLS-analysis. *Journal of Chemometrics*, 1 (1), 41-56.

Wolfson, J. and Hooper, D., 1991. Pharmacokinetics of quinolones: Newer aspects. European *Journal of Clinical Microbiology & Infectious Diseases*, 10 (4), 267-274.

WHOa., 1999. *Guidelines for development of measures to combat counterfeit drugs*. [online]. Geneva, Switzerland: WHO. WHO/EDM/QSM/99.1.

WHOb., 1999. *Counterfeit and sub-standard drugs in Maynmar and Vietnam* [online], Geneva: WHO.

WHO., 2010. Growing threat of counterfeit medicines. *Bulletin of the World Health Organization* [online], 88(4), Pages 241-320.

WHO., 2012. *New global mechanism to combat Substandard/Spurious/Falsely-labelled/Falsified/Counterfeit medical products* [online]. WHO Available from: http://www.who.int/medicines/news/TRA-SE_EMP.pdf [Accessed 15 July2019]

WHO, 2013. *WHO | Deadly Medicines Contamination In Pakistan*. [online] Who.int. Available at: https://www.who.int/features/2013/pakistan_medicine_safety/en/> [Accessed 28 March 2020].

WHO., 2018. *Substandard and falsified medical products*. [online] Available at: http://www.who.int/news-room/fact- sheets/detail/substandard-and-falsified-medical-products [Accessed 16 Oct 2019]

WHO., 2020. *About WHO*. [online] Available at: <https://www.who.int/about> [Accessed 29 March 2020].

Zaitsu, K., Hayashi, Y., Kusano, M., Tsuchihashi, H. and Ishii, A., 2016. Application of metabolomics to toxicology of drugs of abuse: A mini review of metabolomics approach to acute and chronic toxicity studies. *Drug Metabolism and Pharmacokinetics*, 31(1), pp.21-26.

Zhou, L., 2005. 19 *Applications of LC/MS in pharmaceutical analysis. Separation Science and Technology*, pp.499-568.

Zou, H., Hastie, T. and Tibshirani, R., 2006. Sparse Principal Component Analysis. *Journal of Computational and Graphical Statistics*, 15 (2), 265-286.

Council Directive 95/46/EC of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [1995] *OJ L 281/31-50.*

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the code relating to medicinal products for human use [2001] OJ L 311/67

Commission Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use [2003] OJ L 159/46-94.

Commission Directive 2004/24/EC of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use [2004] OJ L 136/85.

Commission Directive 2004/27/EC of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use [2004] OJ L 136/34.

Commission Directive 2008/29/EC of 11 March 2008 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the implementing powers conferred on the Commission [2008] OJ L 81/51.

Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products [2009] L 242/3

Commission Directive 2009/53/EC of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products [2009] OJ L 168/33.

Commission Directive 2010/84/EC of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [2010] OJ L 348/74.

Commission Directive 2011/62/EC of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products [2011] OJ L 174/74

Commission Directive 2016/161/EC of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use [2016] OJ L 32/1

Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use [2001] OJ L 311/67

Council Directive 2002/98/EEC of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC [2002] OJ L 33/30.

Council directive 2016/679/EC of 23 May 2016. on the protection of natural persons with regard to the processing of personal data and on the free movement of such data [2016] OJ L 119/1

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products [1965] (1) OJ No 84/4. (2) OJ No 158/16.

Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products [1975] OJ L 147/9.

Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [1975] OJ No L 147/9.

Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens [1989] OJ L 142/14-15.

Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65 /65 /EEC and 75 /319/EEC and laying down additional provisions for radiopharmaceuticals [1989] OJ No L 142/16.

Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down special provisions for proprietary medicinal products derived from human blood or human plasma [1989] OJ No L 181/44.

Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use [1992] *OJ L 113/1-4*

Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use [1992] *OJ L 113/5-7.*

Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets [1992] *OJ L 113/8-12*

Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use [1992] *OJ L 113/ 13-18.*

Council Directive 92/73/EEC of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to medicinal products and laying down additional provisions on homeopathic medicinal products [1992] *OJ L 297/8-11.*

The Data Protection Act 1988

The Data Protection Act 1988 (2019 Amendments) 2018, SI 2019/419

The Pharmacy Order 2020, SI 2020/231

The Medicines Act 1968

Medicines (Medicines Act 1968 Amendment) Regulations 1983, SI 1983/1724

The Misuse of Drugs Act 1971

The Misuse of Drugs Act 1971 (2012 amendments) 2012, SI 1971/1390

The Prescription Only Medicines (Human Use) Order 1997, SI 1997/1830

APPENDIX:

8.1 Tablet Spectra

Information Given:

- Chemical Name
- Chemical Formula
- Chemical Structure
- NIR MSC-D1 Treated Spectra

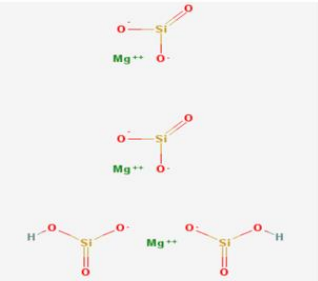
Raw Materials:

- Talc
- Lactose
- Maize Starch

Antibiotics:

- Amoxicillin
- (Additive to Amoxicillin) Clavulanic Acid
- Azithromycin
- Cefuroxime
- Ciprofloxacin
- Clarithromycin
- Erythromycin
- Norfloxacin
- Ofloxacin

Only some of the antibiotics and Raw Materials are used in this appendix to give examples of what was used in this research.

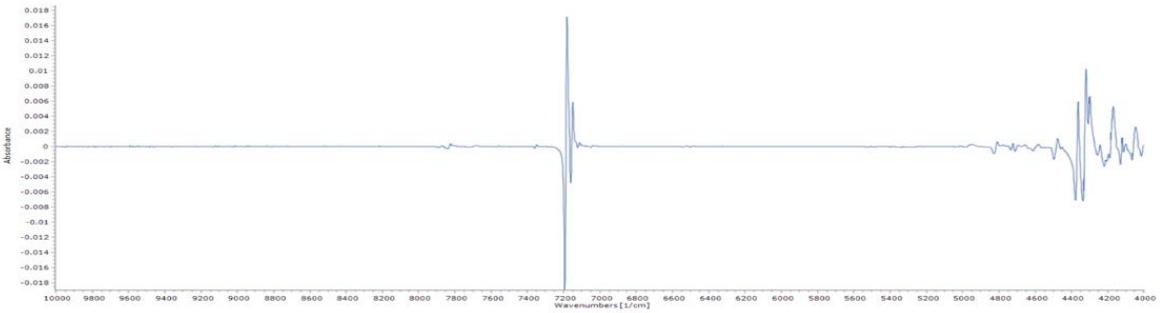


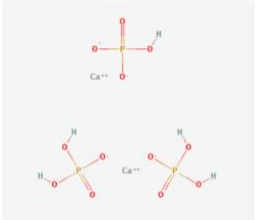
Raw Material Name:

Talc

Chemical Formula:

$H_2Mg_3O_{12}Si_4$



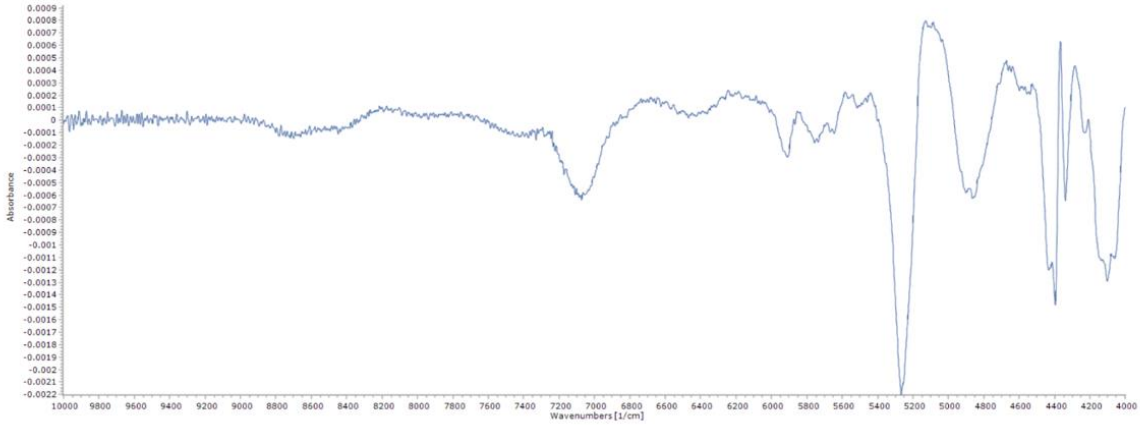


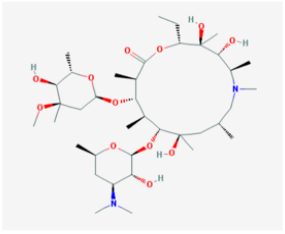
Raw Material Name:

Maize Starch

Chemical Formula:

$Ca_2H_5O_{12}P_3$



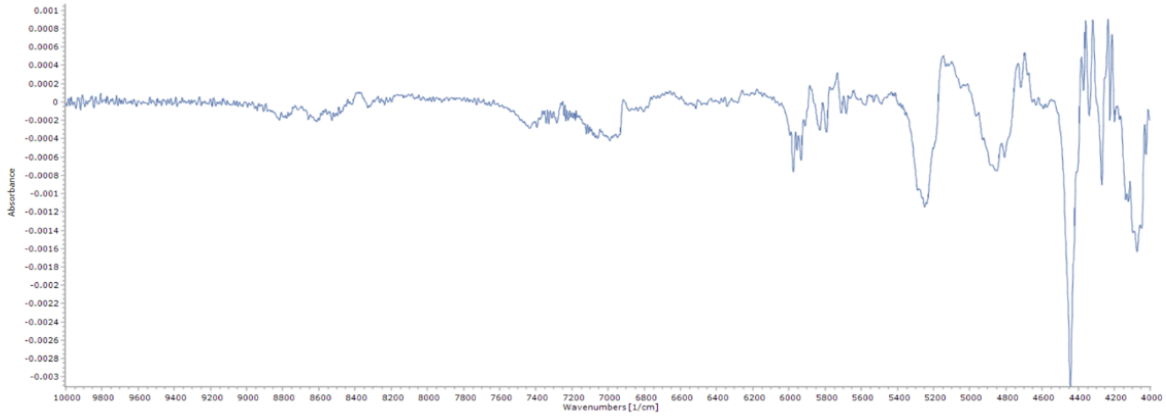


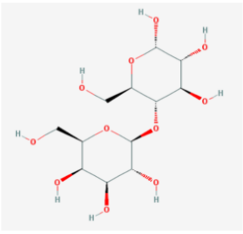
Antibiotic Name:

Azithromycin

Chemical Formula:

$C_{38}H_{72}N_2O_{12}$



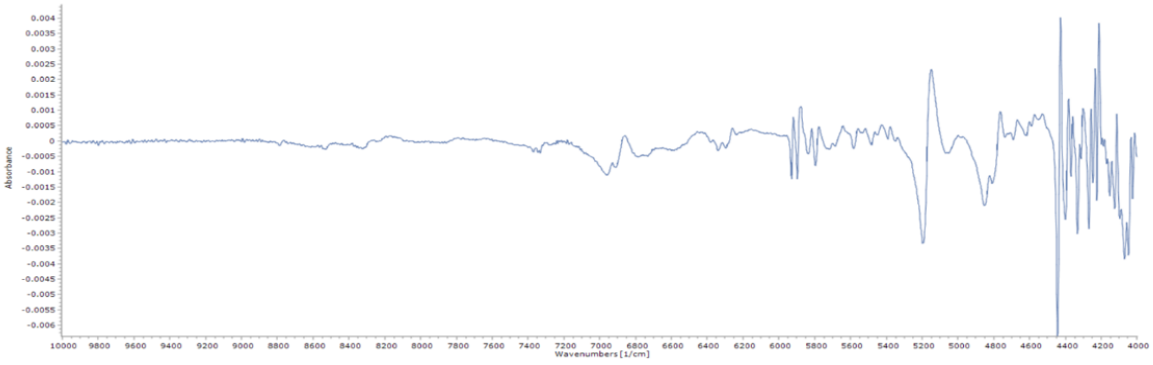


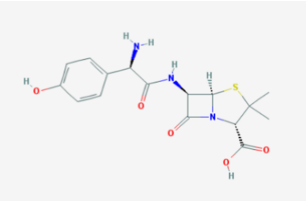
Raw Material Name:

Lactose

Chemical Formula:

$C_{12}H_{22}O_{11}$



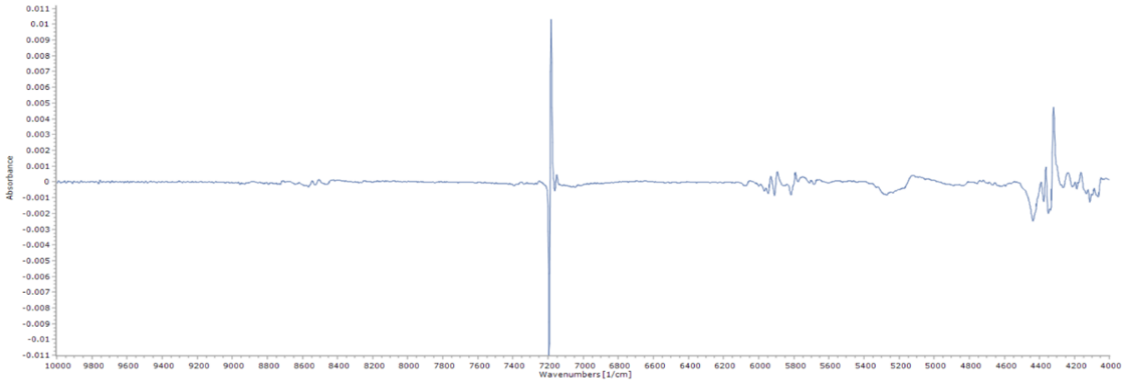


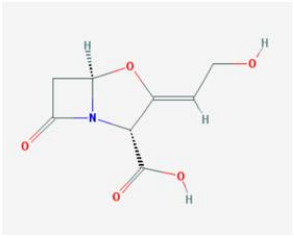
Antibiotic Name:

Amoxicillin

Chemical Formula:

$C_{16}H_{19}N_3O_5S$



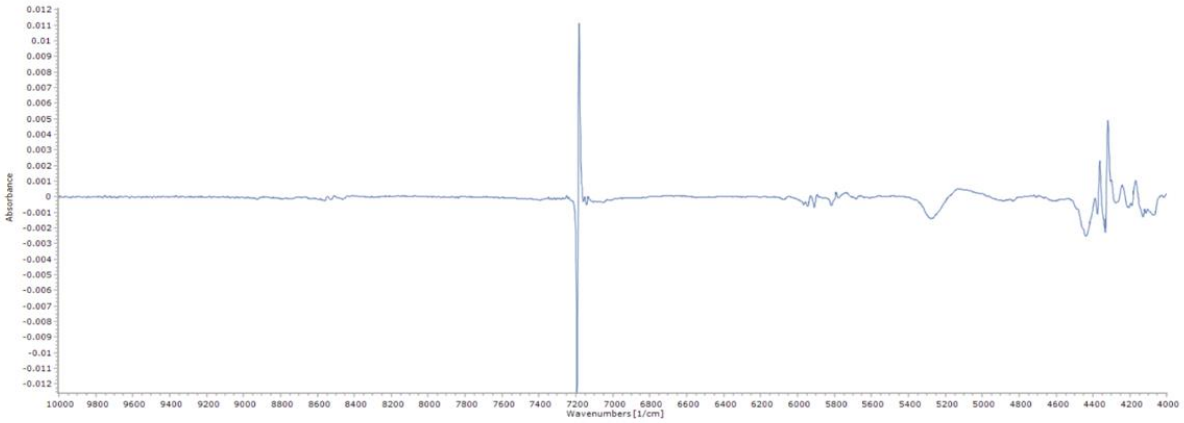


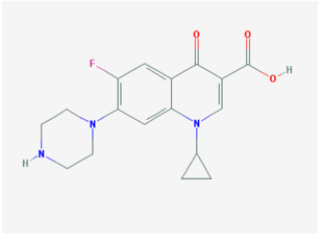
Antibiotic Name:

(Additive to Amoxicillin) Clavulanic Acid

Chemical Formula:

$C_8H_9NO_5$



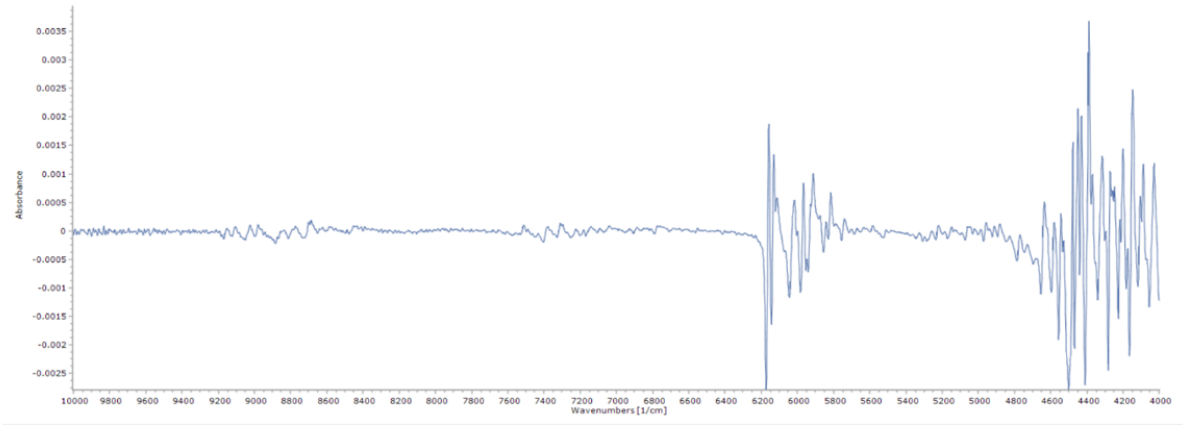


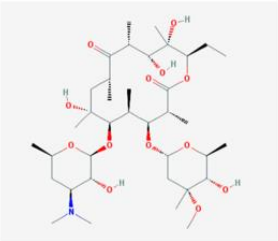
Antibiotic Name:

Ciprofloxacin

Chemical Formula:

$C_{17}H_{18}FN_3O_3$



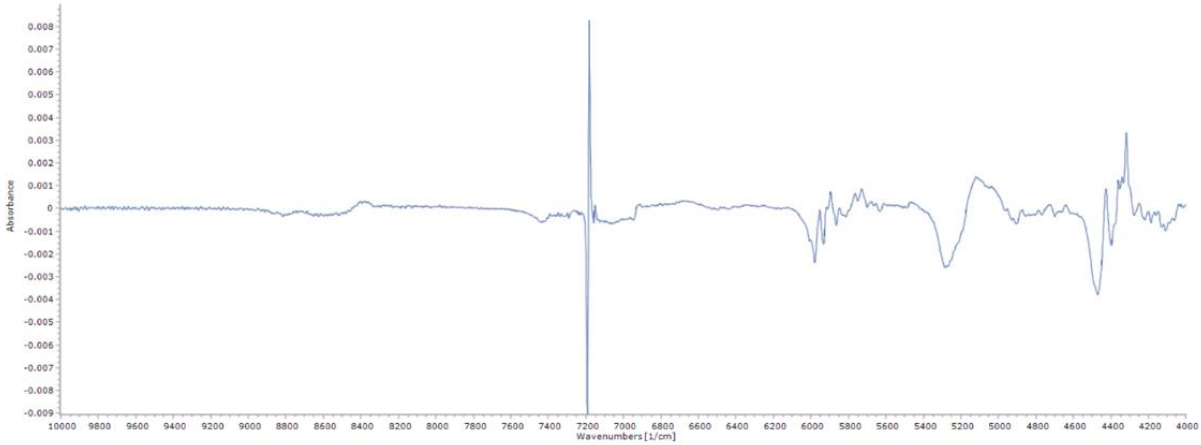


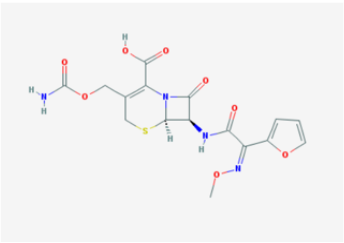
Antibiotic Name:

Erythromycin

Chemical Formula:

$C_{37}H_{67}NO_{13}$



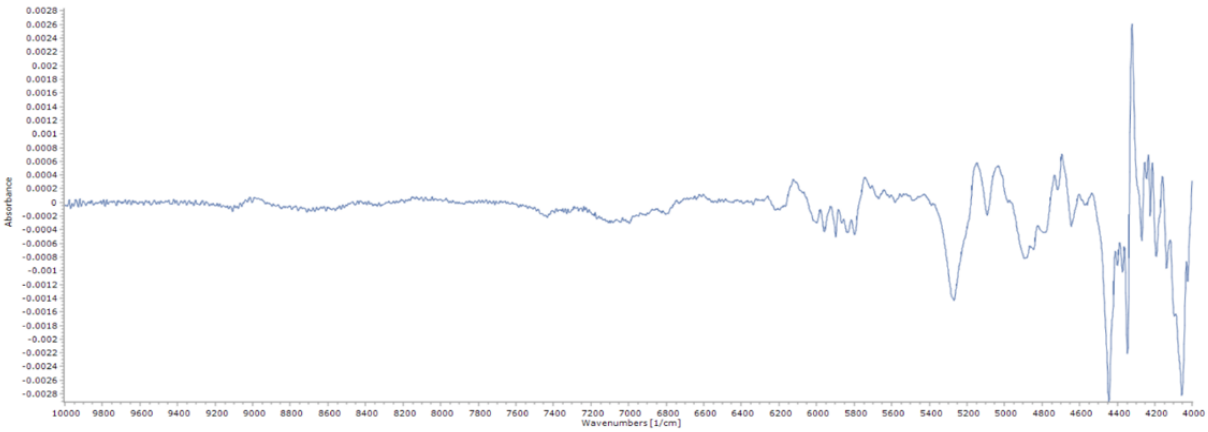


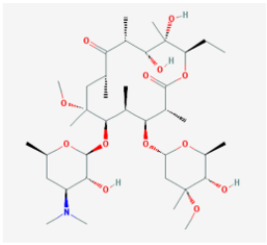
Antibiotic Name:

Cefuroxime

Chemical Formula:

$C_{16}H_{16}N_4O_8S$



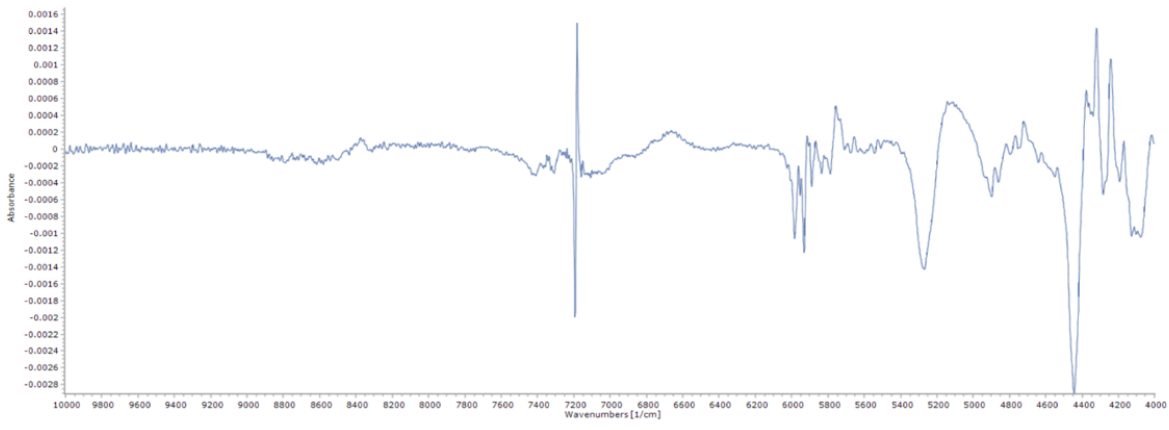


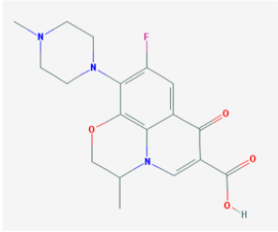
Antibiotic Name:

Clarithromycin

Chemical Formula:

$C_{38}H_{69}NO_{13}$



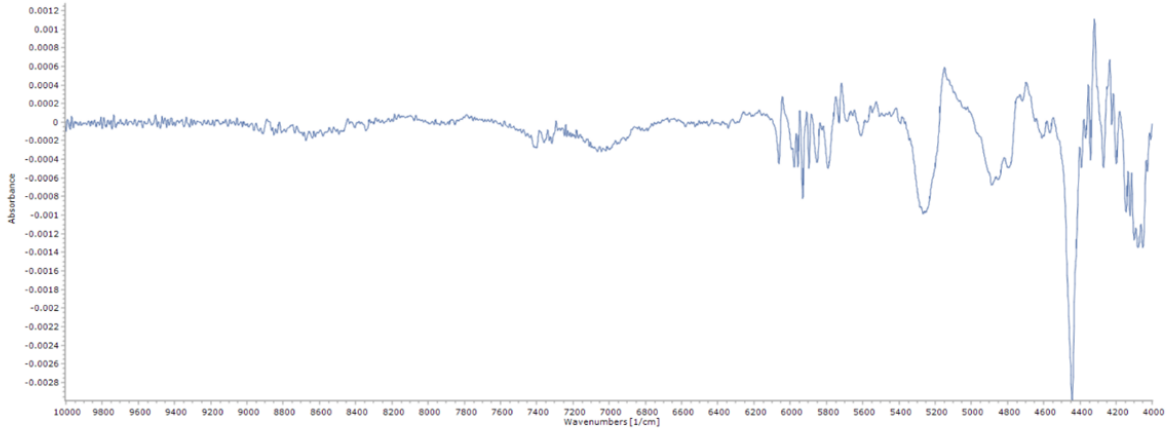


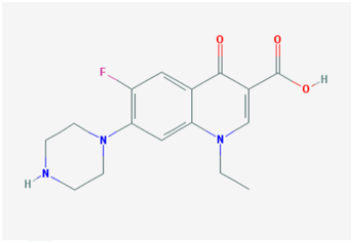
Antibiotic Name:

Ofloxacin

Chemical Formula:

$C_{18}H_{20}FN_3O_4$



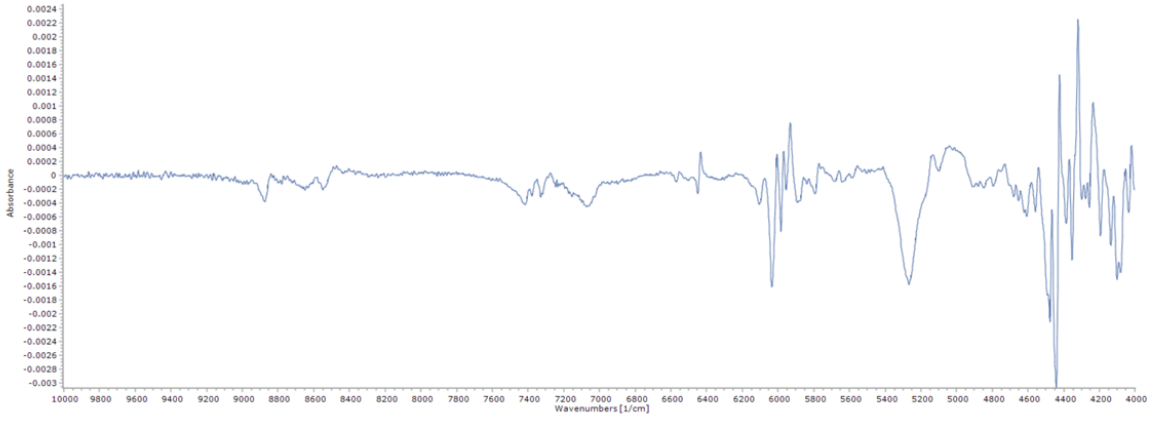


Antibiotic Name:

Norfloxacin

Chemical Formula:

$C_{16}H_{18}FN_3O_3$



8.2 Tablet Data – Batch Information

Product Name	Batch No.	Sample No. Range	API	Dose of API in tablet (mg)	Batch Weight Average (mg)	Batch Average (m/m%)	Manufacturer	Place of purchase	Max Peak Average	Min Peak Average	S/N Ratio Average	Class ID
Kinoxin	00 230507	Sample 221 Sample 222 Sample 223 Sample 224 Sample 225 Sample 226 Sample 227 Sample 228	Ciprofloxacin	500	789	63	Unknown	Unknown	0.00905	-0.0079	9.8	C
Ciflox	0306g	Sample 180 Sample 181 Sample 182 Sample 183 Sample 184 Sample 185 Sample 186 Sample 187 Sample 188 Sample 189 Sample 190 Sample 191 Sample 193 Sample 192 Sample 194 Sample 195	Ciprofloxacin	500	839	60	Dr. Reddy's Laboratories	Ghana	0.0088	-0.0084	8.9	A
Ciproxin	1037498	Sample 144 Sample 145	Ciprofloxacin	500	776	64	Bayer AG Germany	UK	0.0082	-0.0084	8.7	A
Ciproxin	1218405	Sample 142 Sample 143	Ciprofloxacin	250	385	65	Bayer AG Germany	UK	0.0082	-0.0064	7.7	G
Sarf	156c	Sample 288 Sample 289 Sample 306 Sample 307 Sample 290 Sample 291 Sample 292 Sample 293 Sample 294 Sample 295 Sample 296 Sample 297 Sample 298 Sample 299 Sample 300 Sample 301 Sample 302 Sample 303 Sample 304 Sample 305	Ciprofloxacin	500	807	62	Unknown	Unknown	0.1098	-0.0112	9.7	G
Cipro pharm	1657	Sample 196 Sample 198 Sample 199 Sample 202	Ciprofloxacin	500	782	64	Pharma International. Co	Lebanon	0.0061	-0.0057	7.2	G

		Sample 158										
		Sample 159										
Ciproxin	bxb38f1	bxb38f1#1	Ciprofloxacin	500	775	65	Bayer AG Germany	UK	0.0086	-0.0088	9.3	A
		bxb38f1#2										
		bxb38f1#3										
		bxb38f1#4										
		bxb38f1#5										
		bxb38f1#6										
		bxb38f1#7										
		bxb38f1#8										
		bxb38f1#9										
		bxb38f1#10										
		bxb38f1#11										
		bxb38f1#12										
		bxb38f1#13										
		bxb38f1#14										
		bxb38f1#15										
		bxb38f1#16										
		bxb38f1#17										
		bxb38f1#18										
		bxb38f1#19										
		bxb38f1#20										
Ciproxin	20c2002	Sample 168	Ciprofloxacin	500	760	66	Bayer AG Germany	UK	0.0115	-0.0117	9.0	G
		Sample 169										
Ciprofloxacin	it502bz	it502bz#1	Ciprofloxacin	250	389	64	Bayer AG Germany	UK	0.0085	-0.009	9.4	C
		it502bz#2										
		it502bz#3										
		it502bz#4										

		it502bz#5										
		it502bz#6										
		it502bz#7										
		it502bz#8										
		it502bz#9										
		it502bz#10										
		it502bz#11										
		it502bz#12										
		it502bz#13										
		it502bz#14										
		it502bz#15										
		it502bz#16										
Ciprofloxacin	8k27cl	Sample 286	Ciprofloxacin	500	772	65	Telanc Pharma	UK	0.0095	-0.0098	9.0	A
		Sample 287										
		Sample 270										
		Sample 271										
		Sample 272										
		Sample 273										
		Sample 274										
		Sample 275										
		Sample 276										
		Sample 277										
		Sample 278										
		Sample 279										
		Sample 280										
		Sample 281										
		Sample 282										
		Sample 283										

		Sample 284										
		Sample 285										
Quintor	b3997008a	Sample 154	Ciprofloxacin	500	742	67	Unknown	Ghana	0.0185	-0.01771202	14.1	A
		Sample 155										
Ciprofloxacin	b60931	Sample 156	Ciprofloxacin	250	392	64	Dr. Reddy's Laboratories	Ghana	0.0076	-0.00775989	8.8	A
		Sample 157										
Unknown	b61918	Sample 250	Ciprofloxacin	500.000000	787	64	Unknown	Unknown	0.0078	-0.0079	8.3	G
		Sample 251										
		Sample 267										
		Sample 269										
		Sample 252										
		Sample 253										
		Sample 254										
		Sample 255										
		Sample 256										
		Sample 257										
		Sample 258										
		Sample 259										
		Sample 260										
		Sample 261										
		Sample 262										
		Sample 263										
		Sample 264										
		Sample 265										
		Sample 266										
		Sample 268										
Ciproxin	bxb19t1	Sample 138	Ciprofloxacin	500	776	64	Bayer AG Germany	UK	0.0086	-0.0088	9.1	A
		Sample 139										

		Sample 106										
		Sample 107										
		Sample 108										
		Sample 109										
		Sample 110										
		Sample 111										
		Sample 112										
		Sample 113										
Ciproxin	bxcbbf1	Sample 114	Ciprofloxacin	750	1168	64	Bayer AG Germany	UK	0.0078	-0.0080	9.0	A
		Sample 115										
		Sample 130										
		Sample 131										
		Sample 132										
		Sample 133										
		Sample 116										
		Sample 117										
		Sample 118										
		Sample 119										
		Sample 120										
		Sample 121										
		Sample 122										
		Sample 123										
		Sample 124										
		Sample 125										
		Sample 126										
		Sample 127										
		Sample 128										
		Sample 129										

Ciproxin	ccwhv1	Sample 167 Sample 166 Sample 146 Sample 147 Sample 091 Sample 090 Sample 092 Sample 093 Sample 094 Sample 095 Sample 096 Sample 097 Sample 098 Sample 099 Sample 100 Sample 101 Sample 102 Sample 103 Sample 104 Sample 105	Ciprofloxacin	500	767	65	Bayer AG Germany	UK	0.008	-0.0082	9.2	A
Ciproxin	cczlj2	Sample 170 Sample 171	Ciprofloxacin	500	792	63	Bayer AG Germany	UK	0.0087	-0.0089	9.3	A
Ciproxin	cczar2	Sample 164 Sample 165	Ciprofloxacin	500	790	63	Bayer AG Germany	UK	0.0088	-0.0090	9.7	A
Ciprofloxacin	cflh0005	Sample 203 Sample 204 Sample 219 Sample 220	Ciprofloxacin	250	384	65	Micro Labs ltd	Lebanon	0.0172	-0.0155	14.0	C

		Sample 205 Sample 206 Sample 207 Sample 208 Sample 209 Sample 210 Sample 211 Sample 212 Sample 213 Sample 214 Sample 215 Sample 216 Sample 217 Sample 218										
Ciprobay	Ciprobay	Sample 154 Sample 155	Ciprofloxacin	500	690	72	Bayer AG Germany	Lebanon	0.0079	-0.0081	8.8	C
Ciprofloxacin	cpt6004	Sample 152 Sample 153	Ciprofloxacin	500	711	70	Inter-chem Pharma	Tanzania	0.0121	-0.0125	8.6	G
Estecina	x-12	x-12#1 x-12#2 x-12#3 x-12#4 x-12#5 x-12#6 x-12#7 x-12#8 x-12#9 x-12#10	Ciprofloxacin	500	829	60	Norman	Lebanon	0.0101	-0.0104	9.5	A

		x-12#11 x-12#12 x-12#13 x-12#14 x-12#15 x-12#16 x-12#17 x-12#18 x-12#19 x-12#20										
Ciproxin	it10685	Sample 140 Sample 141	Ciprofloxacin	250	389	64	Bayer AG Germany	UK	0.0094	-0.0096	9.3	A
Ciproxin	it2056	Sample 150 Sample 151	Ciprofloxacin	250	337	74	Bayer AG Germany	UK	0.0140	-0.0142	9.5	G
Ciprobay	it501nb	Sample 134 Sample 135	Ciprofloxacin	250	386	65	Bayer AG Germany	Lebanon	0.0095	-0.0097	9.7	A
Ciprofloxacin	kf5703	Sample 229 Sample 230 Sample 248 Sample 249 Sample 232 Sample 233 Sample 234 Sample 235 Sample 236 Sample 237 Sample 238 Sample 239	Ciprofloxacin	500	726	69	Karib Kemi Pharma	UK	0.0081	-0.0081	9.0	G

		Sample 240 Sample 241 Sample 242 Sample 243 Sample 244 Sample 245 Sample 246 Sample 247										
Accord	m10951	Sample 055 Sample 056 Sample 073 Sample 074 Sample 057 Sample 058 Sample 059 Sample 060 Sample 061 Sample 062 Sample 063 Sample 064 Sample 065 Sample 066 Sample 067 Sample 068 Sample 069 Sample 070 Sample 071 Sample 072	Ciprofloxacin	500	690	72	Unknown	Unknown	0.0050	-0.0053	6.8	G

Unknown	sf5702	Sample 308 Sample 309 Sample 326 Sample 327 Sample 310 Sample 311 Sample 312 Sample 313 Sample 314 Sample 315 Sample 316 Sample 317 Sample 318 Sample 319 Sample 320 Sample 321 Sample 322 Sample 323 Sample 324 Sample 325	Ciprofloxacin	500	708	71	Unknown	Unknown	0.0116	-0.0117	9.6	G

8.3 Tablet Data – Tablet Components

Product Name	Manufacturer	Batch No.	API	Dose (mg)	Excipients	Tablet No	Tablet Weight (mg)	M/M %
Ciflox	Ernest Chemists Limited	0306g	Ciprofloxacin	500	Microcrystalline Cellulose	1	839	59.59475566
				500	Sodium Starch Glycolate	2	840	59.52380952
				500	Mazie Starch	3	845	59.17159763
				500	Magnesium Stearate	4	837	59.73715651
				500	Hypromellose	5	838	59.66587112
				500	Titanium Dioxide	6	841	59.4530321
				500	Macrogol 400	7	843	59.31198102
				500		8	840	59.52380952
Sarf	UNKOWN	156c	Ciprofloxacin	500	Microcrystalline Cellulose	1	807	61.95786865
				500	Sodium Starch Glycolate	2	809	61.80469716
				500	Mazie Starch	3	806	62.03473945
				500	Magnesium Stearate	4	810	61.72839506
				500	Hypromellose	5	800	62.5
				500	Titanium Dioxide	6	804	62.18905473
				500	Macrogol 400	7	805	62.11180124
				500	Crospovidone	8	807	61.95786865
				500	Polydextrose	9	809	61.80469716
				500		10	808	61.88118812

Product Name	Manufacturer	Batch No.	API	Dose (mg)	Excipients	Tablet No	Tablet Weight (mg)	M/M %
Ciproxin	Bayer AG Germany	bxb38f1	Ciprofloxacin	500	Microcrystalline Cellulose	1	775	64.51612903
				500	Sodium Starch Glycolate	2	776	64.43298969
				500	Mazie Starch	3	777	64.35006435
				500	Magnesium Stearate	4	774	64.5994832
				500	Hypromellose	5	777	64.35006435
				500	Titanium Dioxide	6	779	64.18485237
				500	Macrogol 400	7	778	64.26735219
				500	Glycerol Triacetate	8	772	64.76683938
				500	Macrogol 8000	9	773	64.68305304
				500		10	770	64.93506494
Ciprofloxacin	Bayer AG Germany	it502bz	Ciprofloxacin	250	Microcrystalline Cellulose	1	389	64.26735219
				250	Sodium Starch Glycolate	2	380	65.78947368
				250	Mazie Starch	3	387	64.5994832
				250	Magnesium Stearate	4	386	64.76683938
				250	Hypromellose	5	385	64.93506494
				250	Titanium Dioxide	6	384	65.10416667
				250	Macrogol 400	7	388	64.43298969
				250	Crospovidone	8	387	64.5994832

Ciprofloxacin	Telanc Pharma	8k27cl	Ciprofloxacin	500	Microcrystalline Cellulose	1	772	64.76683938
				500	Sodium Starch Glycolate	2	777	64.35006435
				500	Mazie Starch	3	773	64.68305304
				500	Magnesium Stearate	4	775	64.51612903
				500	Hypromellose	5	778	64.26735219
				500	Titanium Dioxide	6	774	64.5994832
				500	Macrogol 400	7	778	64.26735219
				500	Silica Colloidal Anhydrous	8	773	64.68305304
Ciprofloxacin	UKNOWN	b61919	Ciprofloxacin	500	Microcrystalline Cellulose	1	787	63.53240152
				500	Sodium Starch Glycolate	2	789	63.37135615
				500	Mazie Starch	3	788	63.45177665
				500	Magnesium Stearate	4	789	63.37135615
				500	Hypromellose	5	787	63.53240152
				500	Titanium Dioxide	6	786	63.61323155
				500	Macrogol 8000	7	785	63.69426752
				500	Crospovidone	8	786	63.61323155
				500		9	787	63.53240152
				500		10	789	63.37135615

Ciprofloxacin	Bayer AG Germany	bxb19	Ciprofloxacin	500	Microcrystalline Cellulose	1	776	64.43298969
				500	Sodium Starch Glycolate	2	777	64.35006435
				500	Mazie Starch	3	775	64.51612903
				500	Magnesium Stearate	4	778	64.26735219
				500	Hypromellose	5	777	64.35006435
					Titanium Dioxide			
					Macrogol 400			
					Silica Colloidal Anhydrous			
					Crospovidone			
Ciprofloxacin	Bayer AG Germany	bxcbbf1	Ciprofloxacin	750	Microcrystalline Cellulose	1	1168	64.21232877
				750	Sodium Starch Glycolate	2	1169	64.15739949
				750	Mazie Starch	3	1167	64.26735219
				750	Magnesium Stearate	4	1165	64.3776824
				750	Hypromellose	5	1167	64.26735219
				750	Titanium Dioxide	6	1168	64.21232877
				750	Macrogol 400	7	1164	64.43298969
				750	Povidone (K30)	8	1164	64.43298969
				750		9	1167	64.26735219
				750		10	1168	64.21232877

Ciproxin	Bayer AG Germany	ccwhv1	Ciprofloxacin	500	Microcrystalline Cellulose	1	767	65.18904824
				500	Sodium Starch Glycolate	2	768	65.10416667
				500	Mazie Starch	3	767	65.18904824
				500	Magnesium Stearate	4	768	65.10416667
				500	Hypromellose	5	769	65.01950585
				500	Titanium Dioxide	6	766	65.27415144
				500	Macrogol 400	7	769	65.01950585
				500	Silica Colloidal Anhydrous	8	765	65.35947712
				500	Crospovidone	9	764	65.44502618
				500		10	768	65.10416667
Ciproxin	Micro Labs Ltd	cflh0005	Ciprofloxacin	250	Microcrystalline Cellulose	1	384	65.10416667
				250	Sodium Starch Glycolate	2	385	64.93506494
				250	Mazie Starch	3	383	65.27415144
				250	Magnesium Stearate	4	382	65.44502618
				250	Hypromellose	5	385	64.93506494
				250	Titanium Dioxide	6	384	65.10416667
				250	Macrogol 400	7	385	64.93506494
				250	Silica Colloidal Anhydrous	8	386	64.76683938
				250	Povidone (K30)	9	384	65.10416667
				250		10	383	65.27415144

Estecina	Norman	x-12	Ciprofloxacin	500	Microcrystalline Cellulose	1	829	60.31363088
				500	Sodium Starch Glycolate	2	828	60.38647343
				500	Mazie Starch	3	826	60.53268765
				500	Magnesium Stearate	4	827	60.45949214
				500	Hypromellose	5	828	60.38647343
				500	Titanium Dioxide	6	829	60.31363088
				500	Macrogol 400	7	827	60.45949214
				500		8	826	60.53268765
				500		9	826	60.53268765
				500		10	828	60.38647343
Ciprofloxacin	Karib Kemi Pharma	kf5703	Ciprofloxacin	500	Microcrystalline Cellulose	1	726	68.87052342
				500	Sodium Starch Glycolate	2	725	68.96551724
				500	Mazie Starch	3	724	69.06077348
				500	Magnesium Stearate	4	727	68.77579092
				500	Hypromellose	5	726	68.87052342
				500	Titanium Dioxide	6	728	68.68131868
				500	Macrogol 400	7	725	68.96551724
				500	Silica Colloidal Anhydrous	8	725	68.96551724
				500	Povidone (K30)	9	724	69.06077348
				500		10	726	68.87052342

UNKOWN	UNKOWN	sf5702	Ciprofloxacin	500	Microcrystalline Cellulose	1	708	70.62146893
				500	Sodium Starch Glycolate	2	709	70.52186178
				500	Mazie Starch	3	710	70.42253521
				500	Magnesium Stearate	4	706	70.82152975
				500	Hypromellose	5	707	70.72135785
				500	Titanium Dioxide	6	708	70.62146893
				500	Macrogol 400	7	709	70.52186178
				500	Crospovidone	8	708	70.62146893
				500	Silica Colloidal Anhydrous	9	707	70.72135785
				500		10	708	70.62146893
Zithromax	Pfizer	5HP03E4	Azithromycin	250	Microcrystalline Cellulose	1	320	78.125
				250	Sodium Starch Glycolate	2	329	75.98784195
				250	Mazie Starch	3	330	75.75757576
				250	Magnesium Stearate	4	326	76.68711656
				250	Sodium Lauryl sulphate	5	327	76.45259939
				250	Titanium Dioxide	6	325	76.92307692
					Macrogol 4000			
					Hypromellose			
					Lactose Monohydrate			

Ofloxacin	APS	7F160F	Ofloxacin	200	Lactose	1	356	56.17977528
				200	Maize Starch	2	355	56.33802817
				200	Sodium Starch Glycolate	3	354	56.49717514
				200	Hydrolase	4	355	56.33802817
				200	Magnesium Stearate	5	354	56.49717514
				200	Hypromellose	6	353	56.6572238
				200	Macrogol 8000	7	357	56.02240896
				200	Talc	8	355	56.33802817
				200	Titanium Dioxide	9	357	56.02240896
				200	Yellow Ferric Oxide	10	356	56.17977528
Torlisporin	Laboratories S. A	402	Cephalexin	250	Microcrystalline Cellulose	v1	330	75.75757576
				250	Sodium Starch Glycolate	v2	324	77.16049383
				250	Mazie Starch	v3	327	76.45259939
					Magnesium Stearate			
					Talc			
					Titanium Dioxide			

Eracid	The Jordanian Pharm	30248	Clarithromycin	250	Microcrystalline Cellulose	1	401	62.34413965
				250	Croscarmellose Sodium	2	403	62.03473945
				250	Povidone	3	402	62.18905473
				250	Magnesium Stearate	4	404	61.88118812
				250	Talc	5	406	61.57635468
				250	Anhydrous Silica	6	403	62.03473945
				250	Stearic Acid	7	405	61.72839506
					Hypromellose			
					Hydroxypropyl cellulose			
					Propylene Glycol			
					Vanillin			
					Titanium Dioxide			
					Quinoline Yellow			
					Soya Lecithin			
					Polydimethylsiloxane			

Ketek	Sanofi Aventis	L004	Telithromycin	400	Microcrystalline Cellulose	1	613	65.25285481
				400	Povidone	2	620	64.51612903
				400	Croscarmellose Sodium	3	618	64.72491909
				400	Magnesium Stearate	4	621	64.41223833
				400	Talc	5	616	64.93506494
				400	Macrogol 8000	6	617	64.82982172
				400	Hypromellose	7	615	65.04065041
				400	Titanium Dioxide	8	619	64.62035541
				400	Iron Oxide YELLOW	9	617	64.82982172
				400	Iron Oxide RED	10	618	64.72491909
Augmentin	GlaxoSmithKline	514731	Amoxicillin	625	Magnesium Stearate	1	820	76.2195122
			Trihydrate +	625	Aspartame	2	823	75.94167679
			Potassium	625	Crospovidone	3	832	75.12019231
			Clavulanate	625	Xanthan Gum	4	826	75.66585956
				625	Silicon Dioxide	5	824	75.84951456
				625	Anhydrous Silica	6	826	75.66585956
				625	Sodium Benzoate	7	830	75.30120482
				625	Carboxymethyl Cellulose Sodium	8	829	75.3920386
				625	Strawberry Flavour (Inc. Maltodextrin)	9	824	75.84951456

Lamivir	Cipla	G74331	Lamivudine	100	Microcrystalline Cellulose	1	150	66.66666667
				100	Sodium Starch Glycolate	2	156	64.1025641
				100	Magnesium Stearate	3	155	64.51612903
				100	Hypromellose	4	156	64.1025641
				100	Propylene Glycol	5	159	62.89308176
				100	Iron Oxide YELLOW	6	150	66.66666667
				100	Iron Oxide RED	7	152	65.78947368
				100		8	154	64.93506494
				100		9	155	64.51612903
				100		10	158	63.29113924
Ospamox	Sandox	FW0071	Amoxicillin	500	Magnesium Stearate	1	750	66.66666667
				500	Maize Starch	2	754	66.31299735
				500	Erythrosine	3	755	66.22516556
				500	Quinoline Yellow	4	753	66.40106242
				500	Titanium Dioxide	5	758	65.96306069
				500	Red Iron Oxide	6	752	66.4893617
				500	Gelatine	7	751	66.57789614
				500		8	758	65.96306069
				500		9	756	66.13756614
				500		10	755	66.22516556

Metrozine	Cresent Pharma	368	Metronidazole	400	Povidone	1	515	77.66990291
				400	Magnesium Stearate	2	518	77.22007722
				400	Colloidal Silica	3	517	77.36943907
				400	Maize Starch	4	516	77.51937984
				400		5	518	77.22007722
				400		6	515	77.66990291
				400		7	514	77.82101167
				400		8	516	77.51937984
				400		9	512	78.125
				400		10	517	77.36943907

Cefutil	Pharma International Co	6337	Cefuroxime Axial	500	Sodium Lauryl Sulphate	1	723	69.15629322
				500	Co- Povidone	2	726	68.87052342
				500	Croscarmellose Sodium	3	724	69.06077348
				500	Magnesium Stearate	4	725	68.96551724
					Colloidal Anhydrous Silica			
					Granulated Mannitol			
					Microcrystalline Cellulose			
					Crospovidone			
					Talc			
					Mannitol			
					Starch			
					Titanium Dioxide			
					Aspartame			

UNKOWN	UNKOWN	7043	Doxycycline	100	Sucrose	v1	154	64.93506494
				100	Maize Starch	v2	155	64.51612903
Fambox Duo	Fabop	11633	Amoxicillin &	625	Magnesium Stearate	1	830	75.30120482
			Clavulanic Acid	625	Aspartame	2	834	74.94004796
				625	Crospovidone	3	833	75.030012
				625	Xanthan Gum	4	832	75.12019231
				625	Silicon Dioxide	5	830	75.30120482
				625	Anhydrous Silica	6	831	75.21058965
				625	Sodium Benzoate	7	828	75.48309179
				625	Carboxymethyl Cellulose Sodium	8	829	75.3920386
					Talc			
					Titanium Dioxide			
					Hypromellose			
Noroxin	Algorith S.A. L	R098	Norfloxacin	400	Opa-dry AMB OY-B-28920	1	520	76.92307692
				400	Microcrystalline Cellulose	2	526	76.04562738
				400	Croscarmellose Sodium	3	523	76.48183556
				400	Magnesium Stearate	4	524	76.33587786